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Review

Factors That Contribute to the Use of Stroke Self-Rehabilitation Technologies: A Review

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Abstract

Background: Stroke is increasingly one of the main causes of impairment and disability. Contextual and empirical evidence demonstrate that, mainly due to service delivery constraints, but also due to a move toward personalized health care in the comfort of patients' homes, more stroke survivors undergo rehabilitation at home with minimal or no supervision. Due to this trend toward telerehabilitation, systems for stroke patient self-rehabilitation have become increasingly popular, with many solutions recently proposed based on technological advances in sensing, machine learning, and visualization. However, by targeting generic patient profiles, these systems often do not provide adequate rehabilitation service, as they are not tailored to specific patients' needs.

Objective: Our objective was to review state-of-the-art home rehabilitation systems and discuss their effectiveness from a patient-centric perspective. We aimed to analyze engagement enhancement of self-rehabilitation systems, as well as motivation, to identify the challenges in technology uptake.

Methods: We performed a systematic literature search with 307,550 results. Then, through a narrative review, we selected 96 sources of existing home rehabilitation systems and we conducted a critical analysis. Based on the critical analysis, we formulated new criteria to be used when designing future solutions, addressing the need for increased patient involvement and individualism. We categorized the criteria based on (1) motivation, (2) acceptance, and (3) technological aspects affecting the incorporation of the technology in practice. We categorized all reviewed systems based on whether they successfully met each of the proposed criteria.

Results: The criteria we identified were nonintrusive, nonwearable, motivation and engagement enhancing, individualized, supporting daily activities, cost-effective, simple, and transferable. We also examined the motivation method, suitability for elderly patients, and intended use as supplementary criteria. Through the detailed literature review and comparative analysis, we found no system reported in the literature that addressed all the set criteria. Most systems successfully addressed a subset of the criteria, but none successfully addressed all set goals of the ideal self-rehabilitation system for home use.

Conclusions: We identified a gap in the state-of-the-art in telerehabilitation and propose a set of criteria for a novel patient-centric system to enhance patient engagement and motivation and deliver better self-rehabilitation commitment.

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KEYWORDS

home rehabilitation systems; stroke rehabilitation; telerehabilitation; patient participation; motivation; comparative effectiveness research

Introduction

Background

Stroke has become a global problem [1]. One new case is reported every 2 seconds, and the number of stroke patients is predicted to increase by 59% over the next 20 years [2]. In the United Kingdom alone, more than 100,000 stroke cases are reported annually [1], with impairment or disability affecting two-thirds of the 1.2 million stroke survivors [1]. In the United Kingdom, only 77% of stroke survivors are taken directly to the stroke unit. Due to the high number of patients, in England, for example, the social care costs are almost £1.7 billion per annum. The social care cost varies with the age of the patient: the older the patient, the higher the cost. The cost for a person who has had a stroke was reported in 2017 to be around £22,000 per annum. Thus, cost is one of the main drives for service delivery practices. In that respect, early discharge units have been used due to better outcomes and greater success on rehabilitation. Early discharge units consist of specialized personnel who offer an intensive rehabilitation program to the patient. However, after this intensive program of relatively short duration, the patient is discharged and continues the rehabilitation at home. This is expected to reduce costs by £1600 over 5 years for every patient, according to a 2017 report [1].

Due to increasing pressure to discharge patients early from hospital [3], they rely increasingly on home rehabilitation to improve their condition after discharge. As a result, the need has been increasing for home rehabilitation systems that are not dependent on specialist or clinician operators [1,4,5] while providing service similar to a clinical environment. Technological advances in home rehabilitation have been mainly focused on motor control impairments due to their prevalence in the patient population (85% worldwide [1]).

Rehabilitation in a home environment can prove more efficient than that in a clinical environment, as the home environment supports patient empowerment through self-efficacy [6,7]. The presence of supportive family members and a familiarity with the space are significant contributors to motivation. Additionally, rehabilitation in cooperation or in competition with family members demonstrates higher level of engagement [8].

Though rehabilitation in the comfort of a patient's home seems an attractive option, home environments have limitations that can affect the use of clinical devices. The most prevalent limitations are related to space and the lack of qualified personnel to operate devices. The number of occupants; the patient's mobility, individual personality, and mood disorders following stroke; and sound insulation, home modification requirements, and cost [9,10] also contribute to limitations of home rehabilitation. Finally, different age groups react differently to technology and devices; for example, elderly survivors often do not engage with wearable devices or video games [11]. As a result, stroke rehabilitation requires a person-centric approach that is suitable for the home environment and that does not require infrastructure change in the home.

Enhancing Motivation

The success of stroke rehabilitation depends heavily on personal commitment and effort. Recent studies, for example, on applied psychology in behavior change theories for stroke rehabilitation [12-14], do support that the self-esteem of the patient is limited after stroke. In addition, there is an extended sedentary period due to disability and, thus, different programs of activities are set to motivate the patients. Thus, the patient's motivation and engagement have a critical impact on the success of any routine that is to be encouraged [15]. This is especially critical for devices used at home, since patients are usually interacting with them alone without frequent checks. Indeed, if a device does not provide a high level of engagement or motivation enhancement, it is more likely to be abandoned within 90 days [16]. Motivation levels depend on the individual, their achievements, and their needs at each given point in time. For example, once the patients achieve their physiotherapy exercise targets, they lose motivation for further practice. There are 3 main approaches to enhancing patients' motivation: (1) goal-setting theory, (2) self-efficacy improvement theory, and (3) possible selves theory.

Goal-Setting Theory

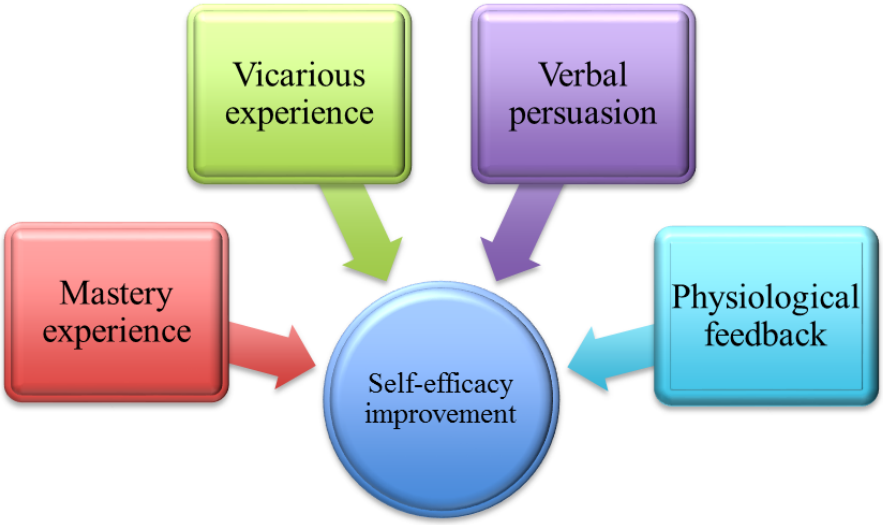
This approach has been proved effective for stroke survivors. According to the goal-setting theory, the patient's motivation can be increased through setting small goals or targets. These need to be realistic, manageable, and well defined for the individual patient. However, they also need to be sufficiently challenging for the patient to be engaged [15,17-19]. Figure 1 presents the main components contributing to motivation enhancement based on the goal-setting theory.

Figure 1. The main components of goal-setting theory.

Self-Efficacy Improvement Theory

Self-efficacy is the individual's ability to appreciate his or her capability to execute a set of actions to manage a situation or challenge [20]. According to this theory, self-efficacy makes patients feel more empowered and more comfortable to overcome difficulties. In the case of rehabilitation, this has been strongly linked with self-confidence in executing activities of daily living (ADL) [21,22] and with better future performance [23,24]. Figure 2 presents the main components contributing to self-efficacy improvement. Completing achievable goals supports mastery and allows engagement with more complex goals. The observation of others provides a vicarious experience, which supports enhanced confidence. Verbal appraisal provides the courage to tackle more difficult goals, while physiological feedback supports the will to improve.

Figure 2. Factors that contribute to self-efficacy enhancement.



Possible Selves Theory

The third theory focuses the patient's motivation on achieving a positive future image of themselves [25]. This approach is based on the patient's psychological condition and their ability to envisage a positive future and a successful recovery. When implemented successfully, this approach creates an optimistic environment leading to better engagement with rehabilitation and faster recovery. However, creating a pessimistic environment can have a negative impact.

Factors Affecting Motivation

Regardless of the approach implemented, several factors affect motivation positively (Figure 3) or negatively (Figure 4). The main contributor to a positive motivation effect is the information available to the patient. This includes acknowledgment of the condition, control of one's actions, achievement of goals, individualized care, overcoming an uncertain psychological condition, and receiving timely feedback [15,23,26]. Motivational feedback can be oral or visual. Also, receiving performance feedback is instrumental in maintaining motivation and engagement. Finally, self-selecting goals and having personal control is a major contributor. Negative factors usually arise from the patient's environment and, thus, care needs to be adapted to these environmental aspects to minimize their impact [27,28].

Additionally, constructive, supportive, and competitive motivational activities, such as specially designed games, can further enhance motivation and engagement with the required rehabilitation activity [8,22].

Based on the above approaches, motivation levels can be increased and engagement maintained at a high level. This is particularly important for home rehabilitation, as it reduces the requirement for caregiver engagement and provides greater control and independence to the patient. Thus, home rehabilitation has a direct impact on the cost of care and the requirement for physiotherapist visits.

Moreover, patients who have an increased capacity to perform daily activities are less dependent on other family members or care providers. This personal improvement in daily activities turns the home environment into a positive contributor to rehabilitation and recovery.

Figure 3. Factors that enhance motivation.

Figure 4. Factors that stop or decrease motivation.

Objectives

We aimed to examine the state-of-the-art in home rehabilitation systems and to assess their suitability and functionality from a patient engagement perspective. Although several review (narrative and systematic) articles have been published on rehabilitation technologies focused on particular areas of the taxonomy (eg, wearable sensor systems review [21] and robotic systems review [29]), to our knowledge, no extensive narrative review of existing home-based rehabilitation technologies to identify criteria for designing future solutions has been done.

Our goal was to make the following contributions: (1) extend the state-of-the-art in assessment of home-based rehabilitation by combining research from 3 research domains: motivation enhancement as part of patient psychology, home rehabilitation technologies, and monitoring technologies through an interdisciplinary approach; (2) provide an in-depth narrative review of home rehabilitation systems that addresses both information and communication technologies and mechanical engineering solutions; (3) develop a patient motivation and engagement analysis of the reviewed technologies; and (4) identify a list of comparative criteria and successful device requirements to address patient motivation and engagement designed based on research findings from all 3 research domains.

Methods

We selected a list of articles and references for review of home rehabilitation systems and monitoring systems to be included in the comparative analysis. The data sources used to search for items to be included in this review were the following databases of academic references, journals with a particular focus on stroke rehabilitation, and web sources: (1) PubMed, (2) Elsevier, (3) IEEE, (4) Springer, (5) Hindawi.com, (6) *Journal of*

NeuroEngineering and Rehabilitation, (7) websites of stroke-related institutions and foundations presenting articles on rehabilitation found through a generic Google search, and (8) Google Scholar (including ResearchGate).

The search criteria included the following keywords and combinations thereof: stroke; devices for stroke rehabilitation; home rehabilitation; rehabilitation engagement; rehabilitation motivation; stroke rehabilitation; telerehabilitation; smart meter; pattern recognition; kinematic analysis; robotic systems; exoskeleton systems; virtual reality; games; mobile applications; individualization; gait analysis; upper limb rehabilitation; balance rehabilitation and/or training.

As the above combination of data sources and keywords returned a vast amount of results, we selected the following inclusion criteria to identify the most relevant sources. (1) Language: English. (2) Date range: within the past 20 years (1996-2018). The majority of articles were published within the past 5 years to reflect the state-of-the-art (since 2014). Older references were made to technologies that substantially shaped the future direction of home rehabilitation systems. (3) Relevance: home or self-rehabilitation was necessary.

Results

Literature Search

The literature search returned a total of 307,550 results after the inclusion criteria were applied as presented in Table 1.

We used the following exclusion criteria to identify the most relevant sources and reduce the number of literature search results: (1) no relevance to stroke rehabilitation in the home environment, (2) trained personnel required to operate the technology; (3) medication or other clinical intervention required, (4) no report of engagement or motivation as a result of using the technology or other form of patient feedback, (5) no description of the technology, (6) no report of usability especially for older people, and (7) no additional contribution to the review findings compared with the previously reviewed articles.

Overall, we read 420 sources, as we excluded the majority by reading the abstracts. A total of 96 sources remained for analysis after meeting the inclusion criteria and having not been eliminated through the exclusion process.

Table 1. Results of the literature search before and after inclusion criteria were applied.

Topic	Results of topic search	Results after inclusion criteria
Devices for stroke rehabilitation	325,000	6800
Home rehabilitation	1,150,000	36,200
Rehabilitation engagement	651,000	17,100
Rehabilitation motivation	128,000	17,300
Stroke rehabilitation	1,640,000	45,800
Stroke; telerehabilitation	8180	3110
Smart meter; pattern recognition	83,200	18,100
Stroke; kinematic analysis	105,000	15,700
Stroke rehabilitation; robotic systems	43,700	16,900
Stroke rehabilitation; exoskeleton systems	15,300	4440
Stroke rehabilitation; virtual reality	41,000	14,100
Stroke rehabilitation; games	47,100	16,900
Stroke rehabilitation; mobile applications	46,500	17,400
Stroke rehabilitation; individualized systems	35,800	17,300
Stroke rehabilitation; gait analysis	112,000	16,000
Stroke; upper limb rehabilitation	138,000	17,200
Stroke; balance rehabilitation	398,000	15,600
Stroke; balance training	799,000	11,600
Total literature search results	5,766,780	307,550

Home Rehabilitation Systems

Overview

To perform a systematic and comprehensive review, we proposed a taxonomy of rehabilitation systems, presented in Figure 5, based on the type of technology presented in the reviewed articles. We obtained the taxonomy on the basis of the therapeutic effect in combination with sensing technology.

Home rehabilitation mainly focuses on motor control impairments due to minimal or no clinical and medical intervention [30,31]. On the other hand, most clinical systems (see left-hand side of Figure 5) have dependencies and are difficult to implement at home. Therapy that requires either

clinical or specialist personnel to assist in execution includes transcranial magnetic stimulation and transcranial direct current stimulation [32], regeneration of neural tissue stem cell therapy [33], and mirror therapy [34,35]. Similarly, treatment of aphasia and cognitive impairments is predominantly within a clinical environment or through specialist intervention [31,36]. As a result, these approaches would require regular home visits or would be impossible to perform away from the clinical environment.

The right-hand side of Figure 5 shows a variety of methods and approaches developed to support home rehabilitation focusing on locomotor training. They differ based on the individual's situation and disabilities [37].

Locomotor training [31,38-42] can be implemented through various methods. One approach is through the use of *exoskeleton devices* [43,44] for gait [45,46] or upper limb [47,48] training. Most large exoskeleton devices reduce clinic personnel costs [49-54] but are inappropriate for home use [55,56]. Some devices in this category have started to have feedback mechanisms incorporated, such as that described by Baran et al [5]. However, these are still very expensive systems requiring a caregiver to guide and support training. Thus, we did not review these systems.

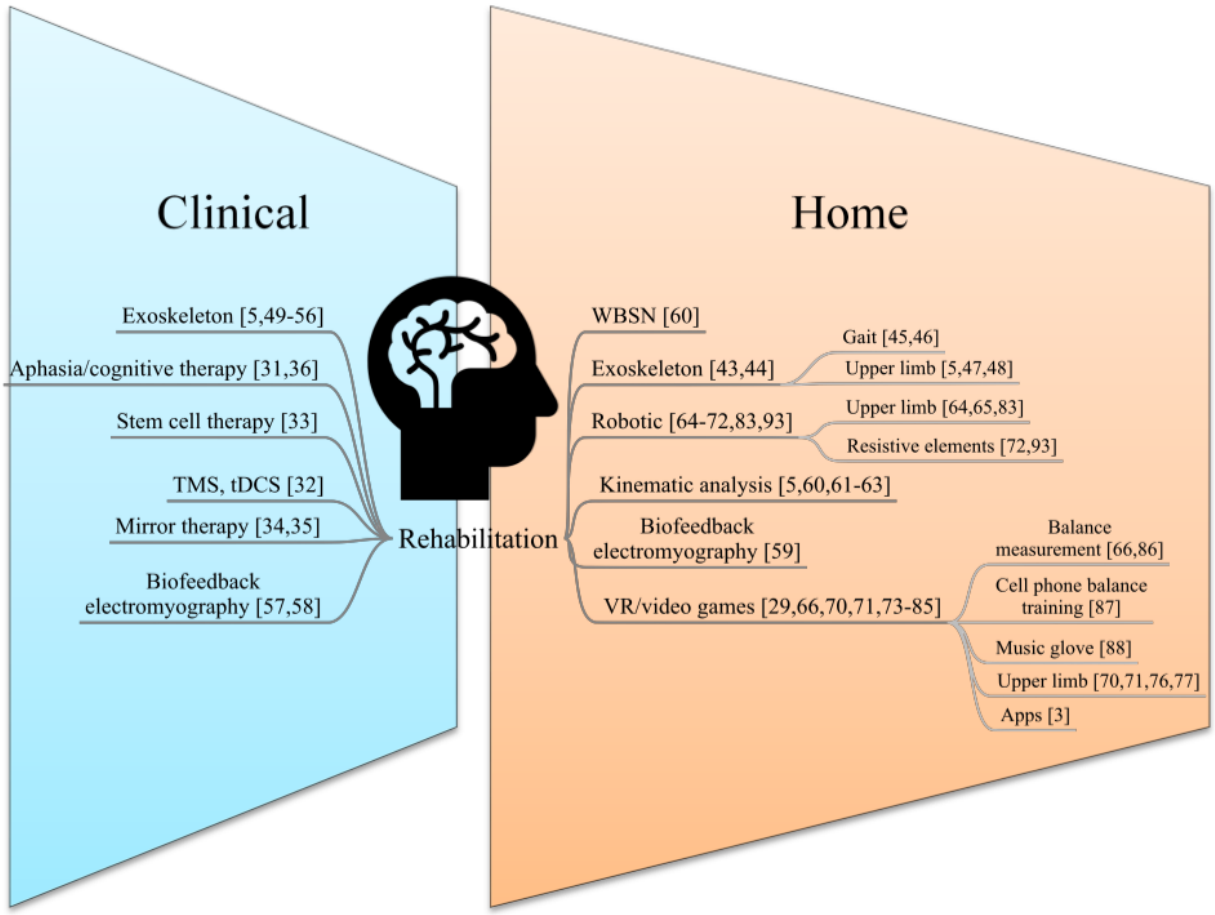
Biofeedback electromyography is based on feedback systems [57,58]. Though mainly designed for clinical use, some devices using this approach have been designed for home use, such as Biomove [59]. However, the disadvantage of this method [59] is the use of wearable equipment, which is not suitable for all patients and particularly the for the elderly [11].

The same challenge is faced by *wearable body sensor network systems* [60]. Additionally, observation by expert or clinical personnel is often needed and, thus, we did not investigate these 2 categories further in this review.

Another approach is to use cameras or wearable sensors for *motion* or *kinematic analysis* [60-63]. Cameras and wearables, however, are considered too intrusive for home use by many patients and individuals [11]. Many applications of cameras and wearables in home rehabilitation systems exist; thus, we reviewed these in detail.

Robotic systems have been heavily investigated [64-71] for home use. However, they face the same challenges of high complexity and cost. This includes systems such as low-cost resistive elements training [72]. However, these systems still do not avoid the requirement for supervision of the exercise. We reviewed systems in this category to identify their ability to enhance motivation and patient engagement.

Figure 5. Taxonomy of rehabilitation systems for stroke patients. VR: virtual reality; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; WBSN: wearable body sensor network systems.



Another area of research interest is the virtual reality and *video game* domain [3,73-84]. Although this is a promising area for home rehabilitation, there are still many challenges. The games are not individualized to the patients' needs; hence, patients lose motivation easily and are not engaged with the activities they need to perform [4,8,15,85]. In particular, elderly patients demonstrate very low engagement with this technology [11]. This category can be expanded to include balance measurement [86], cell phone balance training [87], and even a music glove, which motivates patients with the help of music [88]. We further analyzed systems in this category.

We critically evaluated home-based rehabilitation technologies with a focus on patient engagement as the widely recognized key indicator of success of rehabilitation systems in the reviewed articles. In contrast with *usability*, which is a measure preferred in human-computer interaction studies, *engagement* is not the singular measure of the usability of an interface, but rather of the perpetual retention of the user's interest over a prolonged period of time as defined by Peters et al [14]. Engagement can be the effect of a successful human-computer interaction design in combination with the psychological motivation of stroke survivors for rehabilitation [14]. Based on the literature, engagement is more likely when the feedback is sufficient and well understood by the patient, and the system, apparatus, or device is easy and convenient to use without employing intrusive means and without complex requirements from the user [89].

Kinematic Analysis at Home

In their presentation of a representative example of kinematic analysis systems, Baran et al [5] proposed a home rehabilitation system for upper limb recovery after stroke. They used a specially designed desk and chair to monitor the patient's movement through sensors and cameras. Other examples of kinematic analysis used cameras for upper limb [61] and gait analysis [62,63]. The methods were based either on an expensive camera, to accurately capture fast motion [61,63], or on a laptop and Microsoft Kinect camera sensor, depth image processing, and machine learning [62], to extract the motion patterns, which is relatively difficult to set up and operate.

Wang et al presented another approach for kinematic analysis without the use of cameras. Instead, they proposed a wireless wearable body sensor network system with inertia sensors (accelerometers, gyroscopes, and magnetometers), implemented with 2 wearable sensors per arm to support upper limb rehabilitation. However, the study had several limitations, including the misrepresentation of the Brunnstrom method [90,91] and the lack of feedback provided to the patient.

Kinematic analysis systems rarely provided individualized feedback to the patient. They relied on wearable components or cameras and were of relatively high complexity, making them outside the scope of our review. These are disadvantages, as they contradict the motivation and engagement requirements identified above (see Enhancing Motivation).

Robotic Systems at Home

Robotic systems in this domain have been extensively researched. Zhang et al [64] described an exoskeleton device that they claimed was lighter than similar technologies, to support upper limb rehabilitation. However, the device did not provide feedback to the patient, which would render home rehabilitation impossible. The device was focused on receiving and acting on signals from the patient to increase the task's difficulty. But it did not demonstrate to the patient any positive or negative changes to their rehabilitation exercise.

Similarly, Amirabdollahian et al [65] focused on finger and wrist rehabilitation through a robotic system combined with a computer game to enhance motivation. Additionally, this system incorporated feedback to the health care professional caring for the patient. Nevertheless, the same issues as with wearable components, increased complexity and not being individualized to the needs of the patient, appeared in this device. Nijenhuis et al [83] presented an extension of this work, where individualization and bilateral training were used to enhance motivation. However, this approach still used wearable technology.

Mohamaddan et al [67] addressed ADL, but their device did not provide feedback or keep the patient engaged. The device did not have progressively more difficult or easier exercises to support different stages of the recovery process.

Kohler et al [72] used a simpler approach by combining resistive elements with goal-oriented training. However, the recorded data was presented to the patient in the form of a sinusoidal graph, which is often not understandable information for the patient [92]. Extending research in this direction, Nimmy and Hepsiba [93] provided individualized exercises based on patient monitoring and also provided feedback and comparison with reference exercises. However, the resistive elements used constricted the device's applicability.

Systems in this category demonstrated disadvantages similar to those of kinematic analysis systems. Robotic systems included wearable components, were highly complex, and when feedback was provided it was complicated and not tailored to the individual. These systems lacked engagement and motivation, especially when used by the elderly.

Video Games and Virtual Reality at Home

Some work on demonstrating engagement has been reported for video games and virtual reality approaches. Yano et al [66] presented a system for gait rehabilitation based on body balance training. The device supported slope and stair climbing training. The software received angle positioning data to determine position, but this feedback was not tailored to the patient. Thus, supervised rehabilitation was needed, and engagement was not supported. Similarly, González et al [86] combined balance training with a game environment through Nintendo Wii and Microsoft Kinect platforms. However, they did not investigate engagement with this platform, particularly for the elderly population.

Sivan et al [70] reported on a platform for upper limb rehabilitation in which the patient interacted with a leg support and a joystick and was offered 8 different games. The game became progressively more difficult. However, there was no detailed feedback to the patient when his or her actions did not fully meet the requirements of the game. Additionally, the presence of other people in the home during the game was not

taken into account. The device was difficult to set up. Slijper et al [77] took a similar approach and extended their work to cover bilateral training to enhance engagement. This system supported individualization and feedback, but it was unclear how this system supported ADL.

Johnson et al [71] proposed a software system offering different tasks for upper limb rehabilitation, with extensive feedback, focusing on increasing engagement through individualization of therapy and including bilateral and unilateral therapy. However, the system had several components and used a game environment, which can lead to aversion to the rehabilitation process. Along the same lines, Gorsic and Novak [8] aimed to increase engagement and motivation through the use of competitive or cooperative gaming. However, the game was not individualized to support all users (patients and healthy users).

Friedman et al [88] used a different approach where the focus was on gamification of the patient music experience for motivation enhancement. The device also combined visual feedback through light-emitting diodes installed in the wearable musical glove. However, the study raised the well-known issue of elderly patients reacting negatively to wearable devices. Also, the device was not individualized to support different patient needs.

Wittmann et al [76] harnessed the concept of gradually increasing difficulty to support motivation, through a virtual reality system targeting upper limb rehabilitation and use of several wearable components. The patient's motion was continuously monitored and assessed to calibrate the device and to set tailored goals.

Saposnik et al [3] developed a game as an iPad app that did not use wearable technology. However, the app had several limitations for a variety of patients to engage with this game (eg, age, familiarity, mobility, capacity to hold the device) and provided no explicit feedback to the patient.

Some evidence of motivation or engagement was provided for systems in this category. Some approaches also focused on individualization. However, the main disadvantage was the lack of incorporation into daily activities. Furthermore, the elderly were less engaged and motivation could be hindered, as the benefit in daily life was not directly perceived. Finally, the use of wearable devices or tools was a common trend in these systems.

Monitoring and Home Rehabilitation

Some rehabilitation technologies required renovation and other modifications in the patient's home [9,10,16]. Other challenges for the successful deployment and engagement with home assistive rehabilitation technologies were design and technical limitations [43], and many systems did not meet the acceptance and motivation criteria as reviewed above. Indeed, retrofitting infrastructure in existing homes can be significantly more challenging than designing a smart home that will already be equipped with embedded technology. To avoid these issues, research has mostly focused on smart home environment or monitoring devices that stand alone and do not require redesign of the home [94]. Such systems mostly focus on monitoring generic parameters and provide individualization through pattern recognition algorithms, but do not contribute to rehabilitation activities. Hence, monitoring systems can be tailored to the individual home environment [95-101] and to study individual patterns. To support rehabilitation, their scope would need to be altered to encompass rehabilitation goals, and patient motivation and engagement, while at the same time being transferable (supporting different application domains).

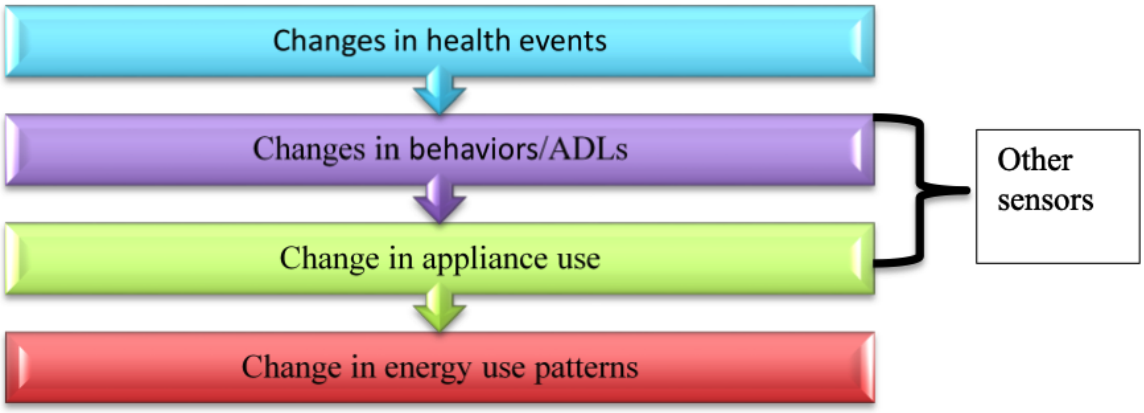
Systems for smart home environments have been proposed for various health-related applications [11,94-101]. They usually require extensive installation of sensors in several locations such as doors, windows, electrical appliances, and furniture. Monitoring devices can provide increasing understanding of the home environment, and of the patient and their condition; they can even provide a diagnosis. Such systems might be more appropriate to support rehabilitation based on performance of daily activities [21,22].

Research in this area has focused on machine learning for information extraction based on recorded data streams [11,94-101]. However, other challenges are introduced when such devices are used, including data security, data correctness, and device operational efficacy [22,101]. Cavallo et al [102] presented an example of such a system targeting rehabilitation. The system provided monitoring and remote supervision, but did not actively support rehabilitation. Some monitoring systems focused on specialist support [102] and behavior analysis [22]. Thus, rehabilitation, motivation, and engagement are outside the scope of these systems (leading to low scores in motivation).

According to Fell et al [22], there is a need for new monitoring devices that incorporate different sensors or input data streams. Figure 6 presents the additional information that can be used to support patient rehabilitation at home. The environment must be monitored and any deviation from the "normal" behavior must be identified. Changes in Figure 6 refer to identification of unexpected behavior, events, or abnormalities identified in the recorded data streams. "Other sensors" refers to the need for data fusion, acquisition of information from multiple sources, and a higher level of information extraction. For example, energy patterns can be identified through active power (smart meter) measurements; appliance use, though, might require other information such as time, temperature, location, and motion. Similarly, a health event may be recorded by a single monitoring parameter (eg, glucose level dropped below a threshold). However, changes in behavior and competence in daily activities require a series of additional measurements (eg, sound, motion, temperature, humidity, gases).

We found a gap in applying monitoring technologies (supported, for example, by machine learning, fusion, or pattern recognition) to rehabilitation that, at the same time, support patients in performing daily activities and enhance motivation. We suggest that, by using these monitoring technologies, *individualization* can be achieved for rehabilitation purposes, via providing appropriate feedback, applying machine learning to the individual patient, and focusing on daily activities, thus meeting the acceptance, motivation, and engagement requirements reviewed above (see Enhancing Motivation).

Figure 6. Monitored qualities for the health and care applications and the need for additional sensor input to monitoring devices [22]. ADLs: activities of daily living.



Comparative Analysis

Tables 2-4 summarize the criteria we selected for the comparative analysis. The methods for selecting the criteria were as follows. For Table 2, we selected these criteria based on the narrative review of motivation and engagement aspects we analyzed (see Enhancing Motivation). For Table 3, we selected these criteria according to commonly used and evaluated metrics in the majority of the reviewed articles. This was additionally informed by the conclusions outlined in the Enhancing Motivation and Home Rehabilitation Systems sections. For Table 4, we selected the criteria to meet other acceptability and economic aspects (including long term usability and transferability), as well as a separate category for the application area presented in the reviewed articles.

We used the extracted information from the reviewed articles to establish the criteria and to identify whether the criteria were met by the proposed systems. For the engagement and motivation criteria, as well as acceptance, all of the reviewed articles reported results on a common basis; thus, we needed no additional steps to cross-validate the reported results.

Tables 2-4 present a detailed comparative analysis of all the aforementioned technologies that were applicable for use in the home environment. We selected the technologies as representative examples of each category we analyzed.

Table 2. Summative assessment of the reviewed systems for the selection of criteria for the comparative analysis: motivation.

First author, year, reference no.	Motivation method				Engaging	Supports daily activities
	Cooperative	Supportive	Constructive	General		
Baran, 2011 [5]	No	No	No	Yes	No	No
Zhang, 2016 [64]	No	No	No	No	No	No
Yano, 2015 [66]	No	No	No	No	No	No
Mohamaddan, 2015 [67]	No	No	No	No	No	No
Sivan, 2014 [70]	No	No	No	Yes	No	No
Johnson, 2007 [71]	No	No	No	Yes	No	Yes
González, 2015 [86]	No	No	No	No	No	No
Wang, 2017 [60]	No	No	No	No	No	No
Kohler, 2010 [72]	No	No	No	No	No	No
Friedman, 2011 [88]	No	No	No	Yes	No	Yes
Nimmy, 2013 [93]	No	No	No	No	No	No
Wittmann, 2015 [76]	No	No	No	Yes	No	No
Slijper, 2014 [77]	No	No	No	Yes	No	No
Nijenhuis, 2015 [83]	No	No	No	Yes	Yes	Yes
Saposnik, 2014 [3]	No	No	No	No	No	No
Gorsic, 2016 [8]	Yes	Yes	Yes	Yes	Yes	No
Fell, 2017 [22]	No	No	No	No	No	No
Cavallo, 2009 [102]	No	No	No	No	No	No

Table 3. Summative assessment of the reviewed systems for the selection of criteria for the comparative analysis: acceptance.

First author, year, reference no.	Individualized	Suitable for the elderly	Nonwearable	Nonintrusive
Baran, 2011 [5]	No	No	No	No
Zhang, 2016 [64]	No	No	No	Yes
Yano, 2015 [66]	No	Yes	No	Yes
Mohamaddan, 2015 [67]	No	Yes	No	Yes
Sivan, 2014 [70]	No	No	No	No
Johnson, 2007 [71]	Yes	No	No	Yes
González, 2015 [86]	No	Yes	No	Yes
Wang, 2017 [60]	No	No	No	Yes
Kohler, 2010 [72]	No	Yes	No	Yes
Friedman, 2011 [88]	No	Yes	No	Yes
Nimmy, 2013 [93]	No	Yes	No	Yes
Wittmann, 2015 [76]	No	No	No	Yes
Slijper, 2014 [77]	No	Yes	Yes	Yes
Nijenhuis, 2015 [83]	No	No	No	Yes
Saposnik, 2014 [3]	No	No	Yes	Yes
Gorsic, 2016 [8]	No	Yes	No	Yes
Fell, 2017 [22]	Yes	Yes	Yes	Yes
Cavallo, 2009 [102]	Yes	Yes	No	No

Table 4. Summative assessment of the reviewed systems for the selection of criteria for the comparative analysis: technological aspects.

First author, year, reference no.	Intended use			Cost-effective	Technologically simple	Transferable
	Monitoring	Rehabilitation	Diagnosis			
Baran, 2011 [5]	No	Yes	No	No	No	No
Zhang, 2016 [64]	No	Yes	No	No	No	No
Yano, 2015 [66]	No	Yes	No	No	Yes	No
Mohamaddan, 2015 [67]	No	Yes	No	Yes	Yes	No
Sivan, 2014 [70]	No	Yes	No	No	No	No
Johnson, 2007 [71]	No	Yes	No	No	No	No
González, 2015 [86]	No	Yes	No	Yes	Yes	No
Wang, 2017 [60]	No	Yes	No	No	Yes	No
Kohler, 2010 [72]	No	Yes	No	Yes	Yes	No
Friedman, 2011 [88]	No	Yes	No	No	Yes	No
Nimmy, 2013 [93]	No	Yes	No	Yes	Yes	No
Wittmann, 2015 [76]	No	Yes	No	No	No	No
Slijper, 2014 [77]	No	Yes	No	No	Yes	No
Nijenhuis, 2015 [83]	No	Yes	No	No	No	No
Saposnik, 2014 [3]	No	Yes	No	Yes	Yes	No
Gorsic, 2016 [8]	No	Yes	No	No	No	No
Fell, 2017 [22]	Yes	No	Yes	No	Yes	Yes
Cavallo, 2009 [102]	Yes	No	No	Yes	No	Yes

Our analysis identified 3 aspects of technologies that we used for comparison: (1) motivation, (2) acceptance of technology, and (3) technological aspects. We selected these aspects for their importance in supporting patients' motivation and

engagement (motivation) and in being incorporated into patients' rehabilitation routines (acceptance, technology).

For each aspect, we identified several comparison criteria. Regarding *motivation*, the criteria are (1) the motivation method used, (2) the patient's *engagement* with the technology, and (3) whether the technology *supports daily activities* as an additional measure of motivation. There are 3 motivation methods: cooperative, supportive, and constructive. When the method used in a technology was not specified, we characterized it as *general*. With respect to *acceptance*, the criteria are (1) *individualization* of the device to meet patients' needs, (2) suitability of the device for *elderly patients*, (3) the use of *wearable components*, and (4) the use of *intrusive monitoring* methods (eg, wearable sensors, on-body sensors, cameras, microphones). Wearable and intrusive methods have a negative impact on acceptance. *Technological aspects* are (1) *intended use* for the technology (monitoring, rehabilitation, diagnosis), (2) *cost*, (3) *complexity*, and (4) *transferability* to other domains.

Regarding intended use, besides our focus of rehabilitation, we also included 2 systems that perform monitoring and diagnostics.

"Yes" in the table highlights that the system met the criteria, which was demonstrated in the published work, subject to our interpretation. "No" indicates that the system did not meet the criteria.

We assessed a system to be individualized or personalized or person centric when it learned or adapted to the needs of a particular patient by incorporating some type of feedback loop mechanism where the device adjusted the requested task(s) to the ability of the patient. Examples of such mechanisms are machine learning approaches and increasing task difficulty. We assessed suitability for the elderly based on Debes et al [11]. We classified nonwearable (on-body sensors, wearable components) and nonintrusive (cameras, microphones) systems according to the system inputs that were used. The intended use of the system can be for rehabilitation, smart home monitoring, or smart home diagnosis of a health condition.

In the analysis, we considered systems that could be purchased by an average household in the United Kingdom to be cost-effective. We considered systems that would require a high capital investment, and thus reimbursement from the health care provider, to be not cost-effective. We considered technologically complex systems to be those that had a significant number of components, required significant training before use, or required extensive installation to be usable in a household. Finally, transferable systems were those that could be used for other rehabilitation purposes and were not restricted to stroke rehabilitation.

As the tables show, no technology met all the selected criteria. Most of the technologies were suitable for the elderly and were nonintrusive. However, most technologies lacked motivation and engagement enhancement through the use of a variety of motivation methods. The developed approaches were technology centric, whereas a person-centric approach is necessary to keep patients engaged and motivated in achieving their rehabilitation goals. Several devices claimed to enhance motivation but produced little or no evidence of patient engagement [5,8,70,71,74,75,81,86]. None of the devices intended for rehabilitation were transferable to other uses. Devices intended for monitoring or diagnosis had the desired transferability features [22,102]. Only 1 of the reviewed technologies proposed for rehabilitation supported individualization [71]; however, it did not meet the requirements for elderly patients and it used wearable components. On the other hand, individualization was supported by monitoring devices that were not intended for rehabilitation use [22,100]. Several technologies we reviewed were inappropriate for home rehabilitation, as they were technologically complex and expensive.

Discussion

Principal Findings

The first rows of Tables 2-4 list all the selected criteria, drawn from our extensive literature review, that must be met for a home rehabilitation system to be engaging and enable stroke recovery patients to meet their progressively ambitious goals or targets. Based on the above analysis, an ideal home rehabilitation device should meet all the identified criteria and requirements. The device needs to avoid wearable or intrusive components. It needs to support enhanced motivation and engagement by being incorporated into the daily activity routine. It must be cost-effective and not complex to install, maintain, and use. It needs to support the needs of all patients, regardless of age and background. Moreover, it needs to be portable and transferable to other domains.

The successful design of an assistive technology or rehabilitation device should take under consideration what the individual should and can achieve during rehabilitation [16]. Quantification and further analysis of the present and future conditions of the patient could overcome difficulties and unforeseen circumstances and could result in better assistive technology design.

Data and patterns from electronic databases are quite important to tailor rehabilitation, as the device can learn patients requirements and goals, adapt to their individual needs, and provide suitable challenges, for example, through machine learning. Individual choice and personal control are mandatory for success (see Monitoring and Home Rehabilitation). Technology design has to follow a person-centric approach considering technology ability levels. Given the developments in smart devices, algorithms, and information extraction, devices can adopt a person-centric approach while meeting the requirements for cost and complexity.

Contributions from the patient's environment can be used to enhance motivation and engagement with the activity. Members of the family or others can provide a competitive or cooperative stimulation. Additionally, rehabilitation incorporated into the completion of daily activities could enhance motivation. Finally, the continuous adjustment of the technology or device to the patient's changing requirements has a more beneficial effect. The device should adapt to increased levels of difficulty to provide stimulation for achieving higher targets.

Thus, a system catering to every occasion, individualized and adapted to support the patient's daily activities in their home

environment, has a higher potential for successful acceptance and engagement. This system should incorporate a device, hardware, and additional software. However, developing such a system for the full range of impairments and rehabilitation tasks is an unrealistic goal. This is due to the requirement for different types of inputs for each condition, the range of rehabilitation goals, the differences between patients, and the differences between home environments. Hence, the successful system should focus on supporting specific daily activities that have measurable outcomes specified in recognized health care rehabilitation tests (see Comparative Analysis).

Conclusion

We reviewed rehabilitation devices for stroke patients in detail. The focus was on systems that are intended for use within the home environment for self-rehabilitation routines. We reviewed several technology domains under the criteria of motivation and engagement enhancement for continued use without the need for clinical or specialist involvement. We demonstrated that the existing approaches do not meet all the criteria in the motivation, acceptance, and technological categories. However, there is evidence that some devices proposed for monitoring instead of rehabilitation might provide solutions to individualization and thus wider engagement and acceptance. We identified the criteria for a device and system that will provide the required level of self-rehabilitation commitment as nonintrusive, nonwearable, motivation and engagement enhancing through a list of motivation methods, individualized, supporting daily activities, suitable for the elderly, cost-effective, simple, transferable, and intended for use in rehabilitation.

Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living

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Review

Immersive Virtual Reality in Health Care: Systematic Review of Technology and Disease States

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Abstract

Background: Immersive virtual reality (IVR) presents new possibilities for application in health care. Health care professionals can now immerse their patients in environments to achieve exposure to a specific scene or experience, evoke targeted emotional responses, inspire, or distract from an experience occurring in reality.

Objective: This review aimed to identify patient-focused applications for head-mounted IVR for acute treatment of health conditions and determine the technical specifications of the systems used.

Methods: A systematic review was conducted by searching medical and engineering peer-reviewed literature databases in 2018. The databases included PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Association for Computing Machinery, Institute of Electrical and Electronics Engineers, Scopus, and Web of Science. Search terms relating to health and IVR were used. To be included, studies had to investigate the effectiveness of IVR for acute treatment of a specific health condition. IVR was defined as a head-mounted platform that provides virtual and auditory immersion for the participant and includes a minimum of 3 degrees of orientation tracking. Once identified, data were extracted from articles and aggregated in a narrative review format.

Results: A total of 58 studies were conducted in 19 countries. The studies reported IVR use for 5 main clinical areas: neurological and development (n=10), pain reduction through distraction (n=20), exposure therapy for phobias (n=9), psychological applications (n=14), and others (n=5). Studies were primarily feasibility studies exploring systems and general user acceptance (n=29) and efficacy studies testing clinical effect (n=28).

Conclusions: IVR has a promising future in health care, both in research and commercial realms. As many of the studies examined are still exploring the feasibility of IVR for acute treatment of health conditions, evidence for the effectiveness of IVR is still developing.

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KEYWORDS

virtual reality; health care; telemedicine; systematic review; mHealth

Introduction

Virtual reality (VR) has recently seen a resurgence of interest, both in the general public and academic communities. Technological improvements in processing, graphics, display, and 3D software have led to the release of several new commercially available VR systems since 2010. As a result, VR systems today cost one-sixtieth of the price, have better performance, and require less specialized hardware than systems from 20 years ago [1].

VR systems immerse the user in a virtual environment by completely replacing the visual environment and possibly aural

sensation. The aim is to achieve a sense of *presence* such that the user perceives themselves as being part of the virtual environment. Key technical factors that help induce presence are accurate and stable tracking of the user's head and possibly body motions, low-latency updating of the visual image provided to the user, a high display resolution, and a wide field of view.

Although commonly used for entertainment, VR is increasingly being used for so-called *serious* applications. Nonimmersive VR has a long history of use in health care; however, in this study, the more recent trends of immersive virtual reality (IVR) for health-related treatment applications are reviewed. IVR presents interesting possibilities for application in health care. Health care professionals can now immerse their patients in environments to achieve exposure to a specific scene or experience [2], evoke targeted emotional responses [3], inspire [4], or distract from an experience occurring in reality [5]. Relevant previous reviews have focused on specific clinical specialties such as mental health [6] or cognitive and motor rehabilitation [7,8]. This study aimed to summarize research across many clinical specialties. Findings are compared with those of related reviews in the Discussion section.

Terminology varies across different fields and from academia to public vocabulary. In this review, IVR is defined as a VR system that provides at least 3 degrees of freedom (DOF) of head orientation tracking (ie, roll, pitch, and yaw) and uses a head-mounted display (HMD) worn by the user. Traditionally, IVR may also include projection-based virtual environments (sometimes called *CAVE* systems). These systems were excluded to align this review with the recent trend of commercially available low-cost head-mounted devices. In addition to head orientation tracking, IVR systems may further provide head positional tracking or hand, controller, or body tracking in conjunction with various other sensory modalities such as haptic feedback.

Non-IVR systems that display a virtual environment to the user on a personal computer or mobile phone display without head tracking were excluded. Such systems have a long history of successful use in health care, most notably in psychology, with several reviews available [9-12]. Finally, this review did not focus on nontreatment applications of VR in health care such as for training.

The primary research question addressed by this review is as follows: what are the patient-focused applications for IVR in health research? This review examines the technical specifications of the systems being used and collates the health conditions being targeted.

Methods

Search Strategy

This review follows the methods described in a published protocol (PROSPERO 2018 CRD42018105512) [13]. Articles were included if they were published after 2010 when low cost IVR technology became commercially available. Only full-text journal articles available in English were included.

Search terms with appropriate amendments (dependent on medical subject headings) were used to search PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Association for Computing Machinery, Institute of Electrical and Electronics Engineers, Scopus, and Web of Science for articles. ProQuest Global was additionally searched for theses. Search terms were (health OR rehabilitation OR telere* OR "digital health" OR ehealth OR "virtual care" OR telemedicine OR telehealth) and ("virtual environment" OR "artificial environment" OR "virtual reality") not (surge*). Where possible, results were filtered to human-focused studies.

Article Selection

After duplicates were removed, titles and abstracts were screened for eligibility. The remaining articles were then read in full to confirm eligibility. Owing to the volume of articles returned, rehabilitation applications of IVR were excluded during the abstract and full-text review.

Studies were included if they related to any population receiving acute disease—specific treatment using IVR. Studies were excluded if they described training for health professionals in IVR (generally surgery education), non–earth-based applications (ie, focused, on space exploration), nonacute treatment applications such as rehabilitation, only described a system or hypothetical system without pilot or efficacy results, or were general well-being IVR systems for nondescript clinical purposes such as mood elevation or incentivizing exercise.

The primary search was conducted by one researcher (CS). Abstracts were reviewed by two researchers (CS and AS), with any disagreement discussed to reach consensus.

Data Extraction and Analysis

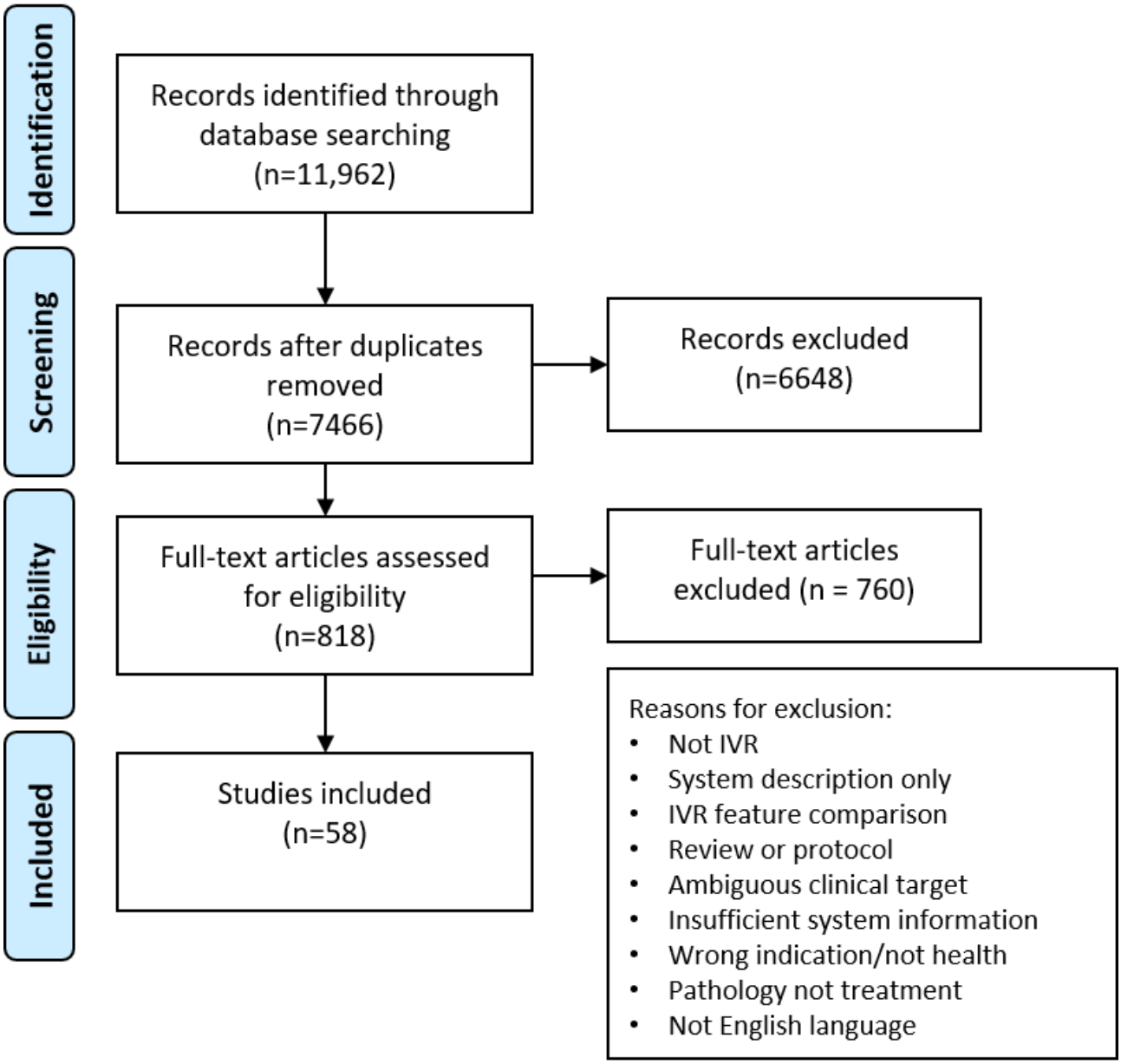
The data extracted included study type (efficacy or feasibility), IVR system, and condition and treatment purpose. Meta-analysis was not completed on the selected studies because of the large variation in identified studies.

Results

Study Selection

Figure 1 shows the article selection process and lists the exclusion criteria. The study extraction and selected results are listed in Tables 1-5.

Figure 1. Article selection process. IVR: immersive virtual reality.



A total of 58 studies were conducted in 19 countries. The studies reported IVR use for 5 main clinical areas: neurological and development (n=10), pain reduction through distraction (n=20), exposure therapy for phobias (n=9), other psychological applications (n=14), and other applications (n=5). Studies were categorized into 3 types: feasibility studies looking at the system and general user acceptance (n=29), efficacy studies testing clinical effect (n=28), and economic analysis (n=1).

What Are the Patient-Focused Applications for Immersive Virtual Reality in Health Research?

Neurological and Development

Ten articles reported that IVR was used for social attention training in children and adults with autism spectrum disorder [14-16]. Owing to the immersive nature of the environment, the individual's attention can be directed in training scenarios [14]. Environments were designed to immerse patients in general social situations [14,17,18] or prepare them for specific social situation such as public bus rides [15]. IVR was used to achieve similar goals for children with intellectual development disabilities [19] and neurodevelopmental disorders [20].

IVR was also used to assist with the treatment of memory and cognitive functioning decline for individuals who had experienced a stroke or Alzheimer disease [21]. These IVR systems enabled individuals to practice undertaking everyday tasks in a simulated environment such as shopping for multiple items [21] or navigating a building structure [22].

Alternatively, IVR was used as a method of cognitive stimulation for patients in a hospital intensive care unit [23]. As these individuals were unable to leave their hospital environment, IVR created an opportunity for them to experience alternate environments to assist with cognitive stimulation [23]. See Table 1 for an overview.

Table 1. Included studies: neurological and development.

Author, year (country)	Immersive virtual reality system	Article type	Condition and treatment purpose	Number of participants	Reported participant age (years)
Gerber et al, 2017 (Switzerland) [23]	Oculus Developer Kit 2	Efficacy	Cognitive stimulation for patients in the intensive care unit	37	20-85
Amaral et al, 2017 (Portugal) [14]	Oculus Developer Kit 2	Feasibility	Social ability in autism spectrum disorder	17	15-26
Bernardes et al, 2015 (Portugal) [15]	Not stated	Feasibility	Social ability in autism spectrum disorder	5	32.2 (4)[a]
Fitzgerald et al, 2018 (Australia) [16]	Oculus Commercial Version 1	Feasibility	Increased learning in autism spectrum disorder	2	25-35
Gelsomini et al, 2016 (Italy) [19]	Google Cardboard	Feasibility	Learn behavioral skills for individuals with intellectual development disabilities	5	Children[b]
Gelsomini et al 2016 (Italy) [20]	Google Cardboard	Feasibility	Functional improvement for individuals with neurodevelopment disorders	10	6-10
Liu et al, 2018 (China) [17]	HTC Vive	Feasibility	Social interaction in autism spectrum disorder	4	5-7
Shahab et al, 2018 (Iran) [18]	HTC Vive	Feasibility	Game therapy for autism spectrum disorder	14	Children[b]
White et al, 2016 (Canada) [22]	Oculus Developer Kit 2	Feasibility	Cognitive changes in Alzheimer disease	1	74
Gamito et al, 2017 (Portugal) [21]	eMagin Z800	Efficacy	Attention and memory after stroke	29	55 (14)[a]

[a]Mean (SD).

[b]Direct quote from article, specific ages for participant/s not reported.

Pain Reduction Through Distraction

In this study, 20 articles reported that IVR was used for patients experiencing pain to distract them by providing alternate sensory input and to treat pain in specific populations with neck pain and phantom limb pain (Table 2).

Table 2. Included studies: pain reduction through distraction.

Author, year (country)	Immersive virtual reality system	Article type	Condition and treatment purpose	Number of participants	Reported participant age (years)
Mosadeghi et al, 2016 (USA) [24]	Samsung Gear VR	Feasibility	Hospitalized patients	30	49.1 (17)[a]
Delshad et al, 2018 (USA) [25]	Samsung Gear VR	Economic analysis	Hospital patients	Not applicable	Not reported
Tashjian et al, 2017 (USA) [26]	Samsung Gear VR	Efficacy	Hospitalized patients	100	54.5 (18)
Ambron et al, 2018 (USA) [27]	Oculus Developer Kit 2	Feasibility	Phantom limb pain	2	Middle aged to late-middle-aged[b]
Amin et al, 2017 (Canada) [5]	Google Cardboard and Oculus Developer Kit 2	Efficacy	Chronic pain	30	23-68
Birnie et al, 2018 (Canada) [28]	Samsung Gear VR	Feasibility	Pediatric cancer	17	8-18
Ebrahimi et al, 2017 (Iran) [29]	Not reported	Efficacy	Dressing changes for burns patients	60	24-40
Faber et al, 2013 (USA) [30]	Cybermind HiRes900	Efficacy	Burns patients	36	8-57
Ford et al, 2018 (USA) [31]	Sunnypeak[c]	Feasibility	Burns patients	10	30-69
Garrett et al, 2017 (Canada) [32]	Oculus Developer Kit 2	Feasibility	Chronic pain	8	31-71
Gold et al, 2018 (USA) [33]	AppliedVR and Samsung Gear VR or Google MergeVR	Efficacy	Phlebotomy	143	15.4 (3)[a]
Henriksen et al, 2017 (France) [34]	Oculus Developer Kit 2	Feasibility	Phantom limb pain	3	45-60
Hoffman et al, 2014 (USA) [1]	Oculus Commercial Version 1	Feasibility	Skin stretching therapy for burns patients	1	11
Jeffs et al, 2014 (USA) [35]	Kaiser Optics SR80a	Efficacy	Dressing changes for burns patients	28	10-17
Nielsen et al, 2017 (Denmark) [36]	HTC Vive	Feasibility	Phantom limb pain	8	21-27
Osumi et al, 2017 (Japan) [37]	Oculus Developer Kit 2	Feasibility	Phantom limb pain	8	43-64
Bahat et al, 2015 (Australia) [38]	Vuzix Wrap 1200VR	Feasibility	Chronic pain and movement	32	40.6 (14)[a]
Bahat et al, 2018 (Australia) [39]	Oculus Developer Kit 1	Efficacy	Chronic pain and movement	90	38.5, 57.5[d]
Scapin et al, 2017 (Brazil) [40]	Samsung Gear VR	Feasibility	Burns patients	2	8-9
Tanja-Dijkstra et al, 2014 (UK) [41]	Vuzix iWear VR920	Efficacy	Dental anxiety related to pain	69	33.1 (13)[a]

[a]Mean (SD).

[b]Direct quote from article, specific ages for participant/s not reported.

[c]These systems are low-cost phone-based head-mounted displays that are not widely commercially available.

[d]Quartile 1, quartile 3.

Distraction

IVR was used to provide patients with sensory information unrelated to their current situation or condition, the immersive nature of the virtual environments being a key factor in this application. Distraction through modified sensory input showed a reduction in pain sensations [5,24,26,32] and has been used to assist with painful procedures or exercises such as phlebotomy [28,33], dental appointments [41], dressing changes [29-31,35,40], and movement therapy for burns patients [1]. IVR has been used in both pediatric and adult populations for this purpose, in the hospital, clinic, and home settings [29-31,35,40].

Treatment

Studies were identified where IVR was used to replicate the treatment method Mirror Box Therapy, where patients use a mirror to create the illusion of an amputated limb still being present [36]. IVR represents a format in which amputated limbs can be simulated and used to complete gamified tasks [27,34,36,37]. IVR was also used to optimize the accuracy with which patients executed neck movement exercises to increase

their range of motion and reduce their neck pain symptoms [38,39].

Exposure Therapy for Phobias

Overall, 9 articles reported that IVR has been harnessed to treat phobias, used as a method of either self-guided [42-44] or clinician-led [2,45,46] exposure therapy for patients (Table 3). Phobias included social phobia [2,42] (social anxiety disorder [SAD]), acrophobia [43,46] (fear of heights), agoraphobia [44,45] (fear of entering open or crowded places), aviophobia [47] (fear of flying), arachnophobia [3] (fear of spiders), and claustrophobia [48] (fear of confined spaces). Many of the IVR environments or activities were personalized for the specific patient, highlighting the benefit of using technology such as IVR for exposure therapy [2,3,49,42,44-45,46].

Table 3. Included studies: exposure therapy for phobias.

Author, year (country)	Immersive virtual reality system	Article type	Condition and treatment purpose	Number of participants	Reported participant age (years)
Bouchard et al, 2017 (Canada) [2]	eMagin Z800	Efficacy	Social phobia (SAD[a])	59	34.5 (12)[b]
Freeman et al, 2018 (UK) [49]	HTC Vive	Efficacy	Acrophobia (fear of heights)	100	30-53
Hartanto et al, 2016 (Netherlands) [42]	Custom	Feasibility	Social phobia (SAD[a])	5	38-64
Hong et al, 2017 (Korea) [43]	Samsung Gear VR	Efficacy	Acrophobia (fear of heights)	48	23.2 (2)[b]
Malbos et al, 2013 (Australia) [44]	Virtual Realities HMD42	Efficacy	Agoraphobia	18	24-72
Maples-Keller et al, 2017 (USA) [47]	eMagin Z800	Efficacy	Aviophobia (fear of flying)	89	21-67
Meyerbroeker et al, 2013 (Netherlands) [45]	WorldViz Vizard 3.0	Efficacy	Agoraphobia	55	18-65
Shiban et al, 2015 (Germany) [3]	eMagin Z800	Efficacy	Arachnophobia	41	18-60
Shiban et al, 2016 (Germany) [48]	eMagin Z800	Efficacy	Claustrophobia	48	18-65

[a]Social anxiety disorder.

[b]Mean (SD).

Other Psychological Applications

Overall, 14 articles reported other psychological application for IVR (Table 4), including self-management in depression [50,51], exposure therapy for posttraumatic stress disorder (PTSD) [52-54], reducing delusions and hallucinations [4,46,55,56], improving unhealthy eating habits [57-60], and reducing attention deficits in schizophrenia [61].

Table 4. Included studies: other psychological applications.

Author, year (country)	Immersive virtual reality system	Article type	Condition and treatment purpose	Number of participants	Reported participant age (years)
Atherton et al, 2016 (UK) [55]	nVisor SX111	Efficacy	Persecutory ideation in paranoid individuals	26	43.4 (16)[a]
Cai et al, 2017 (China) [50]	Not reported	Feasibility	Self-guided symptom management for individuals with depression	12	20-35
Cárdenas-López et al, 2014 (Mexico) [57]	Neuro-VR 2.0	Feasibility	Increased weight loss after gastric band surgery for obesity	3	32-44
Cárdenas-López et al, 2015 (Mexico) [58]	Neuro-VR 2.0	Efficacy	Increased weight loss in obese individuals	24	≥18 and ≤50
Dellazizzo et al, 2018 (Canada) [4]	Samsung Gear VR	Feasibility	Reduction of verbal hallucination symptoms	1	Early 50s[b]
Dietrichkeit et al, 2018 (Germany) [56]	Oculus Developer Kit 2	Feasibility	Recall accuracy for individuals who experience delusions	2	36-44
Freeman et al, 2016 (UK) [46]	HTC Vive	Efficacy	Reduced safety-seeking behavior in individuals with persecutory delusions	30	40.6 (14)[a]
Hussain et al, 2018 (USA) [51]	Oculus Commercial Version 1	Feasibility	Increase in positivity generally and toward seeking help for depressed individuals	12	18-26
Keizer et al, 2016 (Netherlands) [59]	Oculus Developer Kit 2	Efficacy	Body size distortion in anorexia nervosa	30	22 (4)[a]
La Paglia et al, 2016 (Italy) [61]	Neuro-VR 2.0	Efficacy	Attention deficits in schizophrenia	15	29 (12)[a]
Marco et al, 2013 (Spain) [60]	Not reported	Feasibility	Eating disorders	34	15-40
McLay et al, 2017 (USA) [52]	Custom	Efficacy	Exposure therapy in posttraumatic stress disorder (PTSD)	88	33 (8)[a]
McLay et al, 2014 (USA) [53]	Custom	Feasibility	Symptoms reduction in PTSD	28	25-49
Reger et al, 2016 (USA) [54]	eMagin Z800	Efficacy	Exposure therapy for PTSD	162	29.5 (6)[a]

[a]Mean (SD).

[b]Direct quote from article, specific ages for participant/s not reported.

Depression

Both depression-focused studies described self-administered VR therapy that could be used at home. In one case, a preprogrammed virtual avatar prompted individuals to share their experiences with depression with the aim of increasing self-help behaviors [51]. A second application featured integrated neurofeedback for self-management of symptoms at home through interaction with preprogrammed environments [41].

Posttraumatic Stress Disorder

IVR was used in two studies to improve the immersion of the experience for exposure therapy in PTSD treatments [52-54]. Exposure therapy using VR is well documented in the literature; however, only two studies were identified as immersive for this review.

Delusions and Hallucinations

IVR for persecutory delusions allowed patients to be immersed in social environments with progressively more avatars present, which enabled a safe situation to practice being in a social environment [46]. Another IVR experience used virtual immersive social environments to build self-confidence as a mechanism to combat paranoia and persecutory delusions [55]. IVR was also used to ameliorate delusions related to memory recall by using IVR to experience environments and practice recalling details accurately [56].

A case study examined using IVR as a mechanism for therapy for individuals experiencing verbal hallucinations. Using an avatar created in IVR, a therapist was able to virtually embody the persona of the verbal hallucination, allowing the patient a new mechanism of interactive therapy, which showed promising results [4].

Unhealthy Eating Habits

Overall, 4 papers described the results of studies using IVR to assist with acute unhealthy eating habits, including obesity, anorexia nervosa, and general eating disorders [57-60]. In all 4 studies, IVR was used to create a full-body illusion aimed at correcting inaccurate patient perceptions of themselves as a supplement to cognitive behavioral therapy [57-60].

Schizophrenia

Individuals living with schizophrenia received IVR-based cognitive behavioral therapy to undertake attention training tasks [61].

Other Applications

A total of 5 articles were identified where IVR was being used for patient-focused clinical application that did not specifically align with the other categories identified (Table 5). These articles demonstrated the use of IVR for vestibular conditions [62,63], tinnitus [64], multiple sclerosis [65], and balance control for fetal alcohol spectrum disorder (FASD) [66]. Of 3 studies, 2 reported using IVR to optimize patient execution of exercises to reduce vestibular conditions [62,63], including vestibular hypofunction and benign paroxysmal positional vertigo. IVR was also used to assist with specialist clinician-guided tinnitus treatment, in place of cognitive behavioral therapy [64]. Multiple sclerosis patients walked on a treadmill with sensors at their feet and used IVR to improve their gait while avoiding or stepping over virtual obstacles [65]. Children with FASD used IVR to enhance task-specific balance practice exercises, improving their overall balance control [66].

Table 5. Included studies: other applications.

Author, year (country)	Immersive virtual reality system	Article type	Condition and treatment purpose	Number of participants	Reported participant age (years)
Malinvaud et al, 2016 (France) [64]	Not reported	Efficacy	Reduced tinnitus symptoms	148	52.5 (13)[a]
Micarelli et al, 2017 (Italy) [62]	Revelation[b]	Efficacy	Vestibulo-ocular reflex gain in vestibular hypofunction	51	50.5 (9)[a]
Peruzzi et al, 2016 (Italy) [65]	eMagin Z800	Feasibility	Gait improvement in multiple sclerosis patients	8	34-60
Tabanfar et al, 2018 (Canada) [63]	HooToo[b]	Efficacy	Epley treatment for paroxysmal positional vertigo	20	26.4 (7)[a]
McCoy et al, 2015 (USA) [66]	Custom	Feasibility	Sensorimotor balance control training for children with FASD[c]	11	11.4 (2)[a]

[a]Mean (SD).

[b]These systems are low-cost phone-based head-mounted displays that are not widely commercially available.

[c]Fetal alcohol spectrum disorder.

What Are the Technical Specifications of These Systems?

Systems from 58 articles were categorized into 3 groups: commercially available integrated systems, commercially available systems that use a smartphone as a display device, and custom-designed systems that are not commercially available. Of 58 articles, 5 did not provide adequate information to identify the IVR system used, however, did provide adequate photos and use language to convince the authors that IVR was used in the study [15,29,50,60,64].

Where a system is reported to have 0 DOF of head tracking, the referenced studies incorporated an additional head tracking system to make the VR system immersive.

Some studies reported the use of IVR software that may support a variety of hardware devices. These studies were included when the authors were convinced that the reported software version supported IVR hardware as a display option. The software systems reported included NeuroVR version 2.0 (Milan, Italy) [61], WorldViz Vizard version 3.0 [45], and AppliedVR RelieVR [33]. In addition, one study reported the use of a modified HMD that included an eye tracking device [23]. Detailed technical specifications are listed in Tables 6-9.

Table 6. Commercially available, integrated immersive virtual reality systems.

Manufacturer	System	Head tracking DOF[a]	Display resolution	Horizontal FOV[b] (degree)	Number of studies	References
HTC	Vive	6	2160×1200	110	5	Liu et al (2018) [17], Shahab et al (2017) [18], Nielsen et al (2017) [36], Freeman et al (2016) [49], and 2018 [46]
Oculus	Rift Commercial Version 1	6	2160×1200	110	3	Hoffman et al (2014) [1], Fitzgerald et al (2018) [16], Hussain et al (2018) [51]
Oculus	Rift Development Kit 2	6	1920×1080	100	10	Amin et al (2017) [5], White et al (2016) [22], Gerber et al (2017) [23], Amaral et al (2017),[14] Ambron et al (2018) [27], Garrett et al (2017) [32], Henriksen et al (2017) [34], Osumi et al (2017) [37], Dietrichkeit et al (2018) [56], Keizer et al (2016) [59]
Oculus	Rift Development Kit 1	3	1280×800	110	1	Bahat et al (2018) [39]
Kaiser Optics	SR80a	0	1280×1024	80	1	Jeffs et al (2014) [35]
Cybermind	HiRes900	0	800×600	approximately 50	1	Faber et al (2013) [30]
eMagin	Z800	3	1600×600	approximately 43	7	Bouchard et al (2017) [2], Shiban et al (2015) [3], and (2016) [21], Gamito et al (2017) [47], Maples-Keller et al (2017) [48], Reger et al (2016) [54], Peruzzi et al 2016 [65]
Virtual Realities	VR1280	0	1280×1024	60	1	Atherton et al (2016) [55]
Virtual Realities	HMD42	3	800×600	42	1	Malbos et al (2013) [44]
nVisor	SX111	0	1280×1024	102	1	Atherton et al (2016) [55]
Vuzix	Wrap 1200VR	3	1280×720	35	1	Bahat et al (2015) [38]
Vuzix	iWear VR920	3	1280×480	32	1	Tanja-Dijkstra et al (2014) [41]

[a]DOF: degrees of freedom.

[b]FOV: field of view.

Table 7. Commercially available, smartphone-based immersive virtual reality systems.

Manufacturer	System	Mobile device	Head tracking DOF[a]	Display resolution	Number of studies	References
Samsung	Gear VR	Samsung Note 4	3	2560×1440	2	Scapin et al (2016) [24], Mosadeghi et al (2016) [40]
Samsung	Gear VR	Samsung Galaxy S7	3	2560×1440	1	Tashjian et al (2017) [26]
Samsung	Gear VR	Samsung Galaxy S6	3	2560×1440	3	Birnie et al (2018) [28], Gold et al (2018) [33], Hong (2017) [43]
Google	MergeVR	Google Pixel (version not reported)	3	__[b]	1	Gold et al (2018) [33]
Google	Cardboard	Samsung Galaxy Note 4	3	2560×1440	1	Amin et al (2017) [5]
Google	Cardboard	Apple iPod Touch (fifth Generation)	3	1136×640	1	Ford et al (2018) [31]
Google	Cardboard	Not reported	3	__ [b]	2	Gelsomini et al (2016a) [19] and (2016b) [20]
Not stated	Sunnypeak	Apple iPod (version unstated)	3	__ [b]	1	Ford et al (2018) [31]
Not stated	HooToo	Apple iPhone 6	3	1334×750	1	Tabanfar et al (2018) [63]
Not stated	Revelation	Nokia Lumia 930	3	1920×1080	1	Micarelli et al (2017) [62]

[a]DOF: degrees of freedom.

[b]Unknown as mobile device was not reported.

Table 8. Custom immersive virtual reality systems.

System	Head tracking DOF[a]	Display resolution	Horizontal FOV[b] (degree)	Number of studies	References
Memphis	Not reported	Not reported	Not reported	1	Hartanto et al (2015) [42]
STABEL[c]	Not reported	Not reported	Not reported	1	McCoy et al (2015) [66]
VRGET[d]	Not reported	Not reported	Not reported	2	McLay et al (2014) [52] and (2017) [53]

[a]DOF: degrees of freedom.

[b]FOV: field of view.

[c]STABEL: Sensorimotor Training to Affect Balance, Engagement and Learning.

[d]VRGET: Virtual Reality Graded Exposure Therapy.

Table 9. Immersive virtual reality software frameworks.

Manufacturer	System	Number of studies	References
Neuro-VR	Neuro-VR 2.0	3	Cardenas-Lopez et al (2014) [57] and (2015) [58], La Paglia (2016) [61]
WorldViz	Vizard 3.0	1	Meyerbroeker et al (2013) [45]
AppliedVR	RelieVR	1	Gold et al (2018) [33]

Discussion

Principal Findings

This review identified 58 studies from 19 countries that used IVR for acute treatment of conditions. The included studies featured participants ranging in age from 5 to 74 years, with one acceptability study reporting a significant age difference between participants willing to use IVR (younger participants) and those unwilling to use IVR (older participants) [24]. The conditions treated in the included studies were broadly in 5 categories: neurological and neurodevelopment, pain, phobias, psychological applications, and miscellaneous. All the studies used IVR to immerse patients into a virtual environment, but the purposes were different; examples including experience of an environment, exposure therapy, and assistance with accuracy of movement or distraction. The IVR applications presented in the reviewed articles were at different stages of maturity. Approximately half of the reviewed articles tested the feasibility of treatment with IVR, whereas others that were slightly more mature tested the efficacy of IVR compared with conventional treatment methods. This suggests that although nonimmersive VR has a long history of use in health treatment [67], IVR as a tool in treatment and management of health conditions is still a developing area.

A benefit of IVR systems is that the simulated environment can be easily tailored to the individual patient, such as the clinician controlling a virtual embodiment of an avatar that is relevant to the patient's condition, or designing a specific, patient-relevant environment [46,51]; however, such applications require careful system design that takes the clinician's technical abilities into account. Future generations of commercially available IVR systems will likely have an increasing focus on social and multiuser interactions, further enabling interactive treatment methodologies that are already being employed [14,15,44,45].

Future Directions and Implications for Practice

The data indicate that IVR systems are sometimes extended with other sensors and input modalities such as integrating eye tracking [23] or brain-computer interfaces [14]. Although useful in some health settings, such extensions of IVR may not become commonplace in commercial systems designed for general consumers. However, the budding applications of IVR in health care may inform the future development of commercial IVR technology, including considerations such as water resistance for use in water-based therapy regimes or high-moisture environments [68,69]. Some studies also described the use of weight-assisting arms to support an HMD when the patient may not be able to support the weight of the device themselves [1].

It appears that IVR has a promising future in health care, in research and commercial realms. As many of the studies examined are exploratory, the feasibility of IVR for acute treatment of conditions and the evidence for the effectiveness of IVR is still developing. The studies that did examine efficacy demonstrated preliminary evidence that IVR is either as effective as or more effective than their selected conventional therapy. A majority of the studies had low participant numbers and did not extend their analysis to undertake statistical significance testing of a hypothesis. Future research into the effectiveness of IVR could incorporate more rigorous statistical methods to examine effectiveness.

In the studies, it was reviewed here that commercially available IVR systems are not commonly being used for in-home or self-treatment regimes. This highlights a potential application area that could be investigated in the future: the use of IVR in a telehealth or remote health setting.

The early state of IVR technology adoption highlights another area for future work: the development of policy and procedural guidelines for patient safety and security when interacting with IVR technology. For example, such procedures may consider the need for antibacterial design or treatment of face-touching components for sharing of IVR HMDs and calibration of IVR

technology to the individual patient's sensory ability to prevent or reduce simulation sickness. Policies should also consider and address patient data protection issues, and provide adequate guidance on privacy, specifically for biometric or similar data collected when interacting with IVR systems.

Implications for Research

From a research quality perspective, this review highlighted that many studies did not provide adequate detailed technical information about the IVR system being used—this aligns with findings of poor reporting quality from previous reviews [6]. Details such as specific software and hardware versions were not routinely reported in adequate detail for technical systems to be reproducible. Especially in the case of custom IVR systems, it is important for such details to be reported thoroughly to aid research quality, peer-review, evaluation, and reproducibility. This is an area where future studies could improve their reporting. For example, including a photo or diagram of a patient interacting with the IVR system provides a rich source of information for the reader, while adding minimal text to a research manuscript.

Limitations

Owing to the volume of studies, this review had to be limited to acute treatment applications of IVR. IVR has also appeared in health literature as a training tool for health professionals, especially for surgical applications and in rehabilitation to increase compliance with exercise regimes and improve the accuracy of rehabilitation task completion. Any of the several existing reviews can be referred to for more information about the use of IVR in these areas.

Conclusions

Some studies indicate that simulation sickness is still a limiting factor for application of IVR systems in health care [26,70,71]. This is an ongoing area of research in the broader IVR community [71], and future improvements to IVR system design will likely increase the compatibility of IVR technology with the general populace. In the interim, this finding highlights the need for best practice guidelines for IVR system deployment and development. Furthermore, IVR systems are not suitable for all populations—a consideration that is important for health applications. However, IVR technology can be adapted to suit the needs of specific populations such as blind or low-vision patients [72,73]. The emergence of a technical contracting business that specializes in IVR for health applications is a promising step in this direction. To this end, there is a need for close integration of technical and clinical team members to maximize the efficacy of any new or proposed system.

Conflicts of Interest

None declared.

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Abbreviations

DOF: degrees of freedom
FASD: Fetal Alcohol Spectrum Disorder
HMD: head-mounted display
IVR: immersive virtual reality
PTSD: posttraumatic stress disorder
SAD: social anxiety disorder
VR: virtual reality

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Original Paper

Automatic Near Real-Time Outlier Detection and Correction in Cardiac Interbeat Interval Series for Heart Rate Variability Analysis: Singular Spectrum Analysis-Based Approach

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Abstract

Background: Heart rate variability (HRV) is derived from the series of R-R intervals extracted from an electrocardiographic (ECG) measurement. Ideally all components of the R-R series are the result of sinoatrial node depolarization. However, the actual R-R series are contaminated by outliers due to heart rhythm disturbances such as ectopic beats, which ought to be detected and corrected appropriately before HRV analysis.

Objective: We have introduced a novel, lightweight, and near real-time method to detect and correct anomalies in the R-R series based on the singular spectrum analysis (SSA). This study aimed to assess the performance of the proposed method in terms of (1) detection performance (sensitivity, specificity, and accuracy); (2) root mean square error (RMSE) between the actual N-N series and the approximated outlier-cleaned R-R series; and (3) how it benchmarks against a competitor in terms of the relative RMSE.

Methods: A lightweight SSA-based change-point detection procedure, improved through the use of a cumulative sum control chart with adaptive thresholds to reduce detection delays, monitored the series of R-R intervals in real time. Upon detection of an anomaly, the corrupted segment was substituted with the respective outlier-cleaned approximation obtained using recurrent SSA forecasting. Next, N-N intervals from a 5-minute ECG segment were extracted from each of the 18 records in the MIT-BIH Normal Sinus Rhythm Database. Then, for each such series, a number (randomly drawn integer between 1 and 6) of simulated ectopic beats were inserted at random positions within the series and results were averaged over 1000 Monte Carlo runs. Accordingly, 18,000 R-R records corresponding to 5-minute ECG segments were used to assess the detection performance whereas another 180,000 (10,000 for each record) were used to assess the error introduced in the correction step. Overall 198,000 R-R series were used in this study.

Results: The proposed SSA-based algorithm reliably detected outliers in the R-R series and achieved an overall sensitivity of 96.6%, specificity of 98.4% and accuracy of 98.4%. Furthermore, it compared favorably in terms of discrepancies of the cleaned R-R series compared with the actual N-N series, outperforming an established correction method on average by almost 30%.

Conclusions: The proposed algorithm, which leverages the power and versatility of the SSA to both automatically detect and correct artifacts in the R-R series, provides an effective and efficient complementary method and a potential alternative to the current manual-editing gold standard. Other important characteristics of the proposed method include the ability to operate in near real-time, the almost entirely model-free nature of the framework which does not require historical training data, and its overall low computational complexity.

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KEYWORDS

change-point detection; cumulative sum; forecasting; heart rate variability; R-R series; singular spectrum analysis; ventricular premature complexes

Introduction

Background on Heart Rate Variability

Oscillations in the time interval between successive heart beats, referred to as heart rate variability (HRV), have long been known to allow for insight into the intricate control mechanisms of the autonomic nervous system (ANS) [1-4]. Accordingly, research into HRV has attracted considerable attention over the past 4 decades, as evidenced by an exponential growth of published work [5,6].

In a nutshell, heart rhythm and rate can be said to be governed by the 2 competing divisions of the ANS, that is, the sympathetic nervous system and the parasympathetic nervous system. An increased sympathetic input to the sinoatrial (SA) node yields an increase in heart rate (HR) mediated by the release of adrenaline and noradrenaline and the subsequent activation of β-1-adrenoceptors, resulting in an accelerated diastolic depolarization. On the other hand, an increase in the parasympathetic outflow decreases the HR through the release of acetylcholine by the vagus nerve, which binds to and activates M2 muscarinic acetylcholine receptors in the SA node and eventually slows down the diastolic depolarization rate [4,7-9].

Various HRV measures have been established and are usually categorized as either time domain, frequency domain, or nonlinear analysis techniques [2,4]. To a large extent, the popularity of HRV is because of its easy acquisition and seemingly straightforward interpretation.

The Necessity of Preprocessing the R-R Series

It is crucial to realize that by virtue of its very definition, the HRV encompasses only oscillatory phenomena between heart beats resulting from the SA node depolarization [4,10]. While, ideally, all components of an R-R series originate from the SA node, the actual R-R series in both healthy and diseased subjects are contaminated by outliers due to artifacts and heart rhythm disturbances such as ectopic beats (ie, heart beats whose origin is outside of the SA node). Thus arises the necessity to ensure that the HRV analysis is performed on a series representing only the actual normal sinus rhythm (NSR) interbeat intervals, commonly referred to as N-N series (as in normal-to-normal).

The detrimental impact of ectopics on HRV measures is pronounced and well-documented [6,11-17]. In a recent study Stapelberg et al [18] examined the sensitivity of 38 time domain, frequency domain and nonlinear HRV measures to the addition of artifacts in real and artificial 24-hour recordings. In accordance with previous findings, they concluded short-term time domain HRV measures to be more sensitive to the presence of artifacts than their long-term counterparts. Furthermore, frequency domain measures were found to generally be more sensitive than time domain measures, whereas the less commonly used nonlinear measures were shown to exhibit some inherent robustness properties.

Ectopic heart beats are ubiquitous phenomena and not limited to patients with cardiac disorders and diseases. Hingorani et al [19] retrospectively examined the prevalence of cardiac arrhythmias by scrutinizing 24-hour Holter recordings of 1273 healthy volunteers from 22 phase I clinical trials; note that this specific population is not a representative sample of the overall population. The sample was heavily biased in that, consistent with the requirements of phase I clinical trials, subjects were extensively screened by history, physical examination, and laboratory tests and were therefore significantly healthier than the overall population. Crucially, all subjects underwent 12-lead pretrial electrocardiography (ECG) and were excluded if they had any cardiac conduction disorder or disease, including a personal or familiar history thereof. Those exhibiting ≥2 consecutive ectopics as well as bigeminy, trigeminy and quadrigeminy in their 12-lead ECG examination were also excluded. Despite these rigorous exclusion criteria, Hingorani et al [19], among other findings, found premature atrial complexes in 60.8% of the examined Holter records, followed by premature ventricular complexes (PVCs), which were observed in 43.4% of healthy volunteers. While multifocal PVCs occurred in 5.3%, 3.3% exhibited >200 PVCs per 24-hour ECG recordings. A relatively high prevalence of occasional ectopic beats has been reported by numerous other authors as well both in healthy and diseased subjects [20-23].

In summary, the detection and correction of ectopic beats in tachograms are not merely imperative for formal consistency with the HRV definition but arises from the impact of ectopics on HRV measures and the general prevalence of ectopics.

Prior Work and State-of-the-Art

Compared with the overall research interest directed toward HRV applications, the crucial issue of the discrepancy between most real-world R-R series and their respective N-N series has arguably not received as much attention. The actual gold standard of manual R-R series editing, advocated for in the field's relevant guideline by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology Task Force [4], remains unaltered to this day [11,24].

It should be noted that, aiding and abetting the aforementioned exponential growth of the HRV-related (applied) research, a number of well-designed and widely used software packages for the HRV analysis have been developed and made available to the general public; these include, but are not limited to, Kubios [25,26], Nevrokard's aHRV [27], and others [28-30]. More often than not, these commercial software packages tend to be closed source and therefore provide only a limited benefit to algorithm developers. On the other hand, it ought to be acknowledged that they are well suited for the needs of practitioners, as they combine advanced preprocessing and analysis features, intuitive graphical interfaces, and support for various file formats.

In automated approaches the task of the detection and correction of outliers is usually tackled as a two-step process.

First, outliers in the R-R tachogram are detected, usually by straightforward thresholding based on a fixed percentage difference to previous intervals or their SD [31], although some more sophisticated methods have also been proposed [12].

Second, the detected (regions of) artifacts from step 1 are either discarded (thereby reducing the effective length of the tachogram), substituted by preceding uncorrupted intervals or by intervals obtained through interpolation, with linear and cubic spline interpolation being the most popular techniques [11].

Objective of This Work

The objective of this study was to introduce a general framework of low computational complexity that allows for an automatic near real-time detection and correction of outliers in the R-R series based on the singular spectrum analysis (SSA). The main novel contributions of this work include (1) the application of a recently proposed model-free lightweight SSA change-point detection (l-SSA-CPD) algorithm [32]; (2) a modification of l-SSA-CPD through the use of an adaptive control limit sequential ranks (AC-SRC) control chart [33] to drastically reduce detection delays; and (3) upon detection of an anomaly, the substitution of the corrupted tachogram segment by an approximation obtained through recurrent SSA forecasting based on a small outlier-free tachogram segment.

An extensive simulation study comprising 198,000 5-minute long R-R series, obtained by randomly inserting varying amounts of simulated ectopic beats in records taken from the MIT-BIH Normal Sinus Rhythm Database (NSRDB), is conducted to assess the artifact detection and correction performance of the proposed algorithm.

Fundamentals of Basic Univariate Singular Spectrum Analysis and Singular Spectrum Analysis Based Change-Point Detection

Recently, this author proposed a low-complexity model-free approach based on SSA and nonparametric cumulative sum (CUSUM) control charts for real-time cardiac anomaly detection, referred to as l-SSA-CPD [32]. It was shown that l-SSA-CPD reliably detects anomalies even when directly applied to unprocessed (ie, no preprocessing was performed) raw ECG and photoplethysmographic records from common databases publicly available through Physiobank [34].

In this study, modifications to the original l-SSA-CPD algorithm will be introduced, and its capabilities will be expanded by adding a recurrent forecasting feature to generate appropriate substitutes of the corrupted tachogram entries. First, however, a brief restatement of SSA and l-SSA-CPD [32] is required.

Basic Singular Spectrum Analysis Algorithm

SSA is a powerful technique of time series analysis owing much of its appeal to an inherent model-free concept combining elements of conventional time series analysis, multivariate geometry and statistics, and signal processing [35]. The univariate basic SSA can be considered as the application of the principal component analysis to the Hankel matrix (obtained through an embedding of the original univariate time series) with the subsequent attempt to reconstruct the original series.

Consider N observations $= (x_1,..., x_N)$ of a univariate time series and a lag-integer or embedding dimension M ($1 < M << N$) also commonly referred to as the window length. The basic SSA algorithm then encompasses the following 4 steps:

1. Embedding $= (x_1, ..., x_N \rightarrow \mathbf{X} \in {}^{M \times K})$

A trajectory matrix $\mathbf{X}$ is constructed by mapping into a sequence of $K = N - M + 1$ lagged column vectors $X_j = (x_j, ..., x_{j+M-1})^T$, $j = 1, ..., K$ of size M, yielding

$\mathbf{X}$ is called a Hankel matrix because of its characteristic of having equal elements on the antidiagonals. One can think of $\mathbf{X}$ as multivariate data with M characteristics and K observations and accordingly X_j of $\mathbf{X}$ as column vectors in the M-dimensional space ^{M}.

2. Singular Value Decomposition of $\mathbf{X}$

Taking the singular value decomposition (SVD) of $\mathbf{X}$ decomposes the trajectory matrix into its orthogonal bases and yields a set of M eigenvalues and eigenvectors. Let the eigenvalues of $\mathbf{X}\mathbf{X}^T$ be $\lambda_1 \geq \cdots \geq \lambda_M \geq 0$ and $U_1,..., U_M$ be the respective eigenvectors. Then, with $d = \max(i,$ such that $\lambda_i > 0)$ denoting the rank of $\mathbf{X}$, the SVD of $\mathbf{X}$ can be expressed as the sum of d elementary matrices

with rank 1 matrices and being the eigenvectors of $\mathbf{X}^T\mathbf{X}$. Accordingly, the decomposition in Equation (2) is completely characterized by the set of so-called "eigentriples" .

Note that owing to the symmetry of left and right singular vectors, the SVDs of $\mathbf{X}$ with lag M and $K = N - M + 1$ are equivalent, entailing the lack of any additional benefit from the use of larger embedding dimensions $M > N / 2$ [32,35-39].

3. Eigentriple Grouping

Consider the task of extracting a particular component or signal of interest from observed data contaminated by various artifacts such as noise. To do so, during the third stage of the basic SSA, disjoint subsets of indices $\{1, ..., d\}$ are determined such that the respective systems of eigenvectors span the subspaces associated with those signal components.

In the example of aiming at the separation of a signal from unwanted noise and other disturbances, this entails determining an appropriate subset of indices $I = \{i_1, ..., i_l\}$, $l < d \leq M$ that span an l-dimensional subspace in ^{M}, denoted as ${}_I \subset {}^{M} = span\{U_I\} = span\{U_{i_1}, ..., U_{i_l}\}$, representing the signal whereas the

remaining eigentriples with $\bar{I} = \{i_1, ..., i_d\}$ / I are said to span the noise subspace $_{\bar{I}} \subset {}^{M} = span\ \{U_{\bar{I}}\}$.

The trajectory matrix component X_I corresponding to the subset I of eigentriples associated with the signal of interest is then

and the component $X_{\bar{I}}$ corresponding to the subset $\bar{I} = \{i_1,..., i_d\}$ I associated with the remainder of the observed signal is

such that the overall SVD of X can be rewritten as

In the case of separability (see, eg, [36] at 17), the contribution of X_I to the entire observed signal X is represented by the respective share of eigenvalues  .

4. Diagonal Averaging

For perfectly separable signal components, all matrices in the expansion of Equation (5) are Hankel matrices, which require that they all have equal entries on their antidiagonals. In real-world problems, however, perfect separability is rarely achievable. While an approximate separability usually suffices, the final fourth step in the SSA algorithm is required, as the matrices X_i from step 3 would have unequal entries on their antidiagonals. Thus, the Hankelization of all X_i is performed, that is, the compliance with the Hankel structure is enforced by taking the average of each antidiagonal and then replacing each element of that antidiagonal with the determined average. This yields

with  being the diagonally averaged matrices.

One can then, for example, easily reconstruct the approximation of the signal of interest through the eigentriples with indices I through the one-to-one correspondence between  and the respective time series  which provides an approximation of either the entire time series  or some components of it, depending on the particular choice of indices I.

Singular Spectrum Analysis Based Change-Point Detection Rationale

The sequential application of SSA for change detection is based on Moskvina and Zhigljavsky [40] (see [39] for an exhaustive discussion; see also [35] for an earlier account of the basic idea). The rationale is to slide 2 (possibly intersecting) moving windows over the time series and to apply the first 3 stages of the basic SSA each time. Think of the first window as adaptively generating a low-dimensional base subspace representation (capturing the main structure in the series) and the second window, which contains at least M new data samples, as generating a test subspace. As both windows are slid over the series, some sort of distance between the base and the test subspace is monitored. If no change-point occurs, the distance remains small, whereas it spikes in the presence of a sudden significant change in the main structure of the series.

The algorithm by Moskvina and Zhigljavsky has been successfully applied to various change detection problems and some improved variations of it have been presented as well (see [32] for a detailed background). Computational complexity, however, ought to be acknowledged as a potentially significant limitation of the said algorithm. Recently, l-SSA-CPD [32] has been proposed as a lightweight alternative. Contrary to the algorithm by Moskvina and Zhigljavsky, which recalculates the SVD of 2 sliding windows each time new observations become available, l-SSA-CPD relies on a nominal low-dimensional signal subspace representation computed only once at startup. As new observations become available, l-SSA-CPD simply allocates them into a vector and calculates a test statistic based on the squared Euclidean distance and the angle between this new data vector and the previously determined nominal reference subspace.

Singular Spectrum Analysis Parameter Selection

The behavior of SSA is largely determined by 2 tuning parameters, namely the window length M and the number l of eigenvalues to be used in the embedding and grouping steps, respectively. While it is undisputed that the successful application of SSA hinges on an appropriate choice of M and l, practitioners are faced with the nuisance that no clear-cut rules as to how they ought to be determined exist.

For a series of length N and window length (or embedding dimension) $1 < M < N$, as previously discussed, there is no additional benefit from using $M > N / 2$ (see, eg, [35] at 69 and[36] at 47). It is widely acknowledged that as the appropriate window length M depends on both the underlying data and the particular application, no universal rule for determining it exists [35-39]. General recommendations vary between $M \approx N / 4$ [37] and $M \approx N / 2$ [35,36]. In the case of a periodic signal with period T, it is important for M to be, at least, equal to T for the SSA to capture the main structure of the series. Furthermore, M should be proportional to T [35,36,38]. Of note, small windows act like a smoothing filter of width $2M - 1$ [36].

Similarly, it is well known that selecting a proper l is also crucial, for issues are known to arise when eigentriple grouping comprises either an insufficient or an excessive number of eigenvalues. More specifically, if l is too small, the SSA is unable to capture the entire signal whereas if it is too large noise components are unwittingly captured. Since the contribution of a particular series component (associated with the corresponding eigentriple) to the entire series is proportional to the respective eigenvalue, it is common practice to select l by identifying the leading eigenvalues through visual inspection of the eigenvalue spectra or by setting a predefined eigenvalue share (see, eg, [35,36,38] for a more exhaustive discussion).

In addition to the above-referred monographs, interested readers are also referred to some fairly recent contributions by Hassani et al [41] and Khan and Poskitt [42,43], which approach the

issue through the concept of separability and information theory, respectively.

In the light of the pragmatic suboptimal approach pursued here, a detailed discussion of the SSA parameter selection is, however, beyond the scope of this study and therefore omitted.

Methods

The Proposed Outlier Detection and Correction Framework

The proposed framework consisted of 2 separate stages, namely the detection and the correction of outlier corrupted segments of the tachogram.

Outlier Detection Using Lightweight Singular Spectrum Analysis Change-Point Detection and Adaptive Control Limit Sequential Ranks Control Charts

Let M, N, l, p, q be fixed integers such that $l < M < N / 2$ and $0 \leq p < q$. Then l-SSA-CPD proceeds as follows:

1. Initialization at $n = 0$

Akin to MZ, the first 3 steps of the basic SSA are applied on the interval $[n + 1, n + N]$ to obtain a low-dimensional nominal subspace $_I = {}_I^{(n=0)}$ which captures the main structure of the series. This involves embedding as in Equation (1) to obtain a trajectory matrix, which, hereafter, we refer to as the base matrix $X_B = X_B^{(0)} = X_B^{(n=0)}$, taking the SVD of X_B and obtaining $_I$ through an appropriate choice of $I = \{i_1,...,i_l\}$, $l < d \leq M$ with $d = \max(i$, such that $\lambda_i > 0)$.

2. Then, for each $n = 0,1,...$ l-SSA-CPD proceeds as follows:

- Construction of a test matrix $X_T^{(n)}$ on the interval $[n + p + 1, n + q + M - 1]$ as

- Computation of the detection statistic $D_{n,I,p,q}$ as

with

and with the angle $\angle(X_T^{(n)}, {}_I)$ taking values in $[0, \pi / 2]$ and accordingly  . $X_j^{(n)} = [x_{n+j}, ..., x_{n+j+M-1}]^T$ are the column vectors of $X_T^{(n)}$ whereas $U_I = [U_{i_1}, ..., U_{i_l}]$ denotes the $M \times l$ matrix of eigenvectors spanning $_I$ and ^{o} denotes the Hadamard (or element-wise) product. Note that throughout this study, $p = N$, $q = N + 1$ is used, that is, the width $Q = q \times p$ of the test matrices $X_T^{(n)}$ used always equals 1. In other words, each test matrix is actually a single column vector containing M new observations. $Q = 1$ is primarily chosen to allow for an agile response time and to minimize the computational burden [32].

- Monitoring of $D_{n,I,p,q}$ using the AC-SRC Control Chart

To reduce detection delays, instead of the sequential ranks CUSUM (SRC) by McDonald [44], as used in the conventional l-SSA-CPD [32], a sequential ranks-based CUSUM with adaptive control limits referred to as AC-SRC [33] is used. AC-SRC is inspired by a distribution-free CUSUM proposed by Chatterjee and Qiu [45] where instead of a fixed threshold a sequence of control limits, determined by the bootstrap estimate of the conditional distribution of the CUSUM test statistic given the last time it was zero, is used. AC-SRC carries the approach of Chatterjee and Qiu over to McDonald's SRC; the main advantage of the SRC (which is that it does not require training data and control limits can thus easily be determined in advance, eg, through Monte Carlo simulations) is retained while detection delays are significantly reduced because of the use of an adaptive sequence of control limits. Furthermore, owing to a trade-off favoring the lower computational burden and simplicity over the optimal performance, AC-SRC lacks some of the refined fine-tuning routines used in the Chatterjee and Qiu method. The author refrains from a detailed discussion of AC-SRC and refers the interested reader to previous studies [33,45].

Let the sequential rank of $D_{n,I,p,q}$ be denoted as

The AC-SRC then starts with the same recursive equation as the SRC, ie,

with $C_0 = 0$ and k a reference constant. Let T_n denote the so-called "sprint length" expressing the time elapsed since C_n was last 0, ie,

Furthermore, let Y_j be a random variable with distribution

Chatterjee and Qiu showed that the conditional distributions of $C_n | T_n$ in Equation (11) are easier to handle than the unconditional distribution of C_n and under some regularity conditions (see [45] and references therein for details), depend only on j and the underlying process generating distribution, but not on n. Then, for any positive integer $j_{\max} \leq n$, the distribution of C_n can be approximated by means of the conditional distributions in Equation (11) as

with $Y^* \sim C_n | T_n > j_{\max}$ and I being the indicator function.

It can be shown that [44], given the observed process is in-control, the quantities $R_n / (n + 1)$ in Equation (10) are independent and discrete uniform on  . Herein lies the key advantage of AC-SRC, in that for some fixed j_{max} and k one can determine a sequence of control limits  from

with  representing a simulation of Equation (10) for up to some $N_{AC\text{-}SRC}$ wherein the quantities $R_n / (n + 1)$ are substituted by the set of random variables  as discrete uniform on  . The sequence of control limits  can then easily and without the need for training data samples be determined by means of Monte Carlo simulations as outlined elsewhere [33].

The AC-SRC signals a change to have occurred if

or if

To limit the computational burden, it is recommended to calculate control limits only up to a reasonably small j_{max} after which the control limit is kept fixed at $h_{AC\text{-}SRC_{j_{max}}}$. In addition, following recommendations by Chatterjee and Qiu, the reference constant k is set proportionate to the expected average sprint length $E\{T_n\}$. Throughout this work, k was empirically calibrated such that  , whereas the average run length (ARL) was set to a nominal ARL_0=500. A detailed discussion as to the empirical calibration of control charts would, however, be beyond the scope of this work [33]. Note that as k increases, accordingly j_{max} decreases $E\{T_n\}$, that is, the likelihood of C_n bouncing back to 0 increases [33,45]. For the particular use case examined here, the use of a small j_{max} to allow for agile change detection is recommended (see Tables 1-4 and the respective discussion in the next section).

Finally, as with the SRC in the conventional l-SSA-CPD algorithm, the control chart is reinitialized after a change has been detected (by setting C_n=0 and T_n=0) to allow for the detection of multiple and potentially nearby change-points [32].

Monitoring of the l-SSA-CPD test statistic $D_{n,I,p,q}$ with N=20, M=10 by means of AC-SRC with j_{max}=8, $E\{T_n\}$=6 is showcased on a 5-minute tachogram excerpt of record 16,273 MIT-BIH NSRDB artificially contaminated with 2 and 8 ectopics in Figures 1 and 2, respectively. Note the remarkably low detection delay due to the use of AC-SRC.

Outlier Correction Using Recurrent Singular Spectrum Analysis Forecasting

Once an outlier has been detected at say $n=\tau$, accounting for the inherent detection delay and accordingly an uncertainty as to the exact outlier location, the interval $[\tau - \Delta_1, \tau]$, is designated as corrupted tachogram segment. Note that Δ_1 depends on the (average) detection delay and should be chosen carefully. However, it need not be exact or otherwise optimal. Then, a second interval of length Δ_2 immediately preceding the corrupted one is used to obtain an anomaly-free forecast to substitute the corrupted segment with.

The rationale of the proposed framework is depicted in Figure 3, with green and yellow rectangles representing the designated uncorrupted and corrupted segments and the detected change highlighted in red.

As the proposed method operates sequentially as new observations arrive, an appropriate uncontaminated data segment (either uncorrupted to begin with or previously cleaned) to serve as a basis for forecasting is always available. While it may be beneficial to use large values for Δ_2 (assuming sufficient past observations were available), keeping Δ_1, Δ_2 as small as possible is recommended; as doing so allows for near real-time operation and significantly reduces the computational burden. For the purpose of this study, simplicity was prioritized over (more often than not unnecessary) optimality.

Table 1. Detection performance of adaptive control limit sequential ranks with j_{max}=6 and lightweight singular spectrum analysis change-point detection with *N*=20, *M*=10, *Q*=1, 75% of leading eigentriples.

Record	Sensitivity	Specificity	Accuracy
16,265	0.9712	0.9827	0.9825
16,272	0.9415	0.9802	0.9794
16,273	0.9905	0.9910	0.9909
16,420	0.9771	0.9778	0.9777
16,483	0.9953	0.9846	0.9846
16,539	0.9326	0.9878	0.9870
16,773	0.9692	0.9832	0.9829
16,786	0.9722	0.9758	0.9755
16,795	0.8800	0.9922	0.9905
17,052	0.9521	0.9830	0.9825
17,453	0.9768	0.9904	0.9902
18,177	0.9549	0.9757	0.9754
18,184	0.9719	0.9805	0.9803
19,088	0.9711	0.9917	0.9914
19,090	0.9900	0.9745	0.9745
19,093	0.9744	0.9837	0.9834
19,140	0.9689	0.9920	0.9917
19,830	0.9948	0.9909	0.9909

Table 2. Detection performance of adaptive control limit sequential ranks with j_{max}=8 and lightweight singular spectrum analysis change-point detection with *N*=20, *M*=10, *Q*=1, 75% of leading eigentriples.

Record	Sensitivity	Specificity	Accuracy
16,265	0.9335	0.9860	0.9854
16,272	0.8595	0.9850	0.9828
16,273	0.9199	0.9922	0.9913
16,420	0.9141	0.9810	0.9803
16,483	0.9569	0.9893	0.9888
16,539	0.7494	0.9889	0.9863
16,773	0.8781	0.9858	0.9844
16,786	0.9038	0.9779	0.9767
16,795	0.7210	0.9936	0.9897
17,052	0.8259	0.9851	0.9829
17,453	0.9013	0.9933	0.9921
18,177	0.8101	0.9785	0.9771
18,184	0.8508	0.9833	0.9819
19,088	0.8667	0.9924	0.9910
19,090	0.9403	0.9793	0.9789
19,093	0.8920	0.9869	0.9854
19,140	0.8796	0.9946	0.9933
19,830	0.9510	0.9945	0.9941

Table 3. Detection performance of adaptive control limit sequential ranks with j_{max}=12 and lightweight singular spectrum analysis change-point detection with *N*=20, *M*=10, *Q*=1, 75% of leading eigentriples.

Record	Sensitivity	Specificity	Accuracy
16,265	0.8816	0.9875	0.9864
16,272	0.8240	0.9871	0.9844
16,273	0.8710	0.9940	0.9925
16,420	0.8741	0.9850	0.9839
16,483	0.8990	0.9900	0.9889
16,539	0.7218	0.9908	0.9879
16,773	0.8202	0.9871	0.9850
16,786	0.8421	0.9814	0.9794
16,795	0.6619	0.9943	0.9898
17,052	0.7753	0.9893	0.9865
17,453	0.8450	0.9939	0.9921
18,177	0.7539	0.9824	0.9805
18,184	0.7952	0.9853	0.9832
19,088	0.8030	0.9930	0.9909
19,090	0.8869	0.9824	0.9814
19,093	0.8379	0.9892	0.9869
19,140	0.8004	0.9951	0.9931
19,830	0.9063	0.9948	0.9939

Table 4. Detection performance of adaptive control limit sequential ranks with j_{max}=16 and lightweight singular spectrum analysis change-point detection with *N*=20, *M*=10, *Q*=1, 75% of leading eigentriples.

Record	Sensitivity	Specificity	Accuracy
16,265	0.8623	0.9878	0.9866
16,272	0.7947	0.9885	0.9854
16,273	0.8774	0.9942	0.9929
16,420	0.8585	0.9851	0.9838
16,483	0.8950	0.9904	0.9893
16,539	0.7260	0.9920	0.9890
16,773	0.7951	0.9880	0.9857
16,786	0.8022	0.9814	0.9790
16,795	0.6913	0.9941	0.9900
17,052	0.7866	0.9905	0.9881
17,453	0.8176	0.9951	0.9932
18,177	0.7644	0.9841	0.9823
18,184	0.7846	0.9866	0.9847
19,088	0.8119	0.9936	0.9917
19,090	0.8733	0.9837	0.9827
19,093	0.8299	0.9898	0.9875
19,140	0.7949	0.9953	0.9934
19,830	0.8979	0.9952	0.9944

Figure 1. Adaptive control limits sequential ranks cumulative sum (AC-SRC) monitoring with j_{max}=8, $E\{T_n\}$=6, ARL_0=500 of $D_{n,I,p,q}$ with N=20, M=10, Q=1, 75% of leading eigentriples (top) for a 5-minute tachogram excerpt of record 16273 MIT-BIH Normal Sinus Rhythm Database (NSRDB) with 2 artificially inserted ectopics (bottom).

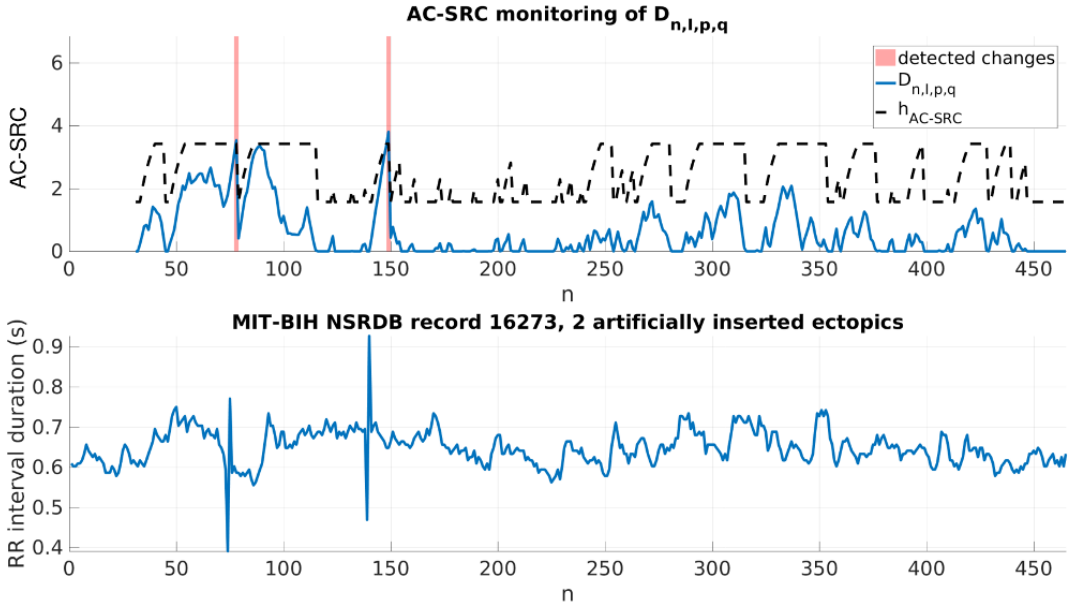


Figure 2. Adaptive control limits sequential ranks cumulative sum (AC-SRC) monitoring with j_{max}=8, $E\{T_n\}$=6, ARL_0=500 of $D_{n,I,p,q}$ with N=20, M=10, Q=1, 75% of leading eigentriples (top) for a 5-minute tachogram excerpt of record 16273 MIT-BIH Normal Sinus Rhythm Database (NSRDB) with 8 artificially inserted ectopics (bottom).

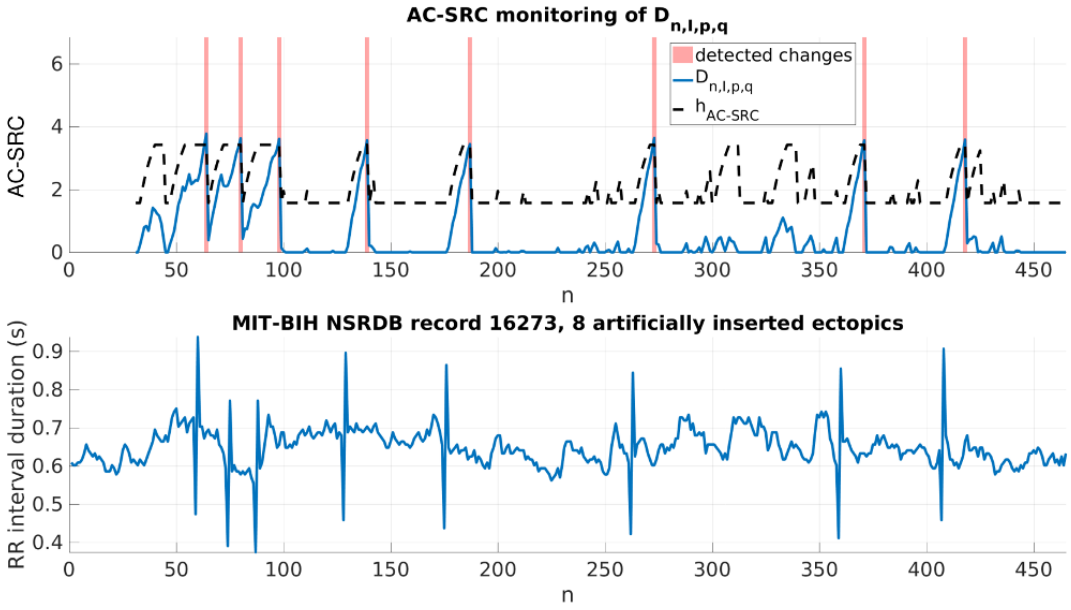
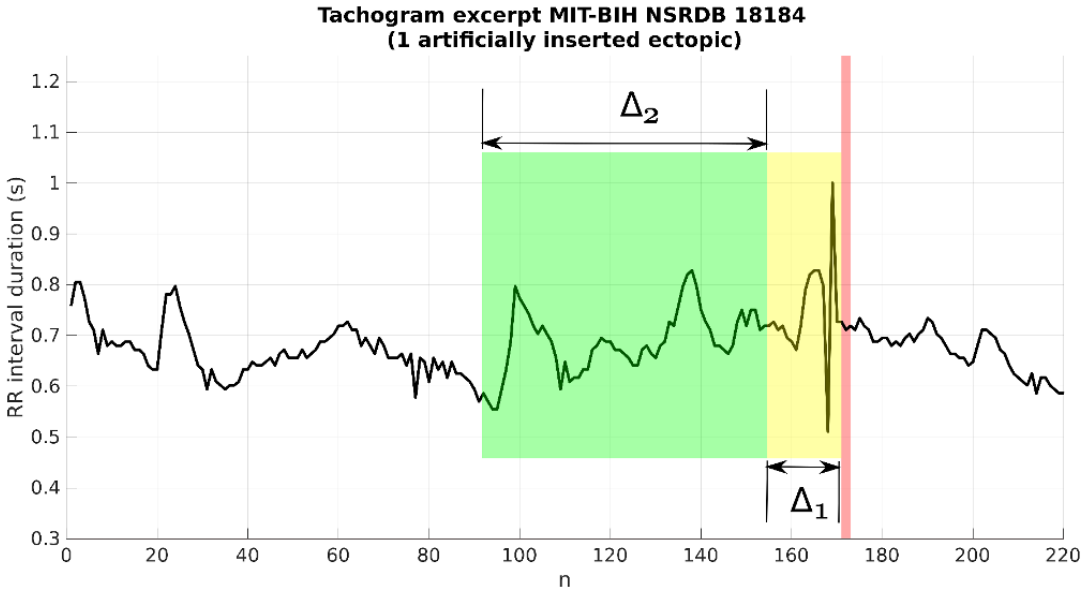


Figure 3. Schematic depiction of the proposed R-R series outlier detection and correction framework. Adaptive control limits sequential ranks cumulative sum with low detection delay is used to monitor lightweight singular spectrum analysis (SSA) change-point detection's test statistic; when it signals (red vertical bar), a segment of length Δ1 immediately preceding the detection is labeled as being corrupted (yellow rectangle) and a larger, yet still reasonably small segment of length Δ2 (green rectangle) is used to construct a trajectory matrix for the recurrent SSA forecasting which eventually yields a short-term SSA forecast of length Δ1 which the corrupted segment is then substituted with.



Time series forecasting plays a crucial role in many scientific fields and arguably also represents one of the most popular (real-world) application areas of the SSA. Note that there exist different approaches for SSA forecasting [46], most notably recurrent and vector forecasting. Refraining from any detailed discussion (see [35-38] for excellent monographs on the subject matter), the recurrent SSA forecasting approach used in this study will briefly be outlined. As with other more advanced capabilities that go beyond the realm of basic SSA, forecasting and missing value imputation (note that the 2 are closely related with the latter being the more general problem incorporating forecasting as a special case) in a way sacrifice some of the model-free beauty and appeal of SSA by invoking certain model assumptions. On the other hand, this appears to be outweighed by the successful application of SSA forecasting in numerous areas [47-52]. Furthermore, Golyandina and Zhigljavsky [36] point out that for short-term forecasts, there is actually only very little use of the imposed model, that is, the series approximately satisfy some linear recurrent formulas.

Consider again a univariate time series $= (x_1, ..., x_N)$ of length N, a fixed embedding dimension M ($1 < M << N$) and the respective trajectory matrix $\mathbf{X} = [\mathbf{X}_1, ..., \mathbf{X}_K]$ with $K = N - M + 1$ as in Equation (1). Let $_r \subset ^M$ be a linear space of dimension $r < M$ and $U_1, ..., U_r$ (ie, the eigenvectors obtained through the SVD of X) be an orthonormal basis in $_r$. Furthermore, let , that is, is the orthogonal projection of the column vector $\mathbf{X}_i$ of X onto $_r$, and its Hankelized counterpart be the trajectory matrix corresponding to the time series . In addition, given a vector $Y = (y_1, ..., y_M)^T \in ^M$, let $Y^\nabla \in ^{M-1}$ denote the vector consisting of the first $M - 1$ components of Y and similarly Y $\Delta \in ^{M-1}$ the vector consisting of the last $M - 1$ components of Y. Set $\nu^2 = \pi_1^2 + \cdots + \pi_r^2$ where $\pi_i|_i=1, ..., r$ denotes the last component of the eigenvector U_i. Assuming $_M = (0, 0, ..., 0, 1)^T \notin _r$ (ie, $_r$ not to be a vertical space), ν^2 represents the squared cosine of the angle between $_M$ and $_r$ and $\nu^2 < 1$ holds. The last component y_M of any vector $Y = (y_1, ..., y_M)^T \in _r$ can then be shown to be a linear combination of its first $M - 1$ components $y_1, ..., y_{M-1}$ (ie, of Y^∇)

with vector $A = (a_1, ..., \alpha_{M-1})^T$ being

Note that the representation in Equation (15) does not depend on the choice of the basis $U_1, ..., U_r$ in $_r$.

With the required notation now having been introduced, the time series can be defined as

with being the reconstructed series as in basic SSA and $y_{N+1}, ..., y_{N+N_F}$ the recurrent SSA forecast of length N_F.

Two examples of the automatic detection and correction of outliers using the method proposed in this study are shown in Figures 4 and 5 and compared with the benchmark approach of replacing the corrupted segment with an immediately preceding block of R-R data, referred to as block replacement [28]. Note how in both cases, while all outliers have been detected and corrected, there are ectopic-free segments of tachogram which have also been corrected because of false alarms.

Figure 4. Ectopic beats detected on a 5-minute tachogram excerpt of record 19093 MIT-BIH Normal Sinus Rhythm Database (NSRDB) with 6 artificially inserted ectopics using lightweight SSA change-point detection with N=20, M=10, Q=1, 75% of leading eigentriples and adaptive control limits sequential ranks cumulative sum with j_{max}=6, $E\{T_n\}$=4, ARL_0=500 are corrected by means of the proposed method with $\Delta_1=M$, $\Delta_2=N$ (top) or by replacing the corrupted segment of length Δ_1 with the immediately preceding block of equal length (bottom).

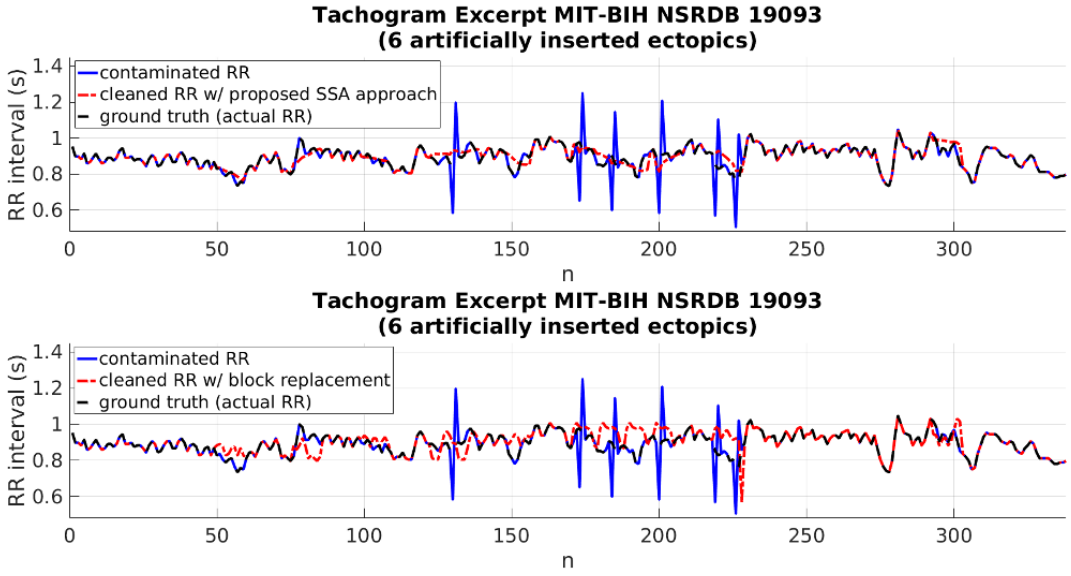
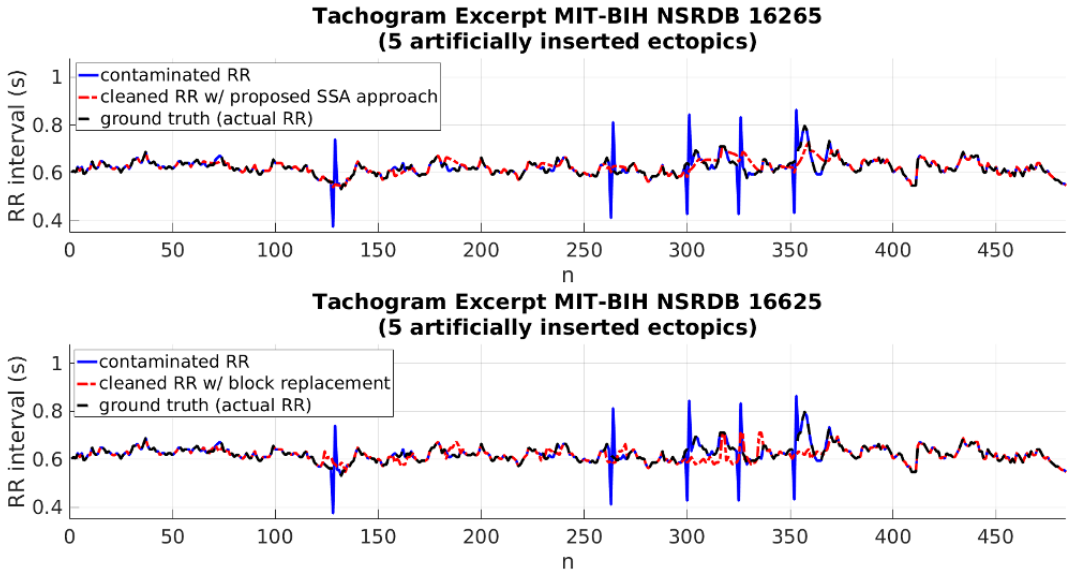


Figure 5. Ectopic beats detected on a 5-minute tachogram excerpt of record 16265 MIT-BIH Normal Sinus Rhythm Database (NSRDB) with 5 artificially inserted ectopics using lightweight SSA change-point detection with N=20, M=10, Q=1, 75% of leading eigentriples and adaptive control limits sequential ranks cumulative sum with jmax=6, E{Tn}=4, ARL0=500 are corrected by means of the proposed method with Δ1=M, Δ2=N (top) or by replacing the corrupted segment of length Δ1 with the immediately preceding block of equal length (bottom).



Performance Evaluation

The performance and utility of the proposed method are evaluated using records that are publicly available through Physiobank [34]. More specifically, excerpts of all 18 records in the MIT-BIH NSRDB are used. The European Society of Cardiology/North American Society of Pacing and Electrophysiology Task Force guideline [4] recommends to perform the HRV analysis on ECG recordings of at least 5 minutes, and the said length can be considered as the accepted standard for the short-term HRV analysis. Accordingly, for each of the 18 records in MIT-BIH NSRDB excerpts corresponding to the first 5-minute period of NSR are collected. Note that the records in MIT-BIH NSRDB are cardiologist-annotated, that is, they have manually been checked for errors in beat detection and labeling. Thus, one can circumvent the step of QRS complex-detection and use the R-R intervals as provided (and validated by experts) by Physiobank directly. For all 18 records the first 5 minutes were free of ectopic beats and therefore selected. However, it will be pointed out that 4 records contained a couple of extreme outliers (most likely measurement errors), which were removed manually.

Textbox 1. Artificial premature ventricular complex obtained by modifying two consecutive tachogram values.

1. RR(tau)=RR(tau)-RR(tau)/3;
2. RR(tau+1)=RR(tau+1)+RR(tau+1)/3;

Specifically, the 4 affected records were records number 16,272, 18,177, 19,088, and 19,140, for which 2, 1, 2, and 1 data points were removed, respectively. Besides being readily discernible because they deviate by some order of magnitude from surrounding interbeat intervals, these outliers are also marked as artifacts in the respective annotation files.

Next, the effect of a PVC on the R-R interval was simulated by decreasing the respective entry to 2/3 of its actual value and by increasing the following entry to 4/3 of its value (Textbox 1). That is, for a PVC at say $n = \tau$, one sets

which is consistent with the actual signature of a single PVC (see, eg, [53]) in an R-R series characterized by a premature beat (and accordingly a significantly smaller R-R interval) followed by a compensatory pause (longer R-R interval) followed by a return to baseline (NSR).

Extensive Monte Carlo simulations were then used to determine the performance characteristics of the proposed method, wherein a large number of artificial R-R series based on the 18 5-minute MIT-BIH NSRDB records were created by first randomly drawing an integer between 1 and 6 and then randomly selecting the position(s) within the series where the respective PVCs would be placed (with the constraint that PVCs be at least 5 samples apart).

Results

With the proposed method consisting of 2 stages (detection and correction), a separate analysis of each stage appears appropriate.

Detection Step

In reporting results pertaining to the detection performance of the first stage, established metrics commonly used in the literature are relied upon the sensitivity (*Se*), specificity (*Sp*), and accuracy (*Acc*), which are defined as

and

with TP, FP, TN, and FN representing the number of true positives, false positives, true negatives, and false negatives, respectively. Intuitively, sensitivity quantifies the ability to correctly detect (actual) anomalies, specificity quantifies the proportion of nonabnormal segments that are correctly identified as such, and accuracy combines both of the aforementioned aspects. More formally, *Se* expresses the empirical statistical power, $1 - Sp$ the type I (false positive), and $1 - Se$ the type II (missed detection/false negative) error rate.

As reported previously [32], for an event occurring at a time instance $n = \tau$, one allows for a certain detection delay Δ_d and considers a signal from the AC-SRC control chart as true positive if it falls in the interval $[\tau, \tau + \Delta_d]$. All results presented in this study were obtained using $\Delta_d = \Delta_1 = M$.

Note that the design and calibration of a detection algorithm involves an inherent trade-off between false alarms and missed detections and that furthermore reducing the false alarm rate usually entails an increase in the detection delay. For this specific use case, high sensitivity and short detection delays are arguably of the highest priority; for one wants a high likelihood of detecting all actual outliers (to reliably "clean" the R-R series, thereby transforming it into the respective N-N series) with a manageable (ie, small) detection delay to be able to narrow down the corrupted segments in the series as much as possible. The latter is particularly relevant because the proposed method substitutes the (allegedly) corrupted segment by an approximation of the outlier-free segment obtained using recurrent SSA forecasting; one aims to keep the forecasting horizon small to obtain acceptable results without having to tweak the SSA parameters extensively. This comes at the expense of higher false alarm rates, as is evidenced by the results presented in Tables 1-4.

As in the considered design, $j_{\max}$ is linked to the average sprint length $E\{T_n\}$, better agility is generally achieved with rather small $j_{\max}$ in a use case, as the one considered here, were AC-SRC monitors for large deviations [33,45].

While AC-SRC achieved satisfactory performance over a wide range of values $j_{\max}$ (results not reported here), upon examination of the results reported in Tables 1-4, which are based on 18,000 R-R series, $j_{\max}=6$ was chosen to proceed to the second stage of the proposed method (ie, the correction of corrupted segments of the R-R series).

Correction Step

As mentioned earlier this design choice entails higher false alarm rates, as discernible in the 2 examples shown in Figures 4 and 5, which both exhibit actually uncorrupted segments that have been "corrected" by the proposed algorithm because of false alarms, thereby introducing some distortions. More importantly though, both examples also clearly show that all artificially inserted outliers because of PVCs were detected and appropriately corrected.

Table 5. Average root mean square errors of artificially contaminated R-R series.

Record	$RMSE_{SSA}$[a,b]	$RMSE_{block}$	RRMSE[c]	Percent increase or decrease
16,265	0.0225	0.0251	0.8964	10.36
16,272	0.0239	0.0354	0.6751	32,49
16,273	0.0136	0.0221	0.6154	38.46
16,420	0.0246	0.0326	0.7546	24.54
16,483	0.0162	0.0196	0.8265	17.35
16,539	0.0282	0.0342	0.8246	17.54
16,773	0.0299	0.0509	0.5874	41.26
16,786	0.0249	0.0366	0.6803	31.97
16,795	0.0323	0.0450	0.7178	28.22
17,052	0.0213	0.0414	0.5145	48.55
17,453	0.0256	0.0344	0.7442	25.58
18,177	0.0296	0.0357	0.8291	17.09
18,184	0.0298	0.0450	0.6622	33.78
19,088	0.0151	0.0198	0.7626	23.74
19,090	0.0187	0.0245	0.7633	23.67
19,093	0.0350	0.0439	0.7973	20.27
19,140	0.0123	0.0156	0.7885	21.15
19,830	0.0110	0.0125	0.8800	12.00
Average	0.0230	0.0319	0.7210	27.9

[a]RMSE: root mean square error.

[b]SSA: singular spectrum analysis.

[c]RRMSE: relative root mean square error.

Results pertaining to the second stage of the proposed method are reported in Table 5, wherein the root mean square error (RMSE) is used to quantify the discrepancy between the outlier-cleaned series and the actual (uncontaminated) series. Let  be the uncontaminated N-N series (ie, the ground truth) and  denote our allegedly cleaned R-R series.

Calculation of the RMSE is straightforward,

Furthermore, to better compare the RMSE of the proposed method to its competitor (the commonly used block replacement method is used here for benchmarking purposes), consider also the relative RMSE (RRMSE) given by

Note that if the RRMSE, as given in Equation (18) is <1, it implies that the novel approach presented in this paper outperforms the competing benchmark approach by 100·(1 − RRMSE). It shall be emphasized, however, that the block replacement method as it its applied here (to correct for outliers in the R-R series) uses the first stage of the proposed method as well, its performance should thus be seen in the context of being applied to pretty tight segments of the series that ought to be substituted, which is all because of the AC-SRC l-SSA-CPD algorithm of the first stage of the framework presented in this study.

That being said, the results reported in Table 5, which are based on 180,000 R-R series, show that the proposed method, which substitutes corrupted tachogram segments by an approximation of the respective outlier-free segment obtained by

means of recurrent SSA forecasting, clearly outperforms the competing block replacement method. In fact, it outperforms its competitor for all 18 records (on which the extensive simulations built upon), on average by almost 30%.

Discussion

Background and Relevance

The HRV has long been known to allow for valuable insights into the intricate control mechanisms of the ANS and has a long track record of exponentially growing research interest and output. A crucial prerequisite for any HRV analysis is the exclusion of all artifacts and abnormalities, that is, a clean N-N series is required. Such a clean N-N series is virtually never available, mostly because of various interferences, beats not detected by the QRS complex-detector, and various highly prevalent heart rhythm disturbances.

Compared with the overall research effort directed toward the HRV, the issue of automatic R-R series (pre)processing has received rather little attention. In fact, manual editing still represents the gold standard. It should be noted that every automatic approach comes with risks and benefits; the former lie in the inherently nonzero type I and type II error rates, whereas the latter include, but are not limited to, considerable savings in both cost and time. Considering that error rates for manual approaches are nonzero as well and that they are most likely an increasing function of time (whereas in automatic approaches they are usually not), the choice of which one or which particular combination to use should always be made on an individual basis, considering all requirements and circumstances of the particular case. Accordingly, while the proposed method could be construed as a potential alternative to manual editing, in the light of the above considerations, this author would rather recommend it as a complementary method and or a preprocessing tool.

The main contribution of this work is the introduction of a general framework of low computational complexity that allows for an automatic near real-time detection and correction of outliers in R-R series based on the SSA. While related work pertaining to the use of the SSA in ECG and R-R data processing exists [54], to the best of the author's knowledge, this study is the first to propose a general SSA-based framework that handles both detection and correction of (unwanted) anomalies in the R-R series.

Principal Findings

An extensive simulation study comprising 198,000 5-minute R-R series, obtained by randomly inserting varying amounts of simulated ectopic beats in records taken from the MIT-BIH NSRDB was conducted to assess the artifact detection and correction performance of the proposed algorithm.

It was shown that the proposed algorithm reliably detects outliers in the R-R series and achieved an overall sensitivity of 96.6%, specificity of 98.4%, and accuracy of 98.4%. Furthermore, it compares favorably in terms of discrepancies of the cleaned R-R series compared with the actual N-N series, outperforming a block replacement approach on average by almost 30%. It should also be emphasized that a suboptimal pragmatic approach was pursued, deliberately refraining from an optimization of the various (SSA and AC-SRC) tuning parameters, which would most likely have resulted in further performance improvements at the expense of simplicity and computational complexity.

Other important characteristics of the proposed method include the ability to operate in near real-time, the almost entirely model-free nature of the framework, and the low computational complexity. Moreover, it should be pointed out that the proposed method is not limited to the R-R series but can be applied broadly, as all of its components are deliberately kept as general as possible. This entails the additional benefit of not being limited to the removal of PVCs (although only this has extensively been investigated and tested so far) but rather being able to deal with all kinds of anomalies that may contaminate the observed series of interest.

Limitations and Future Research

This work has several limitations, some of which open (new) avenues for future research.

A major limitation is because of the lack of established and generally recognized and validated procedures other than manual editing, which transforms the performance comparison among competing methods in a nontrivial task. Second, to increase the readability and decrease the length, the paper fails to provide general recommendations and guidelines as to how various tuning parameters should be chosen. Finally, the SSA represents a very active research field, as in the last couple of years, and several promising advances and new developments have been reported, but thus far have not been considered in the research reported in this work. This, however, does not infringe on the relevance of this work, as the objective was to introduce a simple, general framework of low computational complexity and to investigate the use of SSA in both the detection and correction step.

Several of the abovementioned recent developments, however, appear to open promising avenues for future research. In particular, the author intends to expand and improve the work presented here by focusing on the issue of the SSA parameter selection and by considering latest developments, especially pertaining to SSA forecasting. For the latter, the interested reader is referred to recent publications by Hassani and Kalantari [55-58].

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

AC-SRC: adaptive control limits sequential ranks cumulative sum
ANS: autonomic nervous system
ARL: average run length
CUSUM: cumulative sum
ECG: electrocardiography
HR: heart rate
HRV: heart rate variability
l-SSA-CPD: lightweight SSA change-point detection
NSR: normal sinus rhythm
NSRB: Normal Sinus Rhythm Database
PVC: premature ventricular complex
RMSE: root mean square error
RRMSE: relative root mean square error
SA: sinoatrial
SRC: sequential ranks cumulative sum
SSA: singular spectrum analysis
SVD: singular value decomposition

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Original Paper

Modular Catheter Systems in Minimally Invasive Interventional Medical Procedures: Case Study

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Abstract

Background: Medical device catheters that are used in minimally invasive interventional medical procedures all follow the same integrated design and use paradigm. The features and elements of any catheter device are combined in a single unitary construction. A modular approach to the design, construction, and use of these types of interventional catheters may provide significant advantages and benefits not available with an integrated design paradigm.

Objective: This paper aimed to present the design of a modular catheter system and the findings from an initial veterinary use as a case study for the potential of modular catheter systems in general.

Methods: A modular catheter system was designed using commercially available angioplasty balloon dilatation catheters as one module in the system and a custom designed scoring adapter as the other module. The scoring adapter incorporates wires to add scoring features to the angioplasty balloon catheter to improve the dilatation performance during a pulmonary valvuloplasty procedure. The scoring adapter also includes a novel attachment mechanism to couple the scoring adapter to any 0.035-inch guidewire–compatible angioplasty balloon catheter.

Results: The modular catheter system was successfully designed, manufactured, and used in an initial minimally invasive veterinary cardiovascular intervention to treat a case of canine subvalvular pulmonary stenosis. The scoring adapter and angioplasty balloon catheter were successfully combined *tableside* in the operating room at the time of the procedure and used to successfully dilate the subvalvular obstruction.

Conclusions: The successful design and use of the presented modular catheter system demonstrates the feasibility and potential advantages of this type of paradigm to enable physicians to create interventional catheter devices at the time of a procedure guided by the procedural needs.

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KEYWORDS

catheters; angioplasty; balloon valvuloplasty; medical device design; minimally invasive surgical procedures; endovascular procedures

Introduction

Interventional Catheters

Minimally invasive surgical procedures are a relatively new development in medicine. These procedures began with the development of cardiac catheterization, percutaneous angioplasty, and endoscopic procedures as an alternative to open surgery. During its short history, the use of medical device catheters in minimally invasive procedures has grown dramatically, expanding to include treatments for conditions throughout the body. Today, millions of these procedures are performed each year. Even though the number and type of catheters has grown to create new and improved diagnostic and therapeutic procedures, their basic construction paradigm has remained the same, exclusively that of an integrated design approach. With integrated catheter designs, each variant of a

catheter device type is a unique design and stock keeping unit (SKU).

Expanding the product family within an integrated design paradigm to include new configurations of an existing type or to add a new feature requires a unique design and SKU. Given the development and regulatory burden, as well as the carrying cost of inventory for both a manufacturer and hospital, expanding integrated catheter product families and creating new ones can be prohibitive. It is theorized that a modular approach to designing and using medical device catheters for certain interventions could improve access to appropriate devices and lower the overall cost.

The fundamental concept of a modular system is that complex products can be built from subsystems (modules) that are designed independently yet function together as a whole. Design changes made in one module do not affect other modules in the overall product. The interface shared among modules is standardized to allow for greater reusability among product types and adaptability of design [1]. The proposed modular catheter system enables physicians to combine 2 modules (a parent module with an adapter module), via a universal interface (attachment mechanism), to create interventional device catheters at the time of the procedure to meet specific procedural needs.

A modular catheter system of this nature represents a new way to approach the design and use of minimally invasive medical catheters for interventional procedures. A modular system would enable a physician to combine diagnostic, therapeutic, and structural elements to *build* a device catheter to meet a specific need. Examples include the relatively simple combination of a balloon dilatation catheter and scoring elements, as described in this case study. However, the idea could be extended to combine variants of other structural elements or incorporate more sophisticated elements such as advanced imaging sensors, drug delivery elements, ablation electrodes, pressure transducers, and many others. A new modular system paradigm can be used to develop new interventional techniques and therapies by giving physicians the tools to create devices tableside to meet evolving procedural needs.

Scoring and Cutting Balloon Dilatation

Scoring and cutting balloon catheters use scoring elements integrated with an angioplasty balloon to preferentially create dissections along the length of a lesion. There is evidence that adding the scoring element can improve the dilatation efficiency of the balloon, allowing effective dilatation to occur at lower balloon inflation pressures, or improve the dilatation result of resistant lesions [2-4].

A technique has been developed in veterinary medicine that utilizes commercially available cutting balloons to improve the dilatation of subvalvular aortic stenosis in dogs. The technique consists of scoring the fibrotic subvalvular tissue with a cutting balloon and then dilating the scored lesion with a larger, high-pressure balloon to complete the procedure. The idea is that the smaller cutting balloon will score the lesion to make the subsequent high-pressure ballooning more efficient. The scoring step of the procedure creates preferential dissections but does not completely dilate the stenosis. The second inflation with a larger-diameter balloon is intended to complete the dilatation for the final result [5].

This technique appears to be effective; however, the commercially available sizes of the cutting balloons are sometimes too small for these procedures or analogous pulmonary stenosis interventions. The lack of available balloon variants is an opportunity to demonstrate the above-mentioned modular catheter system to create scoring balloon variants using any size of commercially available angioplasty balloon catheters and a single scoring adapter module. The use of a scoring balloon modular system during a cardiovascular intervention of a canine subvalvular pulmonary stenosis has been described.

Goal of the Case Study

The aim of this case study was to demonstrate the potential of a new modular system paradigm in minimally invasive interventional catheters. This paper presents the design of a 2-module catheter system utilizing commercially available angioplasty balloons as one of the 2 modules. The paper further presents the results of using the system in treating a single case of canine subvalvular pulmonary stenosis. The initial use in a veterinary cardiovascular intervention is meant to demonstrate the feasibility of the proposed modular catheter system and not the efficacy of pulmonary valvuloplasty; therefore, only the acute results of the intervention are presented.

The study of medical devices and interventional techniques has long been done in animal models to approximate clinical conditions and demonstrate safety. There is also a historical precedent for treating veterinary patients, dogs, using new interventional surgical techniques before use in humans [6]. The case study presented here follows in that tradition.

Methods

Design Overview

To demonstrate the potential of such a system, a scoring adapter module (scoring adapter), which includes a universal interface (attachment mechanism), was designed to be combined with any commercially available over-the-wire percutaneous transluminal angioplasty (PTA) balloon dilatation catheter that has a maximum guidewire compatibility of 0.035 inches, considered the parent module. The scoring adapter includes nitinol wires, which when combined with the parent module balloon catheter creates a device that combines balloon dilatation with the wire scoring elements to improve dilatation performance, analogous to integrated scoring and cutting angioplasty balloon dilatation catheters.

Modular System Design Strategy

The use of existing stock catheter devices as the parent module was explored as an efficient means to test the concept of modular systems in catheter design and to streamline the development process.

It is recognized that many devices and catheters used in interventional procedures include a lumen for the purpose of employing a guidewire during the procedure. This catheter lumen, which has been designed to be compatible with a

standard guidewire size, can be leveraged to develop a standard interface for a modular catheter system. Commercially available 0.035-inch guidewire PTA balloon catheters come in a variety of balloon sizes and performance characteristics that make such devices an ideal parent module candidate for this case study.

Many challenges exist in designing a modular catheter system, including a robust, secure interface, or attachment mechanism, between the parent module and the adapter module (adapter). This design challenge becomes more difficult with the decision to use commercially available 0.035-inch PTA balloon catheters as the parent module. Although the standardization around a maximum guidewire compatibility of 0.035 inches provides some uniformity in the catheter lumen, there is still variation among brands and models. To accommodate this variation in lumen geometry, a nitinol coil element was designed as the interfacing element on the attachment mechanism integral with the scoring adapter module to interface with the 0.035-inch catheter lumen and connect the scoring adapter with the 0.035-inch PTA balloon parent module.

The attachment mechanism consists of a central tube as the main body with the aforementioned nitinol coil elements bonded to the outer surface of the central tube. To couple the 2 modules together, the central tube of the adapter module is inserted into the distal end of the catheter guidewire lumen of the parent module. As this insertion occurs, the nitinol coil elements, which have been designed to be slightly larger than the guidewire lumen of the 0.035-inch catheters, compress to interface with the 0.035-inch catheter guidewire lumen and anchor the adapter module to the parent module. The adapter module includes a distal tip that remains distal to the end of the 0.035-inch catheter parent module once the attachment mechanism has been fully inserted into the parent module guidewire lumen. Once the adapter module is attached to the parent module, the 2 modules cannot be separated and function as an integrated catheter.

Figure 1 shows an adapter module variant (not the scoring adapter) before attaching to a balloon catheter illustrating the elements of the universal 0.035-inch attachment mechanism. Figure 2 shows sequential images of the interfacing nitinol coil element as it is inserted into the distal end of the 0.035-inch PTA balloon catheter guidewire lumen. It should be noted that the nitinol coil compresses as it is inserted into the parent module. Figure 3 shows the adapter and attachment mechanism of Figure 1 after it is inserted into a PTA balloon catheter.

Figure 1. Adapter module elements.

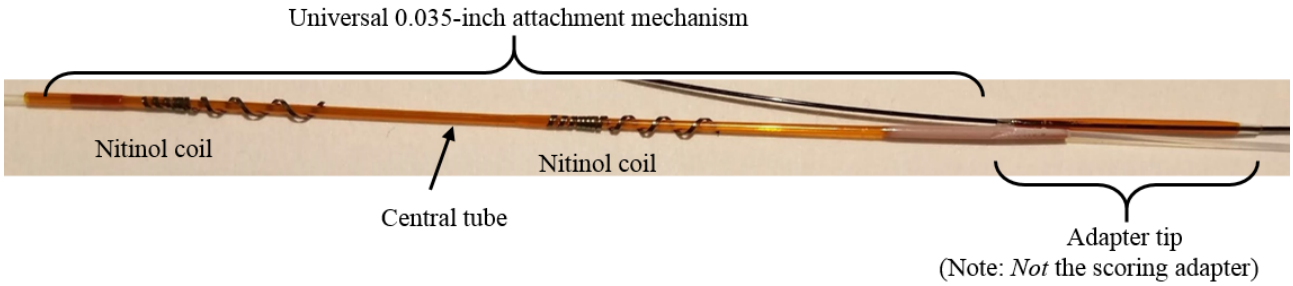


Figure 2. Nitinol coil element during adapter insertion.

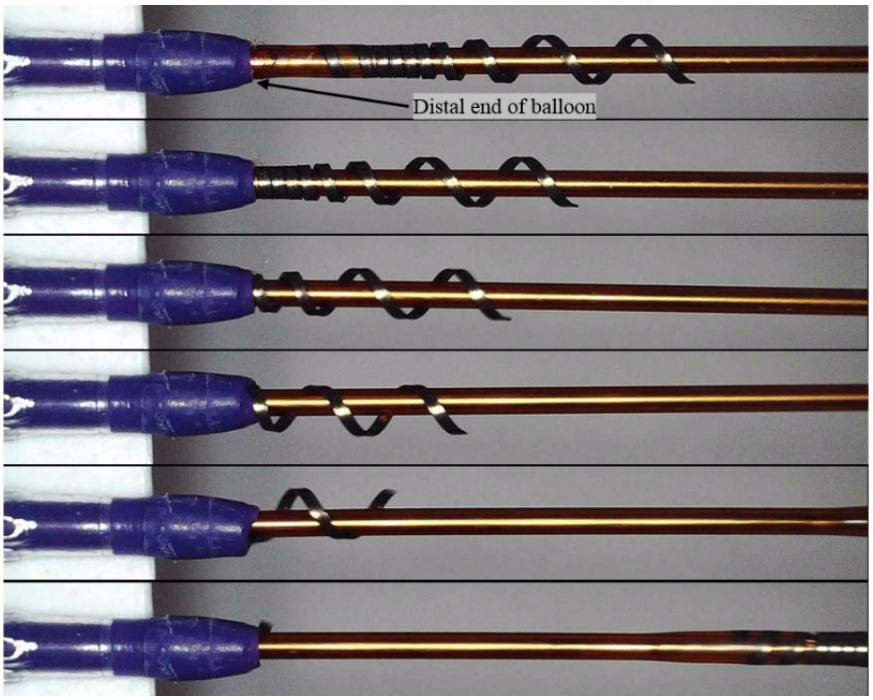
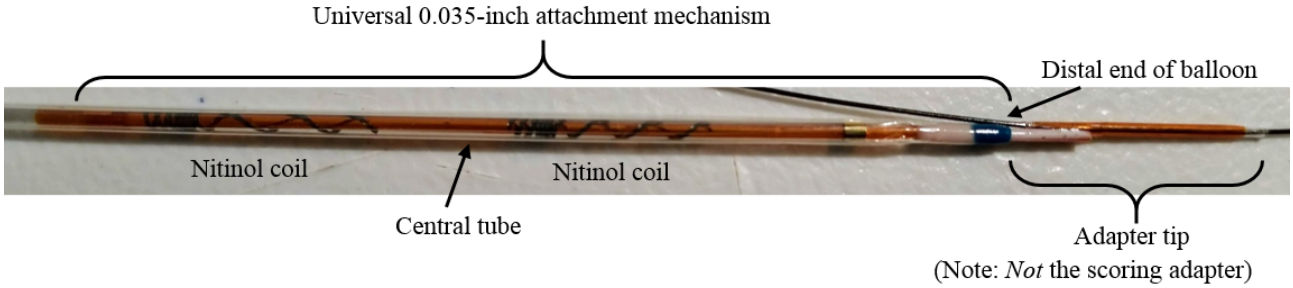


Figure 3. Adapter module attached to parent module (balloon).



Development for Veterinary Use

The veterinary scoring adapter was developed cooperatively by Covellus LLC, a privately held medical device company developing the modular catheter system, and BAS, associate professor of cardiology at Colorado State University. BAS is a diplomate of the American College of Veterinary Internal Medicine, specialty of cardiology, and has completed a fellowship in interventional radiology and endoscopy at the University of Pennsylvania and the Animal Medical Center (New York). The development of the scoring adapter was targeted as a tool to allow the use of the described cutting or scoring followed by high-pressure ballooning technique in congenital pulmonary or aortic stenosis where the stenosis is larger than can be effectively treated with commercially available cutting or scoring balloons. Currently, commercially available scoring and cutting balloons have a maximum diameter of 8 mm.

The scoring adapter design chosen for initial trial veterinary use included 4 nitinol wires 0.006 inches in diameter that are embedded into the scoring adapter tip as the scoring elements. The scoring wires extended proximally about 100 cm, such that the wires would extend proximally out of the access site for the procedure and remain under the control of the operator throughout the procedure. The 4 scoring wires were positioned approximately uniformly around the circumference of the scoring adapter tip. The scoring adapter tip that remains distal to the parent module balloon catheter is composed of a thermoplastic elastomer and has a tapered shape similar to a distal tip of a PTA balloon catheter, with a maximum diameter of 0.063 inches and a length of 0.23 inches. The scoring adapter tip also includes 2 embedded 3-mm-long sections of 0.25-mm tungsten wire, to add extra radiopacity for tip visualization during the procedure. Figure 4 is a partial schematic representation of the scoring adapter module illustrating the tip and position of the scoring wires. Figure 5 shows an image of the scoring adapter module attached to a 0.035-inch balloon catheter, with the adapter elements labeled to further illustrate the described design elements.

Figure 4. Schematic representation of the scoring adapter.

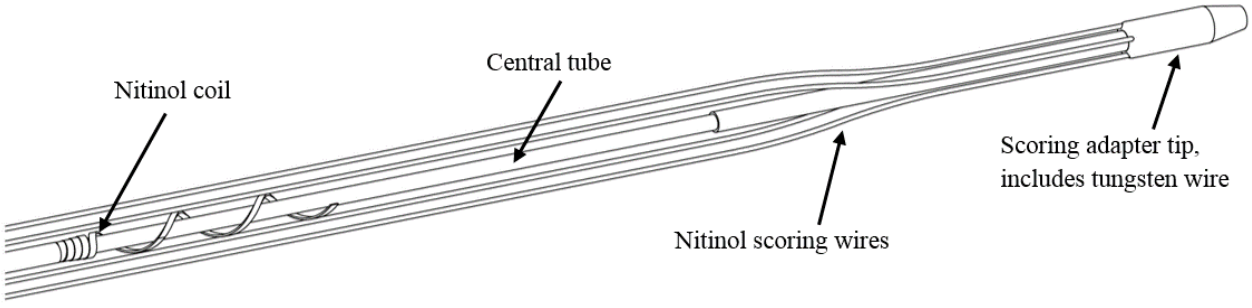
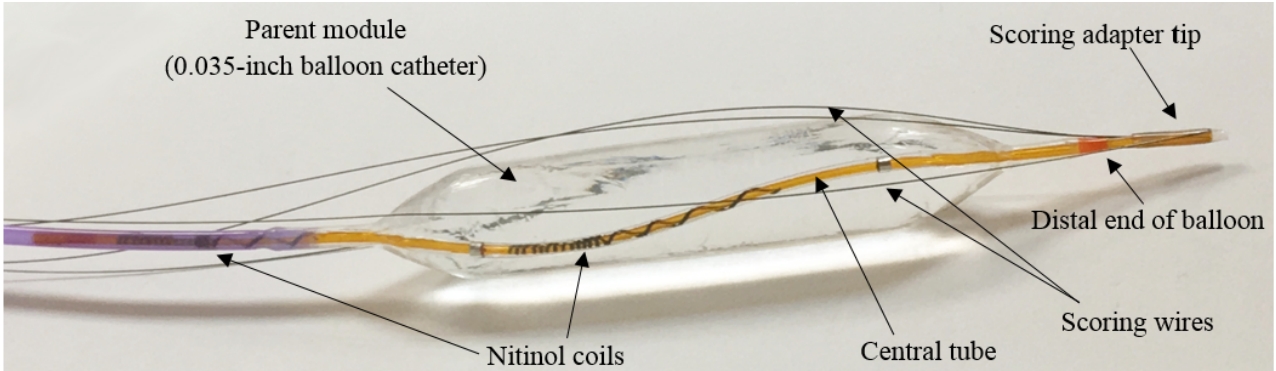


Figure 5. Scoring adapter modular system.



Manufacturing Veterinary Use Scoring Adapter

Covellus LLC manufactured a small lot of scoring adapters for use in this initial veterinary application. Along with the small lot of scoring adapters, Covellus manufactured adapter test samples and attachment mechanism test samples to verify if the manufactured batch of scoring adapters will function as intended, provide adequate securement between the parent module balloon and scoring adapter, and give assurance of sterility of the manufactured scoring adapters. The scoring adapter was packaged in a conventional Tyvek pouch system and radiation sterilized using electronic beam methods.

Results

Preoperative Evaluation

A 7-month-old female Vizsla dog was referred to BAS for balloon pulmonary valvuloplasty. The patient was previously diagnosed with a subpulmonary obstruction on echocardiography following detection of an asymptomatic murmur by the primary care veterinarian. Before the valvuloplasty intervention, the patient underwent a preoperative echocardiogram, where the peak transpulmonary pressure gradient across the obstruction was measured to be 74 mmHg. Figures 6 and 7 show images from the preoperative echocardiogram representing the subvalvular obstruction and the peak transpulmonary pressure gradient measurement. In addition, right ventriculograms during diastole and systole were performed to visualize the subvalvular obstruction as shown in Figure 8.

Figure 6. Preoperative echocardiogram showing the subvalvular obstruction.

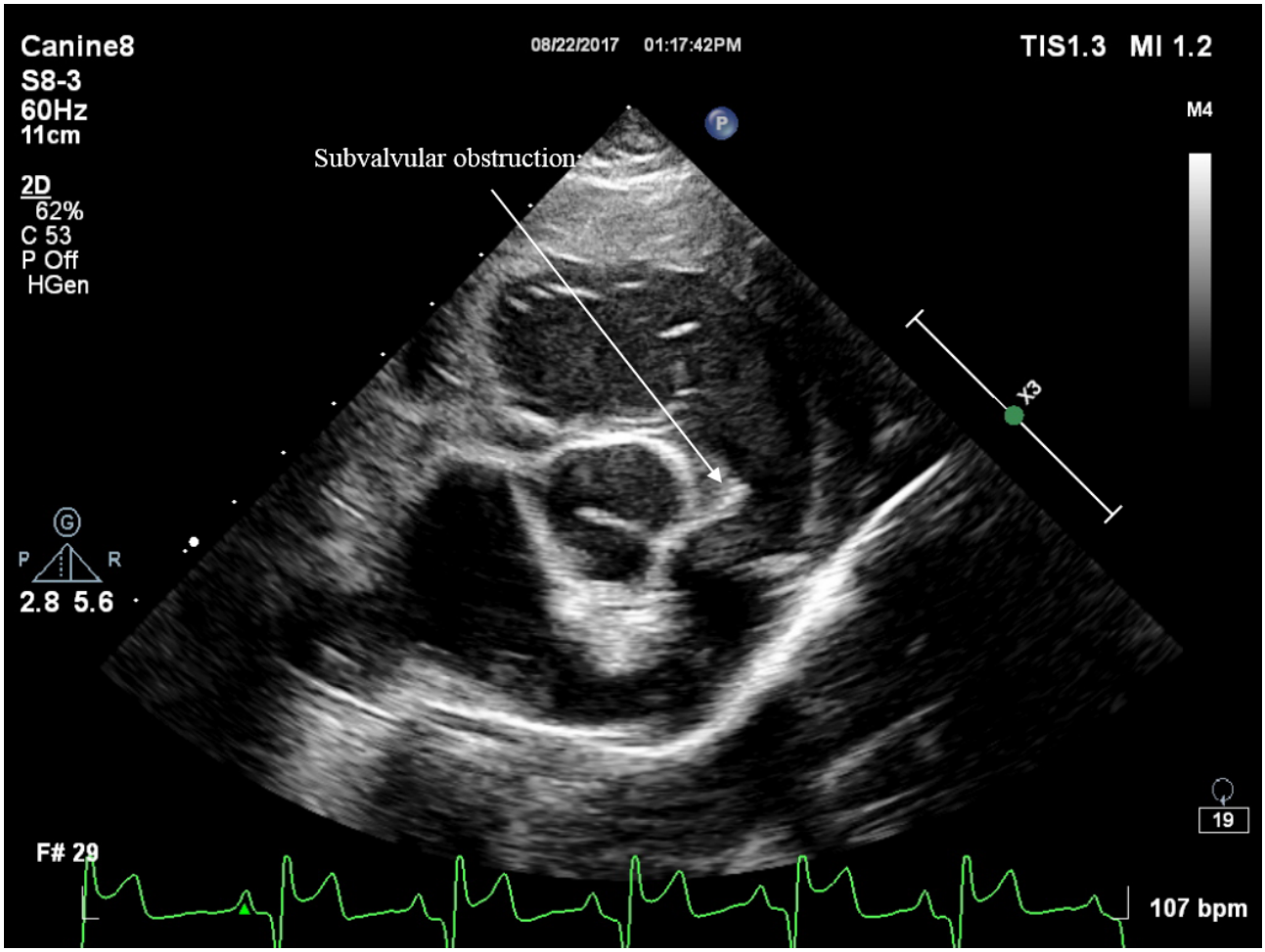


Figure 7. Preoperative peak transpulmonary pressure gradient.

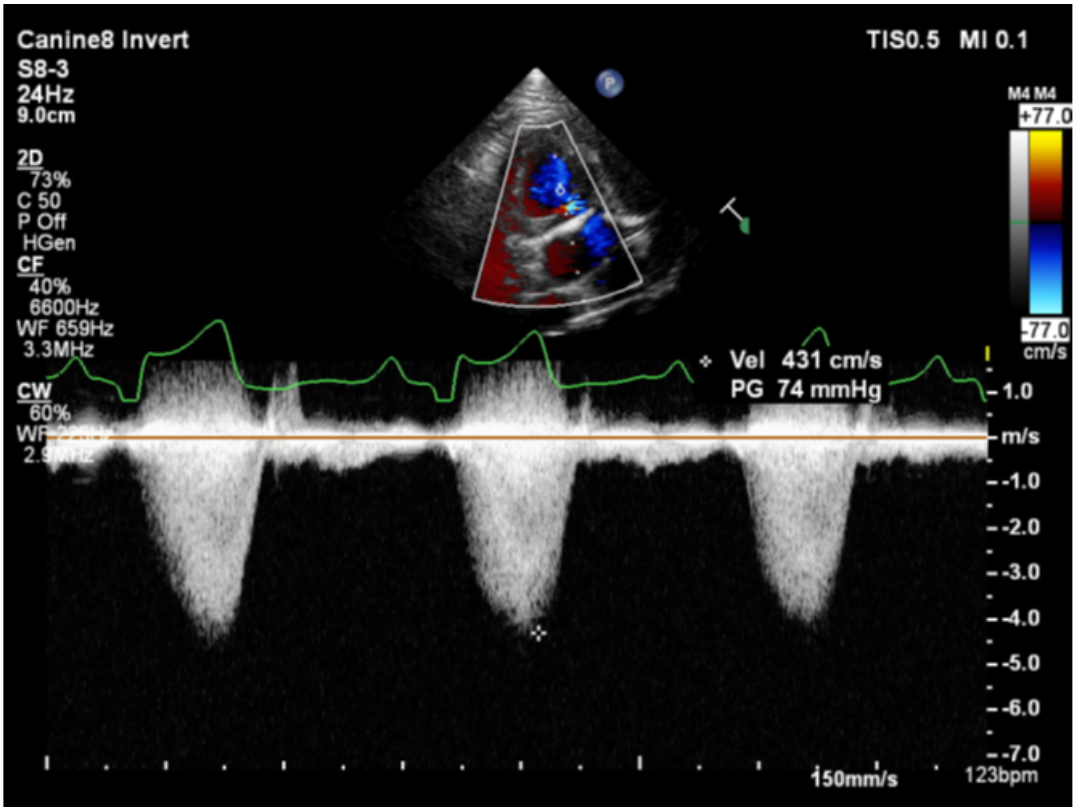
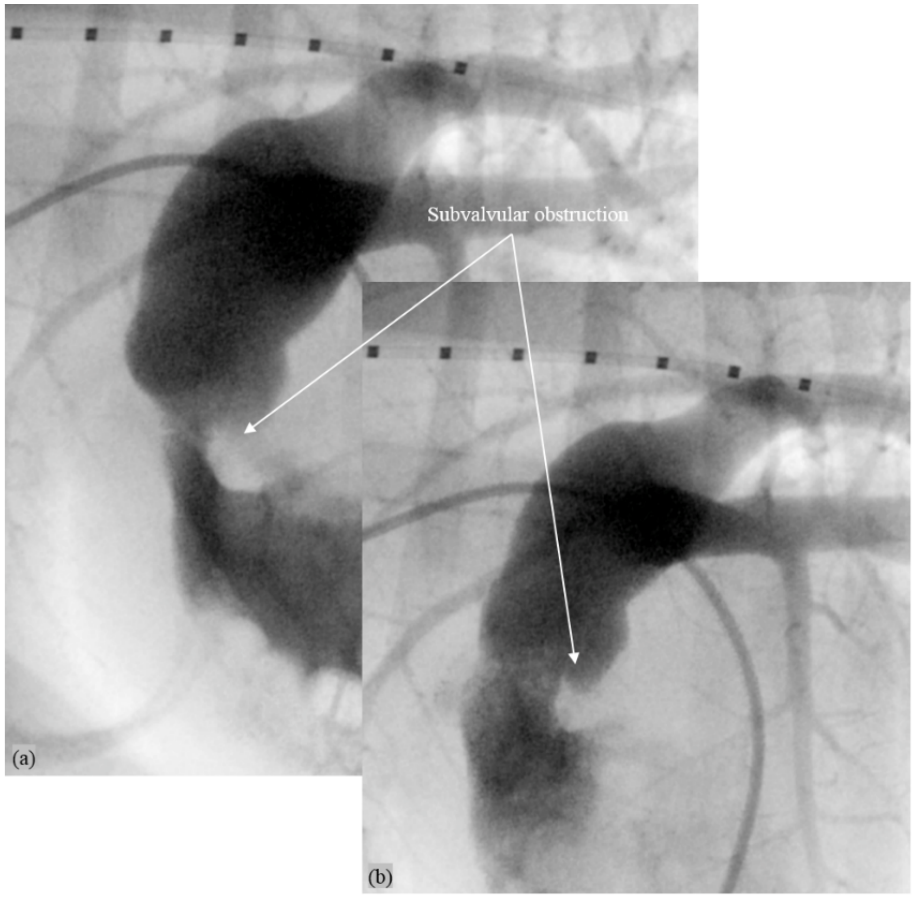


Figure 8. Right ventriculogram showing the subvalvular obstruction in systole (a) and diastole (b).



Procedural Details

To meet the needs of this particular case, BAS chose a 12-mm diameter by 40-mm long Armada 35 model (Abbott Labs) PTA balloon catheter to pair with the scoring adapter for the scoring step of the procedure. The scoring adapter was successfully attached to the Armada balloon in the operating room at the time of the procedure. Figure 9 shows the scoring adapter attached to the Armada 35 balloon (Abbott Labs); it should be noted that this picture was taken following the procedure, so the balloon has been previously inflated but otherwise illustrates the attached adapter.

The scoring adapter and balloon combination was tracked through a 40-cm, 8-Fr Flexor Balkin Sheath (Cook Medical) and over a 200-cm long V-18 control wire (Boston Scientific) to the target site and positioned across the obstruction. The balloon with scoring adapter combination was inflated to the rated burst pressure by BAS. Figure 10 shows the preinflation, midinflation, and peak inflation angiographic images.

Figure 9. Scoring adapter attached to percutaneous transluminal angioplasty balloon.

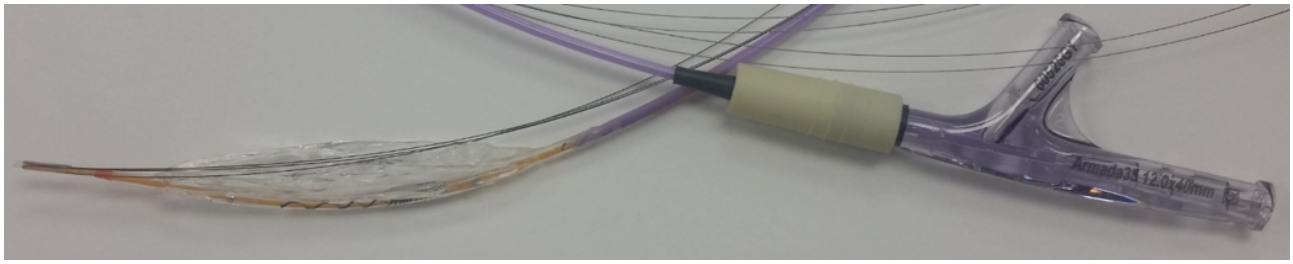


Figure 10. Angiographic inflation images.

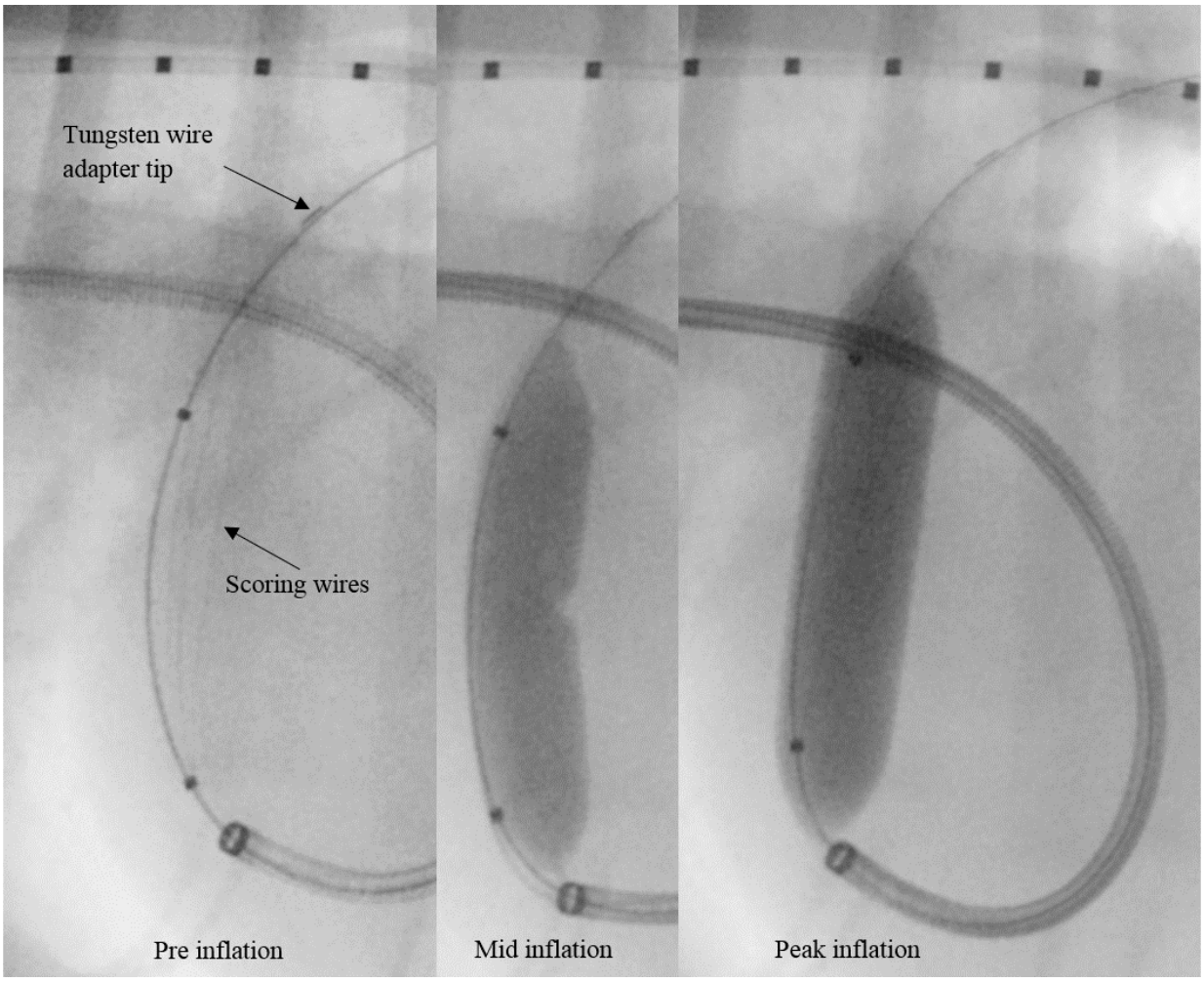
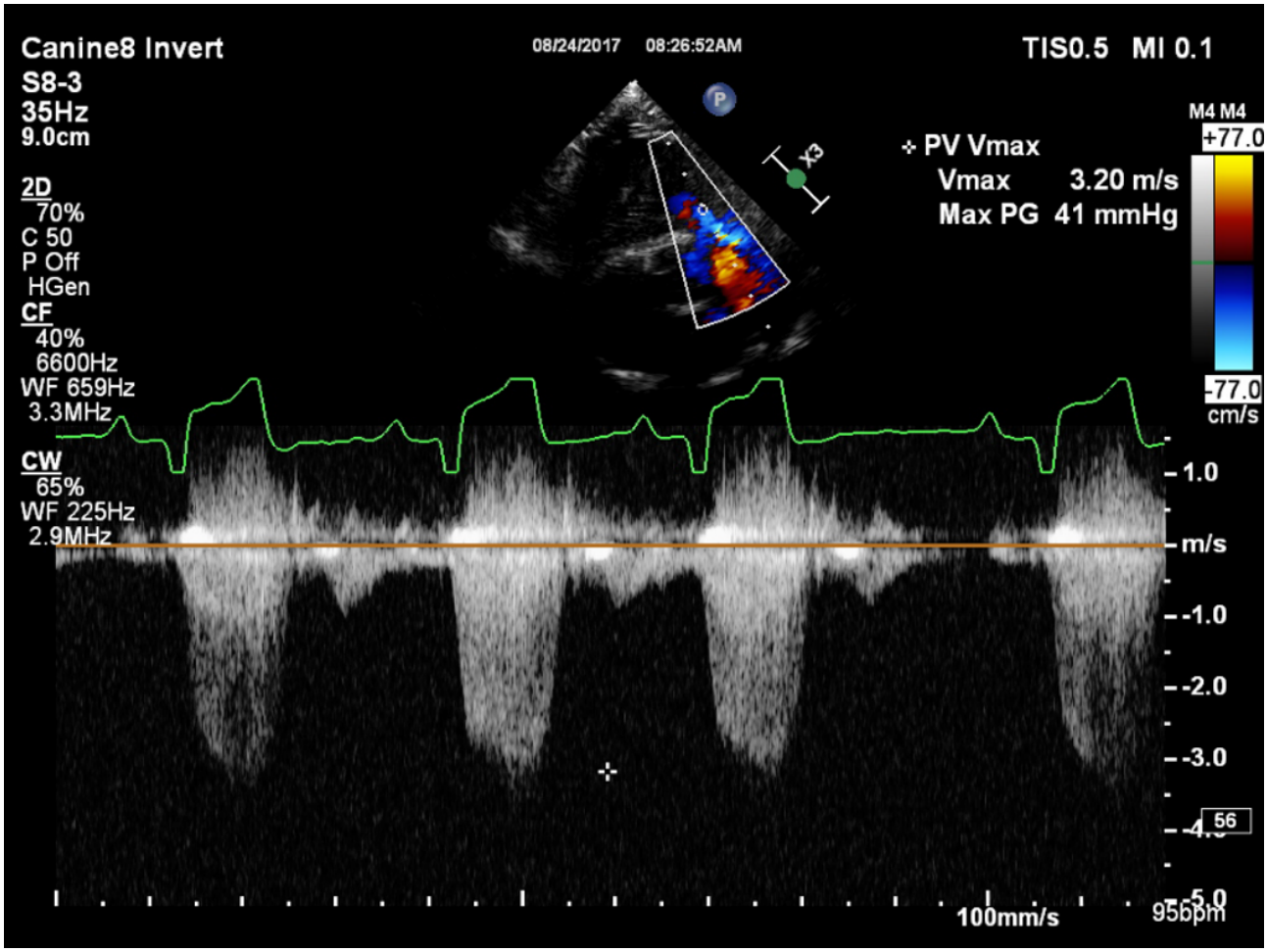


Figure 11. Postoperative echocardiogram.



Procedural Results

The scoring adapter and balloon combination was successfully removed with the 2 modules still completely attached, with no visible damage to the balloon or adapter elements. An 18-mm diameter by 40-mm long ATLAS GOLD PTA balloon catheter (BARD) was used for postscoring high-pressure balloon dilatation. The peak transpulmonary pressure gradient dropped to 41 mmHg, as measured during the postoperative echocardiogram (see Figure 11).

Discussion

Principal Findings

The transpulmonary pressure gradient was reduced from 74 mmHg preoperative to 41 mmHg postoperative. A transpulmonary pressure gradient of 41 mmHg is considered mild and should lead to an improved prognosis and long-term outcome. In addition, this is a better result than typically achieved with conventional ballooning for subvalvular pulmonary obstruction. The result indicates the modular catheter system design utilizing commercially available PTA balloon catheters as the parent module functioned like an integrated scoring balloon catheter in this procedure. This case illustrates how a modular catheter system can be used to create interventional catheters that are not otherwise available and, therefore, improve access to appropriate devices.

The objective of this case study was to demonstrate the feasibility of the proposed modular catheter system and not the efficacy of pulmonary valvuloplasty; therefore, only the acute results of the intervention are presented. Furthermore, the dog traveled to Colorado State University from another state, limiting our ability to obtain postoperative echocardiograms beyond the initial day 1 postoperative study.

Conclusions

The attachment mechanism and modular catheter system was successful. The attachment mechanism provided a means to combine the parent balloon module with the scoring adapter module at the time of the procedure, such that the procedural need guided the creation of a *new* scoring balloon of a diameter that would not have been available otherwise. This case study is proof of concept of a modular system that represents a new paradigm of device catheter construction and use for minimally invasive interventional procedures.

Acknowledgments

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Conflicts of Interest

BB is the CEO of and a shareholder in Covellus LLC.

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Abbreviations

PTA: percutaneous transluminal angioplasty
SKU: stock keeping unit

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Original Paper

An Analytics Framework for Physician Adherence to Clinical Practice Guidelines: Knowledge-Based Approach

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Abstract

Background: One of the problems in evaluating clinical practice guidelines (CPGs) is the occurrence of knowledge gaps. These gaps may occur when evaluation logics and definitions in analytics pipelines are translated differently.

Objective: The objective of this paper is to develop a systematic method that will fill in the cognitive and computational gaps of CPG knowledge components in analytics pipelines.

Methods: We used locally developed CPGs that resulted in care process models (CPMs). We derived adherence definitions from the CPMs, transformed them into computationally executable queries, and deployed them into an enterprise knowledge base that specializes in managing clinical knowledge content. We developed a visual analytics framework, whose data pipelines are connected to queries in the knowledge base, to automate the extraction of data from clinical databases and calculation of evaluation metrics.

Results: In this pilot study, we implemented 21 CPMs within the proposed framework, which is connected to an enterprise data warehouse (EDW) as a data source. We built a Web–based dashboard for monitoring and evaluating adherence to the CPMs. The dashboard ran for 18 months during which CPM adherence definitions were updated a number of times.

Conclusions: The proposed framework was demonstrated to accommodate complicated knowledge management for CPM adherence evaluation in analytics pipelines using a knowledge base. At the same time, knowledge consistency and computational efficiency were maintained.

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KEYWORDS

clinical practice guidelines; care process model; visual analytics; clinical decision support

Introduction

Clinical practice guidelines (CPGs) are systematically developed statements that assist clinicians in making decisions about appropriate patient care for specific clinical circumstances [1]. Since the nature of CPGs includes complicated clinical knowledge, it is known to be challenging not only to formulate clinicians' logics into the form of guidelines, but also to translate and implement these guidelines properly into clinical tasks and processes. Therefore, a number of studies have tried to develop systematic ways to implement CPGs [2,3], including computer-aided clinical decision support (CDS)-based approaches that enable personalized and timely implementation of CPGs [4-6] and knowledge-based approaches to systematically transform complicated knowledge of CPGs into clinical decision and practices [7-9].

Since clinical knowledge within CPGs originated from evidence of best practices, realization of CPGs in practice has had a positive impact on clinical workflow and patient outcome [10-14]. Therefore, it is important to measure and evaluate physicians' adherence to CPGs in order to understand how providers are following guidelines in the postimplementation phase [15,16]. This evaluation may be an interdisciplinary project involving domain experts, knowledge engineers, and

data analysts, among others. Domain experts should derive evaluation logics and metrics from CPGs and document them by collaborating with knowledge engineers. To perform this evaluation, database engineers should create queries based on the definitions and run them against the clinical database. As a result of data extraction, evaluation outcomes would be delivered to consumers (ie, clinical champions or management leaders), often in the form of Web-based reports.

The problem is that knowledge gaps always exist while transforming logics of CPGs into evaluation-definition documents, developing queries, and generating reports. For example, translating definitions into computationally executable queries may vary by individual knowledge engineers and data developers [17]. Once analytics are delivered, consumers can only see the resulting data, but would lack an understanding of what logics were used to extract the numbers. If analytics are being delivered in a regular manner and evaluation logics are modified, it becomes confusing to know whether a report was made based on an old or new definition. In particular, analytics have become more integrated and automated by integrating data pipelines, report generation, and delivery workflow; this may involve more knowledge translation into the framework and may require a systematic method of management [18,19].

Knowledge gaps are caused by the difficulty of handling too many data points, miscommunication between domain experts and developers, misinterpretation of guidelines, loss of authorship of documents, and revision and update of knowledge sources [20]. This may result in data inconsistency across the analytics pipeline, causing consumers to experience a lack of trust regarding the analytics results. Consumers may be confused and may feel that “these numbers don’t make sense,” but it is difficult to understand the problem with the current analytics process and where it lies in the pipeline.

To address this limitation, we propose an analytics framework whereby data and visualization pipelines are integrated with a knowledge base. A knowledge base is a tool designed to store clinical knowledge content in a systematic way by managing attributes of content authorship, version, and relationship between resources [21,22]. We used a knowledge base as a key component to store CPGs, their adherence definitions, and their executable queries, so that the related documents in their different forms could be managed with metadata and easily shared by domain experts, query developers, and analysts. In addition, we connected data pipelines to executable queries in the knowledge base so that a change of query can be immediately incorporated into the analytics pipelines.

In a pilot study, we adopted locally developed CPGs used in our health care system, resulting in a care process model (CPM). We developed an integrated analytics framework that consists of a knowledge base that employs CPMs in different forms: a commercial data pipelining tool, Alteryx, connected to our clinical database and a commercial visualization tool, Tableau, to generate reports. We built a dashboard that provides views for adherence by physicians to 21 CPMs. Over an 18-month-long proof-of-concept project, we ran a working group to analyze CPM adherence and to manage definition revisions. We investigated how the use of the knowledge base contributed to the filling of knowledge gaps and automating of analytics pipelines with computational efficiency.

Methods

Subject: Care Process Models

In this study, we used CPMs that were created using locally developed CPGs in our health care organization and that were designed to reduce clinical variation, improve quality, and support local preferences [23]. The CPMs were published and managed by clinical programs, which are made up of clinical expert groups consisting of clinical champions, medical directors, nursing administrators, data managers, and data analysts. Over the last 20 years, clinical programs have developed over 120 CPMs that cover a variety of clinical conditions and procedures, such as hypertension, heart failure, breast cancer, appendicitis, and acute myocardial infarction, among others.

CPMs were originally developed as paper or electronic documents containing descriptions of target problems or procedures, logics of decision-making, and recommended actions. Traditionally, CPM implementation was conducted through the involvement and education of care teams and providers. Over the last four years, we have installed a new enterprise-wide electronic health record (EHR) system in our hospitals and clinics in Utah, USA. We have also started developing computationally executable CPMs inside the EHR system using a variety of decision-support components, including order sets, decision-support rules, and care pathways (ie, decision flow and state-based order recommendation tools), among others.

In addition to CPM implementation, there was a strong need from the clinical leadership to monitor and evaluate how providers are complying with CPMs. Analyzing such data may allow us to understand how well-embedded CPMs are within clinical practices and may allow us to gain insights into how to improve best practices within them. However, it has been challenging to quantitatively measure whether CPMs were used as intended after implementation, since key data points for the evaluation are complicated to define and capture. In addition, time-consuming manual data processing to calculate evaluation metrics was required. To address these problems, clinical programs and informatics specialists initiated an effort to build a framework that creates a systematic approach for data extraction and visual analysis within the evolution cycle of CPM development, implementation, and improvement.

To correctly evaluate adherence to CPMs, three types of information should be defined. First, since CPMs are developed to treat patients with certain conditions, a target population (ie, patient cohort) should be identified. Specifically, a combination of inclusion and exclusion criteria should be defined, including patient demographics, diagnosis, lab results, and medications. Second, metrics to quantitatively measure CPM utilization for the defined target population should be defined. A timeline of when to develop the metrics, typically key concepts extracted from logics and actions in CPMs, should be included since it is unrealistic to capture all of the concepts within the CPMs.

Examples of key concepts include the following: *diagnosed with pneumonia*, *image ordered for d-dimer*, or *1-90 days old with a fever(≥38°C)*. Third, an adherence formulation is needed that would be used to count credits given to providers or care units who utilized CPMs as intended for target patients.

Although CPMs are well-described guidelines, it is often challenging to derive the key information above, as the nature of the CPMs are composed of complicated, domain-specific knowledge and often contain ambiguity. In addition, it is difficult to connect the derived key concepts to data points—often tables or columns in clinical databases—in real-world data sources. Thus, a multidisciplinary collaboration effort may be required in order to transfer knowledge between the various experts below:

1. Domain knowledge expert: an expert, author, or publisher of CPMs. This individual would be responsible for interpreting and defining the highest levels of evaluation criteria.
2. Domain data expert: an individual with both clinical domain and database expertise. This individual would be responsible for translating CPM knowledge and linking concepts to data points in databases.
3. Informatics expert: an expert in clinical knowledge management. This individual would be responsible for communication between domains.
4. Database engineer: a database expert. This individual would be responsible for developing and maintaining database tables for CPM relationship information.
5. Data analyst: a database expert. This individual would be responsible for developing data pipelines for analysis.
6. Business intelligence developer: an expert in report development.

Problem Statement

The problem we are addressing is that knowledge gaps often exist while translating logics CPMs from domain experts into analytics pipelines. For example, domain experts may define the diagnosis of pneumonia at a high level in the original CPMs. However, the disease should be clearly defined to extract real data from the clinical database, including diagnosis codes in standard terminologies, types of patient visits, clinical context, problem status, and exceptions. Gaps may exist while clarifying such information by mapping incorrect data points, miscommunication, misinterpretation, changes in CPM contents, and changes in data sources. Such inconsistency could result in confusion and distrust of data quality for analytics consumers. In the current analytics environment there is no tool to track and investigate what the gaps are and where they exist.

To address inconsistencies in knowledge translation and improve analytics productivity, we aim to adopt a knowledge base that will help us manage the content across the whole CPM evaluation process. A knowledge base is a component in our EHR system that manages the authoring, review, publication, delivery, and versioning processes that surround clinical knowledge assets for consumption within these frameworks. Typically, clinical knowledge sources may be order sets, decision support rules, nursing protocols, clinical guidelines, and patient education resources. Any knowledge-based content can be a source for a knowledge base, such as concept definitions, formulations, executable queries, and design concepts of visualizations. These assets can be consumed by a human (ie, in the case of narrative clinical care guidelines) or by a computer (ie, rule bases for consumption by inference engines), or they can be aligned for consumption on both ends of the spectrum [21].

There are practical benefits to using a knowledge base for CPM analytics: (1) storing and sharing all the knowledge resources in a centralized place, instead of local storage or exchanging content by emails, to reduce miscommunication and redundancy; (2) being able to manage knowledge resources with unique numeric identifiers and metadata, including author, version, and history of revisions; and (3) making knowledge resources consumable with data analytics tools. In addition, a knowledge base may be useful for end-user data consumers by giving them more contextual information about the data with answers to questions such as “Who defined the definitions of the measures?”, “How were the measures calculated?”, and “What changes have been made?”

Selection of Care Process Models and Deriving Key Measures

As part of a pilot study to evaluate adherence based on the proposed framework, we selected 21 CPMs. Our selection criteria were as follows: (1) clinical utility and popularity of the CPM, (2) whether the CPM was already implemented within our EHR system, (3) the ease with which the CPM allowed the definition of evaluation metrics, and (4) whether data points related to the CPM were fully or partially collected in our clinical information systems. For the selected CPMs, we worked with CPM publishers in clinical programs to derive the three types of information for adherence evaluation defined in a previous section. The adherence rate (%), defined in the equation below, represents physician utilization of designated CPM components for a group of patients who are intended to be treated by the CPM:

> Adherence (%) = (number of cases treated using the CPM) / (number of cases intended to be treated by the CPM)

Since the definition above is highly abstracted, there were diverse details regarding how to practically calculate the adherence. For example, to calculate the numerators, we determined what types of decision-support components were used to implement the CPMs (eg, order set) and which were used to connect key concepts to real data points (eg, order set ordering history). We found that 10 of the 21 CPMs (48%) were implemented as physician order sets, or small groups of order sets, whereas the rest were implemented through combinations of care pathways and decision-support rules.

Table 1. Summary of care process model (CPM) adherence definitions.

Clinical program (adherence definitions, n; queries, n)	CPM name	Cohort-defining condition	Decision-support component
Oncology, 1, 3	Lung, breast, or colon cancer	Diagnosis and chemotherapy	Order set
Pediatrics, 1, 1	Febrile infant	Vital sign or a report	Care pathway
Neuroscience, 1, 1	Acute stroke	Problem and admission time	Order set
Primary care, 4, 4	Diabetes	Age and diagnosis	Care pathway
	Hypertension	Diagnosis	Care pathway
	Acute sinusitis	Diagnosis and medication	Care pathway
	High blood pressure	Diagnosis	Care pathway
Cardiovascular, 1, 3	Heart failure	Age, admission, and diagnosis	Order set
	Acute myocardial infarction	Age, admission, and diagnosis	Order set
	Coronary artery bypass graft	Age, admission, and diagnosis	Order set
Musculoskeletal, 1, 1	Total hip or knee surgery	Procedure	Order set
Surgical service, 1, 2	Appendicitis	Procedure	Order set
	Cholecystectomy	Procedure	Order set
Behavioral health, 3, 3	Depression	CDS[a] rule and diagnosis	Care pathway
	Suicide prevention	CDS rule	Care pathway
	Mental health integration	Clinical document and clinic visit	Care pathway
Women and newborn, 1, 2	Jaundice	Newborn	Care pathway
	Neonatal hypoglycemia	Observation, rules, and age	Care pathway
Intensive medicine, 4, 4	Pneumonia	CDS rule	Care pathway
	Pulmonary embolism	Order, imaging, diagnosis, and care pathway use	Care pathway
	Pediatric sepsis in emergency	CDS rule	Care pathway
	Pediatric minor head trauma	CDS rule	Care pathway

[a]CDS: clinical decision support.

The denominators were used to identify CPM-specific patient cohorts. For example, the denominator for the adherence rate of the hypoglycemia CPM was defined as a combination of (1) whether certain decision-support rules related to hypoglycemia were fired, (2) whether a patient has a history of hypoglycemia according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), and (3) whether specific nursing documents were recorded.

Below are examples of detailed key concepts to be included in the definitions:

1. Cohort (denominator): clinical inclusion and exclusion criteria, patient master index, encounter, facility, care unit, decision-support rule firing criteria, clinical form used, etc.
2. Utilization (numerator): Order set usage, order set title, version, content, orderable items, customized order sets, care pathway title, components in care pathway used, etc.
3. Adherence: adherence definition, aggregation level by patient, encounter, provider, unit and facility, etc.

A group of experts with different backgrounds reviewed these concepts, documented the definitions, and built queries. Table 1 shows a summary of the derived CPM adherence definitions.

Results

Development of Framework

We developed the analytics framework by integrating several homegrown and commercial tools. For the knowledge base, we used Intermountain's knowledge repository that our organization has used over the last 10 years. We adopted Alteryx as a tool for data analytics pipelines and Tableau as a tool for visual transformation and Web-based dashboard development. We used our enterprise data warehouse (EDW) as the data source, which is an integrated clinical data repository for research and quality improvement that stores over 100 billion records tied to encounters, lab observations, diagnoses, procedures, medications, and billing over 20 years. We also used CPM-centered database tables in our EDW that were developed by clinical programs, which store condition-specific patient cohorts, quality metrics, and outcomes for clinical research and quality improvement.

Figure 1 depicts the architecture and flow of knowledge in the framework. Domain experts in clinical programs translate paper-based CPMs to adherence definition documents. Structured Query Language (SQL) developers create queries based on the documents and deploy them into the knowledge

base on the Web (see Figure 2). Alteryx imports the SQL information from the knowledge base to run against the EDW; Alteryx then exports the cohort and metrics as a Tableau-specific data file to a Tableau server so they can be visually transformed by Tableau to automatically generate charts on the Web. In the dashboard, links are embedded in the charts, enabling users to view the original CPM documents and queries used in the knowledge base.

Figure 3 shows a CPM in various forms during knowledge transformation: human-readable PDF document (top left); logics of the CPM are implemented as an order set in a computerized physician order entry (CPOE; bottom left); adherence definition document (top right); and computerized adherence logic as a SQL (bottom right). Since these knowledge content components in different forms originated from one source, they are semantically linked to each other with authorship, translation record, and version history.

Figure 1. Architecture diagram of the knowledge-based analytics framework for care process model (CPM) adherence. EDW: enterprise data warehouse; SQL: Structured Query Language.

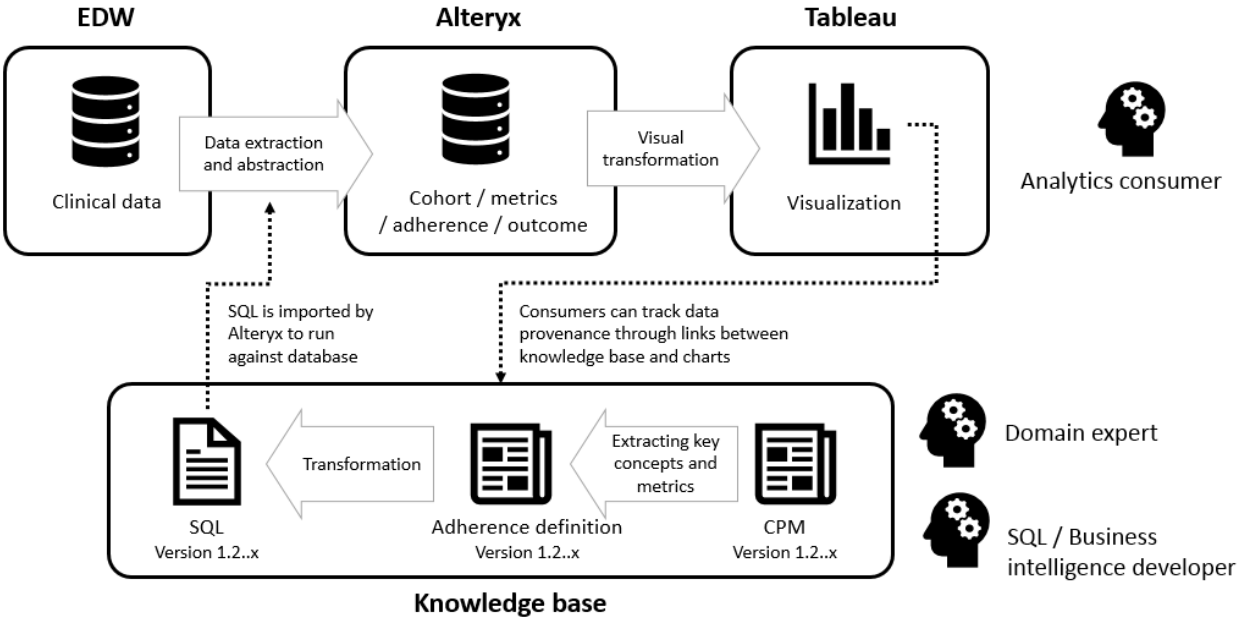


Figure 2. Screenshot of the care process model (CPM) knowledge content components uploaded into the online knowledge repository.

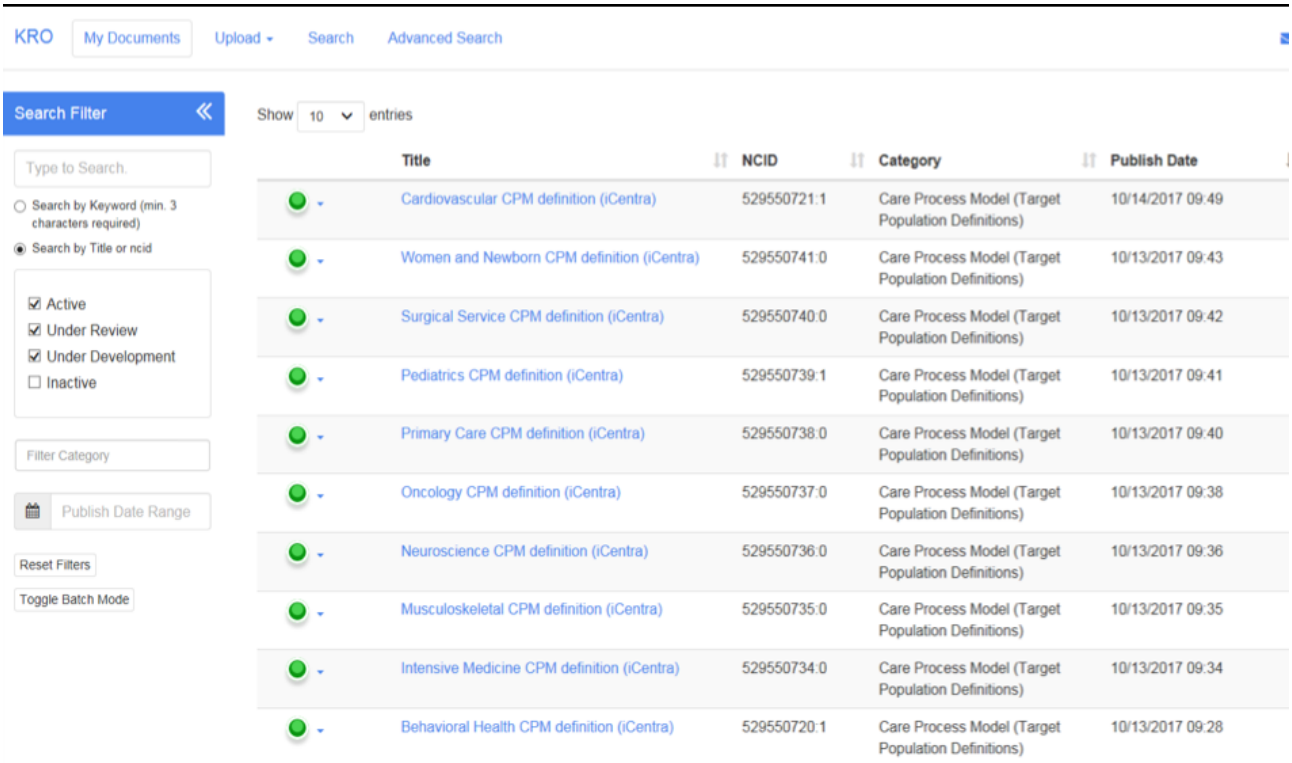
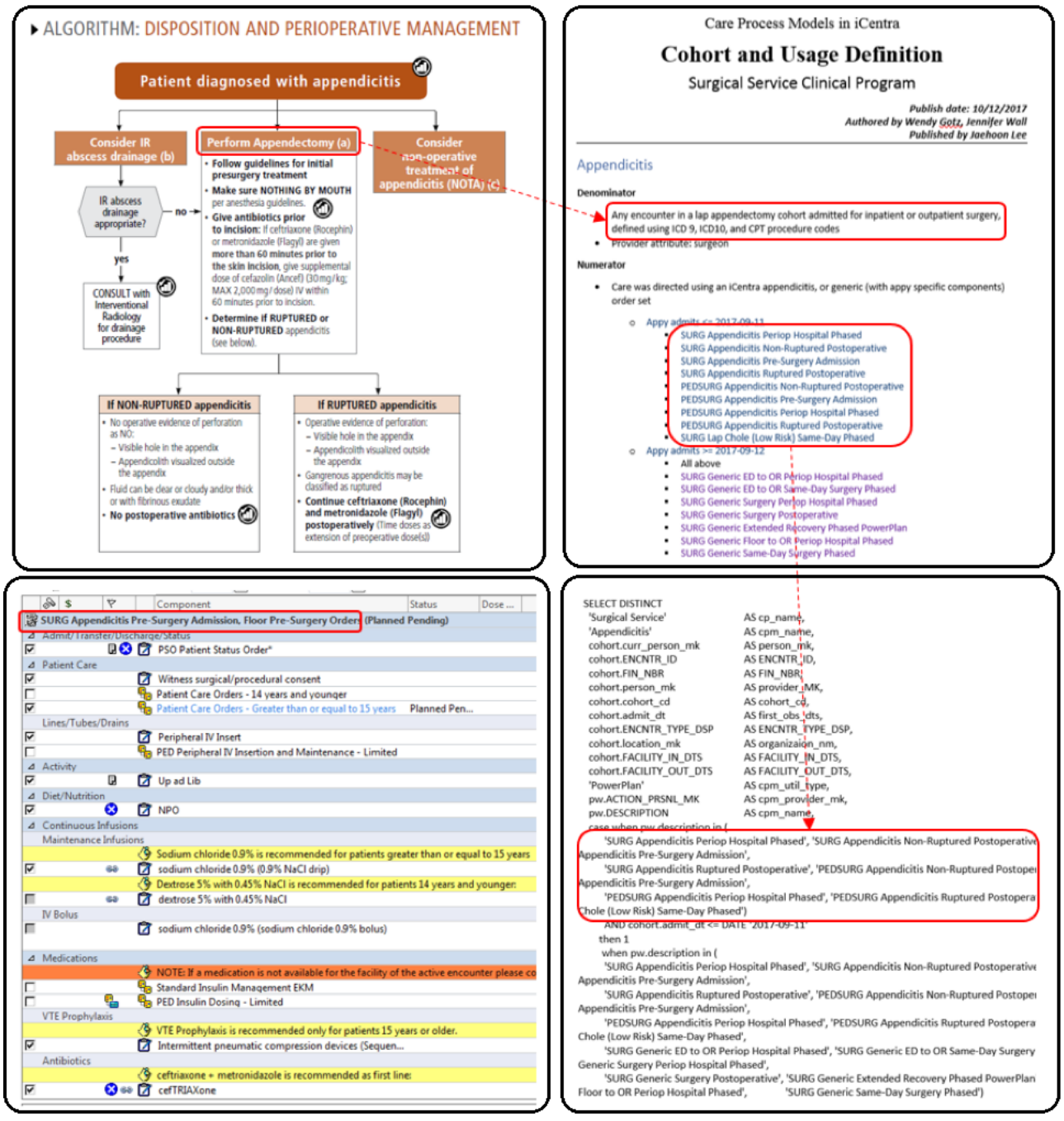


Figure 3. Evolution of care process model (CPM) knowledge. Top left: an original PDF document; bottom left: a surgical order set inside a computerized physician order entry (CPOE) that implemented logics of the CPM; top right: a narrative text of evaluation criteria; bottom right: Structured Query Language (SQL) to extract adherence metrics. The red boxes and arrows represent the transformation of concepts and logics from one form to another. Source: Cerner PowerChart. Used with permission by Cerner Corporation.



Development of Dashboard

We developed a Tableau-based dashboard in a production environment that is accessible to clinicians and researchers in our organization through secured user access. It employs five detailed views for each representative CPM adherence in different contexts and scales.

1. Main view: this view provides an overview of adherence trends at the highest level. It consists of a bar chart representing the average cumulative rates of CPM utilization and a line chart showing the monthly average over time (see Figure 4). Each CPM is marked with different color. A filter to the right of the bar graph narrows down the data by *facility*. Average adherence rates range from 0% to 100%, with 0% indicating that no physician used any CPM for the specific condition-based cohort and 100% indicating that all physicians used CPMs for all associated relevant cases.
2. Facility view: this view is used to monitor the monthly average adherence rate by hospitals. This view consists of a dual chart that represents the percent adherence rate by month and the number of encounters where CPM was used or not used.
3. Provider view: this view shows the summary of CPM utilization by individual providers. Users can select a

provider in the filter on the right, then the view narrows down by patients treated by the selected provider (see Figure 5).

4. Encounter view: this view provides detailed actions in CPM utilization at the encounter level. A table view includes patient identifier, provider, length of stay, CPM used, and enrolled date and time.
5. Patient view: this view provides a summary of CPM-based treatments for a patient.

Data Extraction and Early Usage Pattern

Data pipelines were scheduled to run regularly, with different refresh frequencies depending on CPMs and data sources. As of July 1, 2018, the number of patients eligible for 21 CPMs was 230,669 and the number of encounters was 377,507. For those target patients, 7895 providers utilized CPMs at least once. Total adherence rate across all the CPMs during the period was 8.8%.

Figure 4. Main view of the Tableau–based care process model (CPM) utilization dashboard (screenshot).

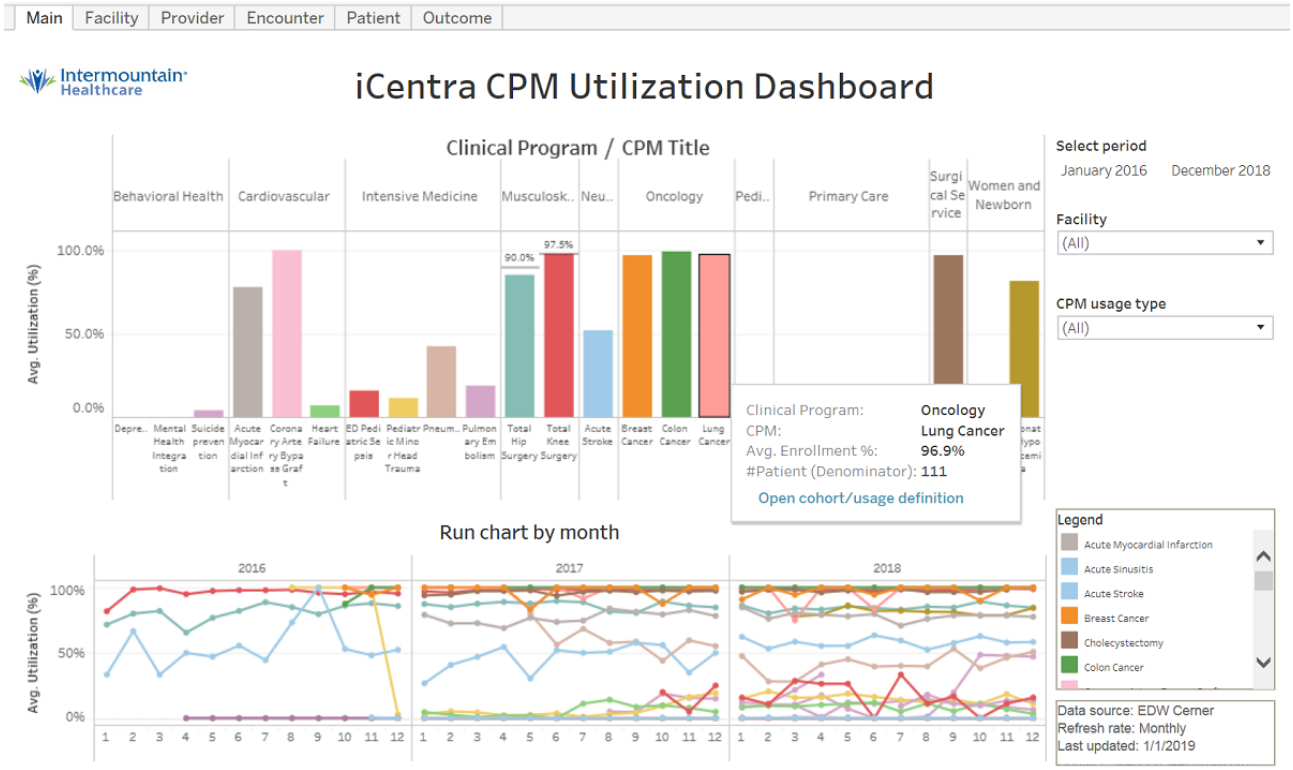


Figure 5. Provider view of the care process model (CPM) utilization dashboard (screenshot).

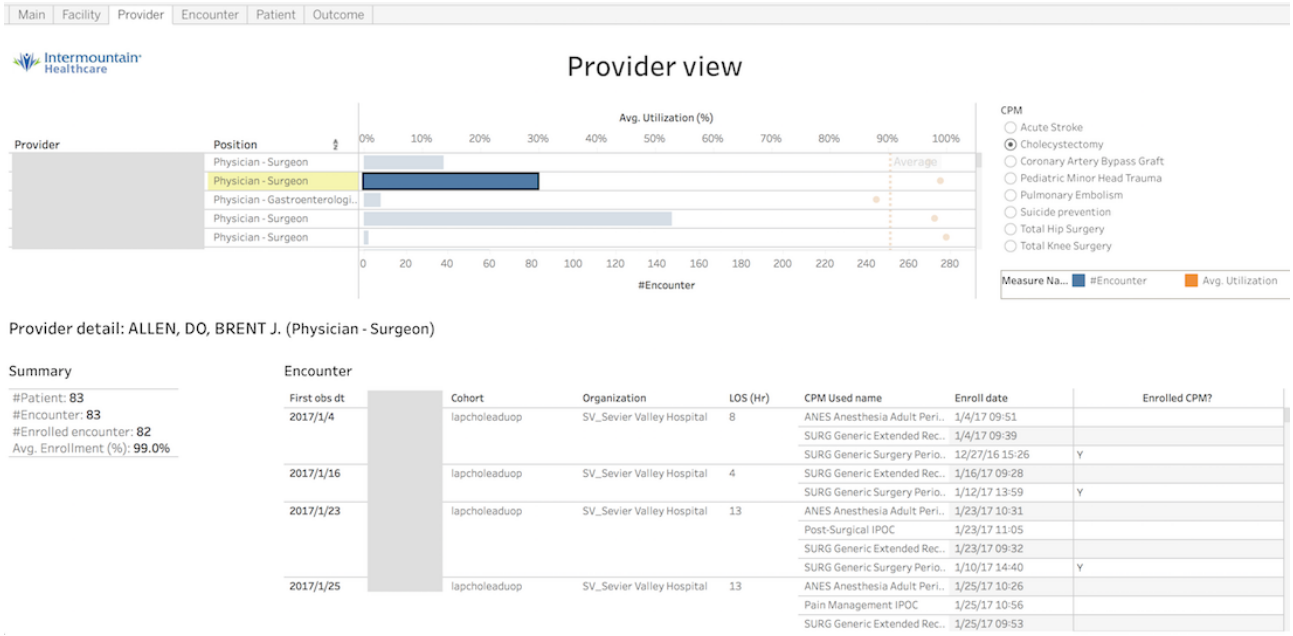


Figure 6. Dashboard usage pattern showing number of daily sessions and number of distinct users. The blue bar represents the number of users that accessed the dashboard and the orange line represents the number of distinct users.

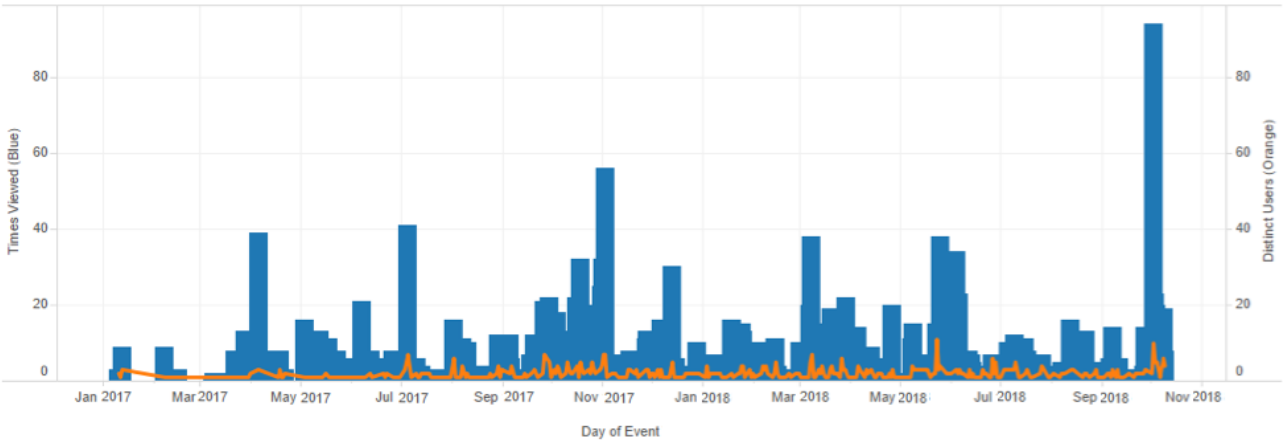


Table 2. Care process model (CPM) adherence revision history since dashboard implementation.

Clinical program	Number of revisions	Type of revision
Oncology	2	Amendment of adherence definition; new data source
Pediatrics	3	Amendment of adherence definition; new data source
Neuroscience	2	Amendment of adherence definition
Primary care	2	Amendment of adherence definition
Cardiovascular	2	Amendment of adherence definition
Musculoskeletal	1	Amendment of adherence definition
Surgical service	1	Amendment of adherence definition
Behavioral health	4	Amendment of adherence definition; new data source; new facility
Women and newborn	2	Amendment of adherence definition; data-quality improvement
Intensive medicine	4	Amendment of adherence definition; new CPM component

We analyzed user sessions of the dashboard using a Tableau system monitoring report, as represented in Figure 6. Test and administration users were excluded from the analysis. Overall, the usage pattern was stable with minor seasonal effects and spikes.

Data Provenance: Tracking Revisions of Care Process Model Adherence Definitions

Since implementation, we set up monthly meetings involving clinical programs, CPM implementation leadership, data analysts, and knowledge engineers. These meetings were meant to (1) monitor CPM adherence data, (2) review current adherence definitions and discuss room for improvement, and (3) discuss ways to encourage providers to use CPMs. During the pilot study period, a number of revisions to the definitions were made (see Table 2). Many of the revisions included amendments to the definitions, while some included the addition of new data sources to the EDW or resolving data-quality issues. Definitions were updated with revisions in the knowledge base and the links to the Alteryx pipelines were automatically renewed.

As seen in the bottom portion of Figure 4, the adherence rate steadily increased since implementation. We believe there are two practical reasons for this increase. One is that clinical programs have encouraged their clinicians to utilize CPMs, through CPOE training, physician education, etc. The other reason is that some clinical programs revised their adherence definitions. For example, the *oncology program* expanded CPM-designed order sets, which resulted in an increase of the numerator. The *intensive medicine program* revised the definitions of their target patients by narrowing them down to specific facilities, which resulted in a decrease of the denominator.

Discussion

Comparison With Prior Work

Several studies have used knowledge engineering tools for translation of CPG logics to implement them into practice for the purpose of knowledge standardization and computational automation [4-9]. Unlike in those studies, we used knowledge engineering tools for managing knowledge transformation within analytics processes. Compared with prior work, our original results included (1) validating the usefulness of knowledge management tools within analytics processes, (2) validating the feasibility of integrating knowledge management tools and an analytics framework, and (3) demonstrating the proposed approach using empirical clinical data from local EHR systems.

Limitations

Although the main contribution of this study is the use of knowledge management, we did not quantitatively analyze the improvement in the consistency of knowledge in transformation or the productivity of analytics pipelines. Rather, we demonstrated it qualitatively, including determining which functionalities of the knowledge base were able to support the consistency of CPM-related knowledge in the development and maintenance phases. We will conduct further analyses in the future as we collect additional data. This will include adding more CPMs with complex clinical settings and practices, including chronic conditions and comorbidities that span multiple encounters, locations, and providers.

In this study, we simplified the adherence definitions to include whether a designated CPM component is used or not used for a target patient, although there may be many variations. We will continue to add more detailed definitions of adherence, including how specific order items or content within CPM components are used. By doing so, we can investigate the mechanism of CPM utilization (ie, use of standard clinical guidelines) and how this can change patient care or clinical workflow.

Conclusions

This case study demonstrated that the proposed analytics framework could accommodate complicated knowledge management and data pipelining for CPM evaluation using a knowledge base, while maintaining computational efficiency. It is expected that the benefits of using a knowledge base will be more significant as we add complicated clinical guidelines into the analytics framework.

Authors' Contributions

JL developed the framework, built the dashboard, performed data analysis, and designed the study. NCH helped design the study, provided knowledge base consultation, collaborated with clinicians, and validated the feasibility of the architecture and the results of data analysis. The authors do not have any funding or financial support associated with this project.

Conflicts of Interest

None declared.

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Abbreviations

CDS: clinical decision support
CPG: clinical practice guideline
CPM: care process model
CPOE: computerized physician order entry
EDW: enterprise data warehouse
EHR: electronic health record
ICD-10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems
SQL: Structured Query Language

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Original Paper

Perspectives of Orthopedic Surgeons on the Clinical Use of Bioprinted Cartilage: Qualitative Study

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Abstract

Background: Over the past 60 years, no technique used for treating cartilage disorders has been completely successful. Bioprinting provides a highly anticipated, novel alternative solution to this problem. However, identifying barriers to this new technology is crucial in order to overcome them when bioprinting reaches the implementation stage. This kind of research has been declared essential because clinical efficacy and safety studies alone do not always lead to successful implementation.

Objective: This qualitative study aimed to explore the stance of orthopedic surgeons on the use of bioprinted cartilage grafts for cartilaginous lesions. The study sought to summarize and classify the barriers and facilitators of this technique and to identify the key factors for successful implementation of bioprinted cartilage in routine clinical practice.

Methods: A qualitative thematic analysis method was used to evaluate data obtained from semistructured interviews and from focus groups. Data were collected between June 2017 and February 2018. Interviews focused on the collection of expert opinions on bioprinted cartilage.

Results: The perceived barriers to the adoption of this technology were (1) awareness of a lack of information on the status and possibilities of this technology, (2) uncertainty regarding compliance with current health care regulations and policies, and (3) demands for clinical evidence. The facilitators were (1) lack of surgical alternatives, (2) the perception that research is the basis of the current health system, and (3) the hope of offering a better quality of life to patients.

Conclusions: The results of this study are preliminary in nature and cannot be generalized without a broader group of participants. However, the key factors identified provide a frame of reference to help understand the challenges of bioprinted cartilage and help facilitate the transition toward its clinical use. These findings will also provide information for use at multidisciplinary meetings in scientific societies; create bridges between researchers, orthopedic surgeons, and regulators; and open a debate on the funding of this technique and the business model that needs to be developed.

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KEYWORDS

bioprinting; orthopedic surgeons; qualitative research; cartilage; expert testimony

Introduction

Background

Traumatic cartilage lesions and arthritis are two of the most prevalent chronic diseases worldwide. According to data from the Global Burden of Disease Study [1], the number of people suffering from disorders caused by such diseases has increased from 140 million in 1990 to 242 million in 2013. Cartilage is a highly hydrated and specialized tissue providing a low-friction surface and resistance to erosion and diarthrodial joint load, allowing for effective articular movements. Unfortunately, the function and structure of cartilage are often damaged by trauma or ageing, adding to the fact that cartilage has a low capacity to self-heal.

Treatment of these diseases is still a challenge, and an effective solution remains to be found. These defects or lesions can last for years and can lead to arthritis [2]. Current repair techniques for cartilage lesions can be divided into two main groups: bone marrow stimulation and transplantation techniques [3,4].

The potential of regenerative medicine and tissue engineering is now recognized worldwide. These new techniques are responsible for "shifting the paradigm in health care from symptomatic treatment in the 20th century to curative treatment in the 21st century" [5-7]. Currently, three-dimensional (3D) printing is used for several applications in the medical field, for example, in the printing of patient-specific osteotomy guides. Other surgical specialties use 3D printing to study the disease pathology in a patient and practice with a 3D-printed model before surgery [8].

Bioprinting refers to the use of 3D printing to combine cells, growth factors, and biomaterials to create tissues and organs mimicking the features of their natural counterparts [9]. Bioprinting generally uses the extrusion-based method, which consists of the layer-by-layer deposition of cells through bio-ink, creating a structure similar to the natural tissue that can be used in tissue engineering and medicine. Bioprinting, which emerged in 2004 with the use of additive manufacturing, combines cells, gels, and several biocompatible elements in a single scaffold, which can replace injured issue with a complex structure that contains several components, including structural and cellular constituents. The external shape and internal architecture can be modeled based on clinical images. Ideally, cartilage creations aimed to fill cartilage defects should be similar to the extracellular matrix to keep cells in their place and preserve a space for the tissue that will grow there [10]. Levato et al published that although the most suitable types of cells for bioprinting are well known, more research needs to be conducted regarding zonal organization of cartilage [11]. There is also the need to study the complex mechanical behavior of cartilage under compression, as a result of sliding and shear [12].

However, barriers and challenges for implementing a new technology must not be underestimated, and it is essential that they are addressed in advance to guarantee the widespread application of bioprinting once it has reached its maturity. Research focused on this has been highlighted as crucial, since clinical efficiency and safety do not always lead to successful implementation. A recent editorial [13] encouraged implementation research at the beginning of development.

Objectives

This qualitative study aimed to explore the stance of orthopedic surgeons on the use of bioprinted cartilage grafts for cartilaginous lesions. We sought to classify the barriers and facilitators of this new technology and identify key factors that need to be considered for successfully implementation of bioprinted cartilage in routine clinical practice.

Methods

Study Design

The applied design consisted of a hybrid inductive and deductive thematic analysis, which allowed for interpreting gross data extracted from in-depth, semistructured interviews with orthopedic surgeons. This methodology was chosen to best reflect the perspective of interviewees.

Inclusion Criteria

For inclusion, orthopedic surgeons had to (1) have more than 5 years of experience in the field, (2) be currently working in a hospital, and (3) be actively performing surgery. No contacted participants were excluded.

Ethical Compliance

All participants were volunteers and agreed to participate in the interview or focus group. All were provided with the Ethics Research Committee document and signed the informed consent form. Authorization by the University Research Committee of University of Vic – Central of Catalonia (Spain) was granted (record number 28/2017).

All participants were informed in advance about the nature of the project, risks, advantages, and alternatives and their rights as research subjects. Measures were taken to ensure the data collected remained confidential; participants' safety and privacy were protected during and after the study.

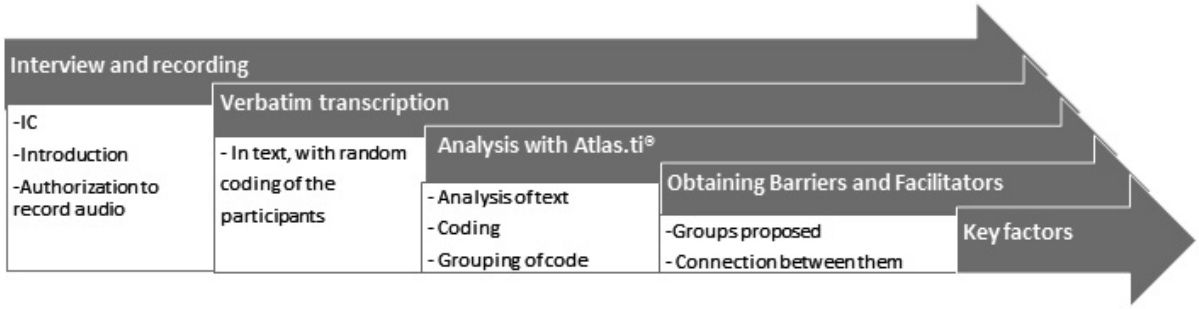
Participant Selection

All participants were contacted via email, signed the informed consent form, and authorized the recording of the interview. Participants consisted of 18 orthopedic surgeons, ages 35-67. The group included 15 men and 3 women. Six were heads of units and 12 were specialists.

Interview Structure for Data Generation

In 2001, Patton [14] created a list of 6 question types that could be formulated based on behavior or experience, opinion or values, feelings, knowledge, and perception; those questions aimed to obtain demographic or background data. Our guideline included the following themes: 3D printing, bioprinted cartilage, cell origin, current needs, rejection, expectations, and suggestions.

Figure 1. Flowchart of the interview process. IC: informed consent.



The interviews began by exploring the participants' knowledge regarding the medical applications of 3D printing and bioprinted cartilage. Questions on the use of stem cells were an important element of the interview, as much research is currently being conducted on mesenchymal cells obtained from umbilical cord tissue, adipose tissue, and bone marrow. The use of induced pluripotent stem (iPS) cells was also explored.

Questions related to current needs were aimed to corroborate the lack of efficiency in existing surgical techniques and the importance of research to find new practices. Questions on the expectations and reluctance of surgeons regarding the use of bioprinted cartilage sought to understand reasons for and against usage if the opportunity arose. The final section of the interview allowed for them to analyze the current situation and talk about future possibilities.

The interviews were always done with the same system (see the flowchart in Figure 1).

Recording the Interviews

The interviews and focus group discussions were conducted between June 2017 and February 2018. To protect the identity of all participants, each participant was codified to a randomly generated number that was then used in all study documentation. Their information was kept in a password-protected virtual folder of the university. Interviews were recorded digitally and transferred to the computer, where they were saved with the interviewee number and date of the recording. Informed consent forms were also stored at the university.

A single interview was conducted for each of the 18 participants, with the introduction providing context for the interview. The shortest and longest interviews were 25 minutes, 7 seconds and 43 minutes, 11 seconds, respectively. In total, we recorded 10 hours and 18 minutes of interviews.

Most interviews were conducted in the workplace of the interviewee, except for 4 participants who chose to have the interview in a coffee shop.

Recording the Focus Groups

Two focus groups were put together, and participant privacy was guaranteed in the same way as for the interviews. The first group consisted of 8 people, and the recording lasted 45 minutes, 23 seconds. The second group consisted of 5 people, and the recording lasted 74 minutes, 49 seconds.

Global Data Analysis

To ensure thematic integrity, this study used only data obtained from orthopedic surgeons. This analysis aimed to generate a list of relevant concepts that could be extrapolated and categorized. This leads to an inductive approach where topics have been identified by contextual information.

The integrity of the analysis was ensured by the directives established by Shenton [15], which included iterative questioning in data collection dialogues and the construction of an "audit trial," among others. The iterative process of grouping and subgrouping questions and answers led to a series of abstract constructions that were used to create a model to understand the context.

Inductive and Deductive Analysis of the Data

The analysis used mixed elements of inductive and deductive methods to interpret the gross data [16] and explore the attitude and experiences of the orthopedic surgeons interviewed. The flexibility of the approach helped analyze qualitative data from the interviews. The approach was useful in this study due to its large quantity of data.

Codification was reached through discussion and consent. Three researchers continued their discussion until consensus was reached regarding categorization and subcategorization of topics.

Braun and Clarke's [17] methodology, which identifies, analyzes, and describes reporting patterns, was used as a basis for thematic analysis. Due to the exploratory approach, this practical method was thought to fit the needs of the study perfectly. The process of thematic analysis is developed through 6 phases [18]. Phase 1 is becoming familiar with the data; Phase 2 is generating initial codes; Phase 3 is searching for themes and depuration of codes; Phase 4 is reviewing themes and finding those that are important either for reiteration or relevance to the research question; Phase 5 is defining and naming themes; and Phase 6 is producing the report.

Issues regarding trustworthiness were approached as described by Shenton [15], who provides a description of research, collection, and analysis design. The strategies used to ensure

honesty in the interviews include encouragement to be candid and the assurance of the voluntary nature of the interview and the right to withdraw at any chosen moment. Transferability was accomplished by providing contextual in-depth information on the study and the role of the researcher. The researcher guaranteed confidentiality [19]. For data analysis and figure generation, ATLAS.ti version 8.2.34 was used.

Results

The analysis of the interviews and focus groups is presented in Table 1 with the aim of describing the current stance of orthopedic surgeons on cartilage grafting. The Table 1 list is what ATLAS.ti denominates as a "frequency count." It represents the number of times these concepts were identified in the texts. Each point was given a code denoting different levels of classification and abstraction, which were later linked to the established categories.

Within the discursive pattern of clinicians, two argumentative groups were identified, which were classified as facilitators and barriers. From these two groups of codes, the most relevant were selected to establish the key factors that will provide a general perspective on the stance of orthopedic surgeons.

Barriers

The barriers consist of the arguments and opinions put forward by the orthopedic surgeons that reflect the perceived challenges or the lack of information with regards to adopting the technology. Figure 2 shows the links between several components generated by ATLAS.ti. It shows the groupings and connections between the codes.

Lack of Information

The first barrier to be identified, which was coded as "lack of information," had an impact on the following aspects.

Cell Therapy

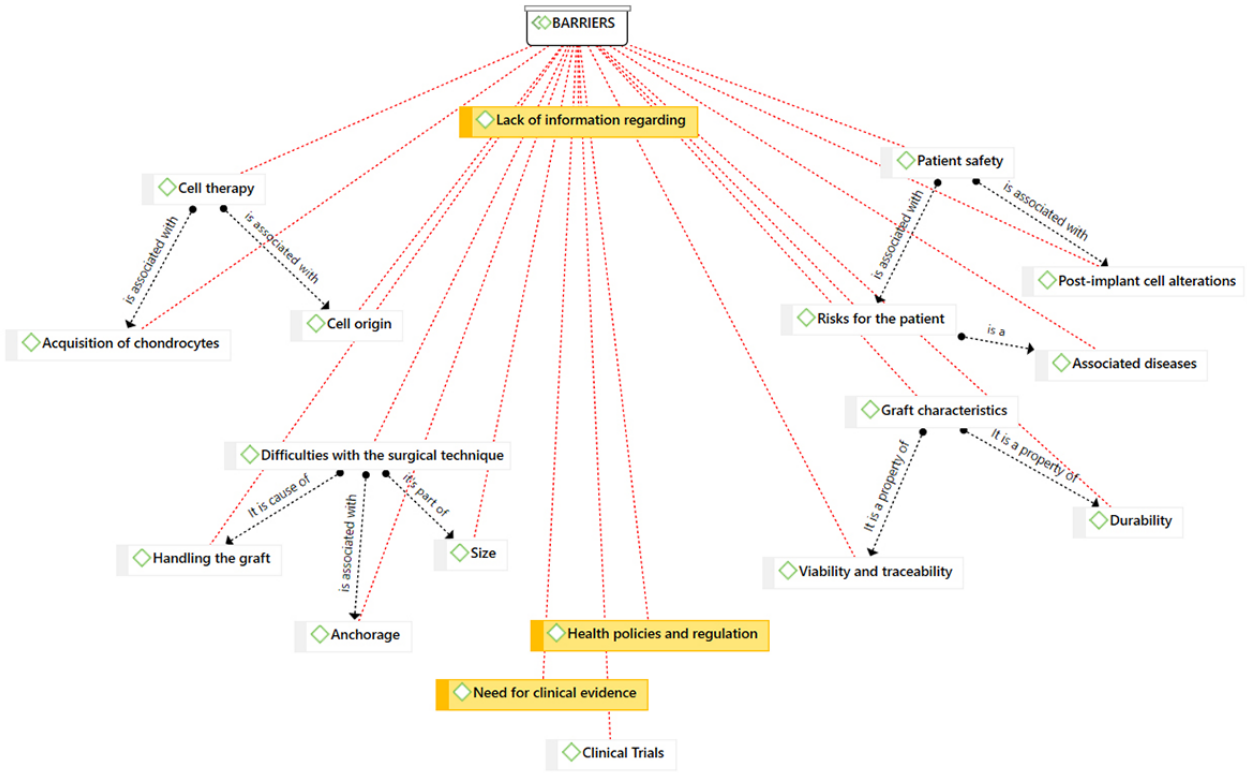
Orthopedic surgeons admitted their lack of knowledge regarding the acquisition and cell origin of chondrocytes. The participants showed great reluctance regarding the origin of the cells. Furthermore, if cell therapy implied the manipulation of unknown-origin cells, their stance was of total rejection. However, the level of acceptance was considerably higher if they knew the cells originated from the patient, even if they knew that they had to be manipulated (numbers in parentheses after quotes correspond to interviewee identity).

> *These constructors imply cell manipulation.* [#D 13]
>
> *We don't know if bone marrow or adipocyte is better, it seems like bone marrow could be useful, but it's not so clear.* [#23]

Table 1. Collected concepts and translation to numbers and codes.

Concepts	n
Need for clinical trials	34
Implantation techniques	28
Viability and traceability of the graft	27
Characteristics of the cartilaginous tissue	25
Small lesions (focal defects and osteochondritis)	24
Durability	14
Safety	14
It's the future	13
Costs	13
Cell therapies	12
Need to wait for clinical results	12
Cell types	12
Current techniques	11
Uncertainty regarding the future	10
Regulation	10
Stem cells	8
Technical difficulties in some articulations	8
Cell viability	8
Teratogenesis	7
Biocompatibility	7

Figure 2. Diagram of the links between several study components.



The better-known stem cell origins were mesenchymal, adipose, umbilical cord, and bone marrow as they are currently being used in other types of therapies.

> *I think mesenchymal cells are the way to go.* [#23]
>
> *There is a huge quantity of umbilical cord stored at the blood and tissue bank…Of umbilical cord cells, of adipose cells, cells of peripheral blood, from the skin; we can obtain cells from many places.* [#5181]

However, when trying to get the participants to discuss the topic in more detail, they appeared confused, especially when discussing iPS cells, which they were not aware of or did not fully understand.

> *The safety of iPS is not clear; there is an infinite number of complications—you can ask Yamanaka or Arnold Caplan.* [#23]

Patient Safety

All interviewees raised concerns regarding issues related to patient security, the graft, and associated diseases. With regards to the patient and the graft, the concerns focused on teratogenesis and the genetic predisposition of the cells in the graft, as well as the long-term behavior of the graft. Participants also showed a concern regarding graft implantation in patients with severe associated diseases, even though this fear does not have scientific merit.

> *Two types of safety: Safety for the patients' lives, of course, and safety in knowing that the graft will grow into cartilage, that you know for certain that this thing will create cartilage.* [#2341]
>
> *Three certainties: One, that these cells behave as we expect them to behave, like cartilaginous cells with no marginalization at all; two, that these cells are viable in the long term; and third, durability. If I am to implant cartilage, I'll want it to last.* [#204]

Difficulties With the Surgical Technique

Participants anticipated difficulties with regards to the shape of the graft, as they were unsure if the printing process could comply with the exact measurements provided by doctors. They also cited the place of injury as a possible difficulty.

> *Again, there's the problem of the three-dimensional structure of the cartilage.* [#2341]
>
> *Not all places are the same. For example, the knee: I think it's viable to insert it on the articular surface of the tibial plateau…Another thing is how it would anchor to the bone, right? But technically I don't see a difficulty here. Now then, it's another thing to insert it on the hip bone, between the cotyloid cavity and the femoral head.* [#6]

The lack of knowledge regarding the shape and manipulation of the graft, together with its characteristics led to a third kind of uncertainty, which we see as a barrier related to the surgical difficulties. Similarly, not being able to visualize the graft as part of cartilage that would adapt to the host left participants doubtful as to whether the graft would be able to anchor itself and stay in place.

> *Ideally, this graft would reproduce the defect exactly.* [#D 13]
>
> *I would use it now, for young people with osteochondritis of the talus or the knee, where you have a two- or three-millimeter.* [#5690]

The size is a factor with the cartilage will it stay in place? [#2901]

How will you fix it there? How? How does it stay there? [#2341]

Another thing I worry about is that this tissue that we insert stays anchored. [#6]

Graft Characteristics

Regarding graft characteristics, the main factors mentioned were viability, durability, integration with the host, and mechanical characteristics of cartilage. For example, participants doubted that the graft would become functional cartilage or develop chondrogenic hypertrophy, which is what happens with current techniques such as the matrix-induced autologous chondrocyte implantation (MACI) procedure.

Needs to have all the characteristics of the original cartilage. [#6]

We need proof that long term there will still be cartilage and not fibrous tissue. [#2901]

Needs to behave biologically like the host's cartilage. We're talking about live cells, right? [#204]

Orthopedic surgeons also questioned the viability and durability of the graft. They were unaware that the aim of the graft is to become integrated to the native cartilage and that the graft's behavior would mimic the patient's native cartilage.

How long will it last? [#6099]

And the viability of these cells, and their possible side effects. [#1753]

Then, what I understand that these cells are viable themselves, it's not that they need to be invaded by the periphery, but that they are viable and live by themselves. [#5181]

Health Policies and Regulation

Bioprinting, like any other product of tissue engineering will have to comply with the current Good Manufacturing Practice regulations enforced by the Food and Drug Administration and/or the European Medicines Agency.

The clinicians stated that they felt there would be a timeframe in which health policies will not be able to provide an effective answer to their questions, which would be problematic for all practitioners using them.

Who will guarantee the manufacturing process until its arrival in the operating room? [#2083]

It's a legal aspect within the framework of drugs, implants, of techniques. We need to see this technique, legally the European guidelines on the use of tissues and cells. [#4821]

Need for Clinical Evidence

As with any scientific innovation, orthopedic surgeons demanded hard clinical evidence be available before they would use bioprinted cartilage. In most cases, this demand materializes as clinical trials and independent clinical research. However, this may be a barrier since clinical trials are not scheduled to take place in the imminent future.

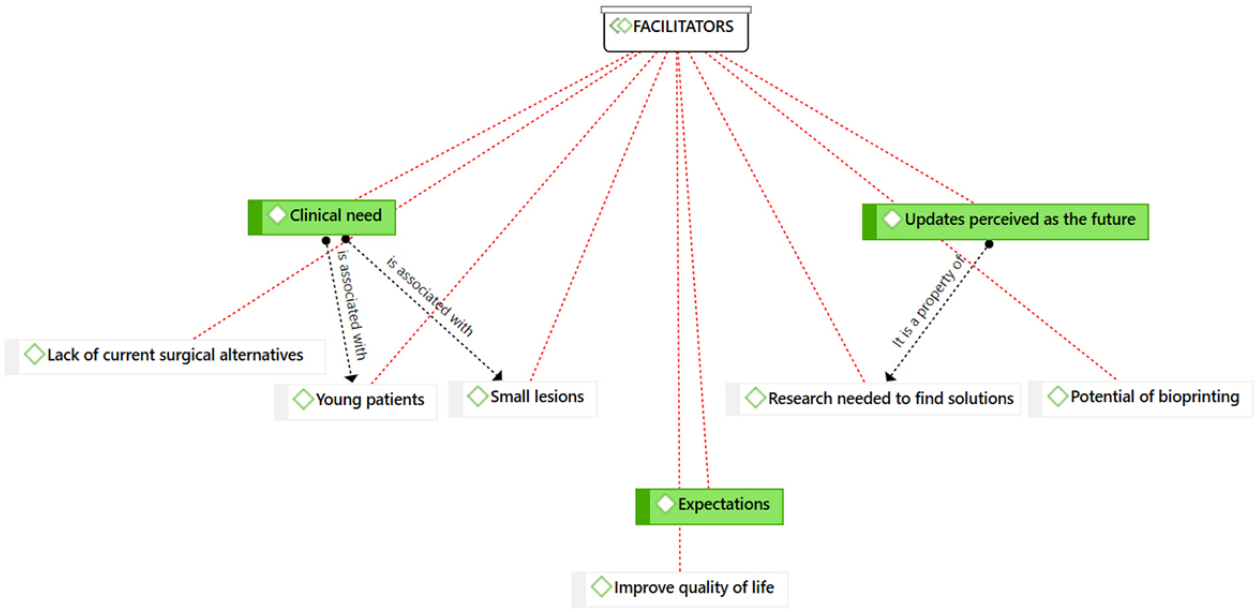
I want more evidence, that is to say, scientific studies that support their efficacy; independent scientific studies. [#2901]

Basically, that there are appropriate clinical trials. [#204]

Facilitators

Facilitators include all entities that encouraged orthopedic surgeons to be more open to new surgical possibilities to improve the lives of patients. In this group, three themes were identified that were essential to the clinicians to catalyze implementation of cartilage grafts (Figure 3).

Figure 3. Diagram of the codes obtained as facilitators.



Clinical Need

Given that current surgical techniques are not able to provide a definitive solution, orthopedic surgeons are open to innovative techniques that can fill a surgical need. However, as they were not aware of the possibilities bioprinting would bring to field, most of the interviewees stated that research into finding new solutions was critical. Several arguments emphasize this need:

> *Especially as we don't have anything that works for these patients right now…if it lasts, say, 40 years, I'd say it's marvelous.* [#2901]
>
> *Nowadays this is something that doesn't have any solution, so of all the things I've heard about maybe this very innovative technique works since no other offer is effective.* [#2083]
>
> *If this works, it's very promising.* [#23]

In this way, the main facilitator identified was the lack of current alternatives, as was to be expected.

Taking this into consideration, orthopedic surgeons, despite the barriers mentioned, are open to this new technology.

We also identified the type of patients that surgeons would be willing to consider treating with bioprinted cartilage implementations. Younger patients were perceived to be better candidates, as they are susceptible to high-risk sports injuries, which often become chronic and difficult to solve in the long term.

> *That is, with young people with partial cartilage lesions, I see it very clearly; with bigger lesions, I am less optimistic* [#23]
>
> *I see it as a solution to young people's pathologies, athletes, that have damage due to chondral lesions and which can happen at any age, but they hinder young people's activity.* [#6]

Additionally, we identified the specific characteristic within this population that significantly improved the acceptance of bioprinting technology, namely the size of the lesion. Orthopedic surgeons were distinctly in favor of using grafts in small lesions (1 or 2 cm at most), in order to accelerate integration with the host. However, they did not show the same certainty with larger lesions.

> *I can see it being used with partial cartilage lesions.* [#2901]
>
> *If the lesions are small, and the joints are not loaded.* [#6356]

Perception of Bioprinting as a Future Treatment

Clinicians agreed that medicine depends on constant research to find solutions to unresolved problems. In other words, they perceived scientific research as a positive entity. Another argument identified the perception of bioprinting as a future solution, with participants being optimistic about graft bioprinting.

> *It is a future solution to important problems for orthopedic surgeons.* [#6346]
>
> *When we talk about the medicine of the future, which is not so far away now, to be able to reproduce the tissue of the patient.* [#204]

Expectations

Faced with an unresolved clinical need and the perception that bioprinting could be a solution in the future, orthopedic surgeons expect to hear about the benefits of this technique. Biocompatibility is not only a favorable factor but is essential to surgical practice. Many current techniques already have these characteristics, and therefore clinicians demand that future solutions meet or exceed these standards.

> *To find a three-dimensional structure that holds the cells, that holds what they must have, and that this three-dimensional structure is biocompatible, degradable, and easy to manipulate.* [#2341]

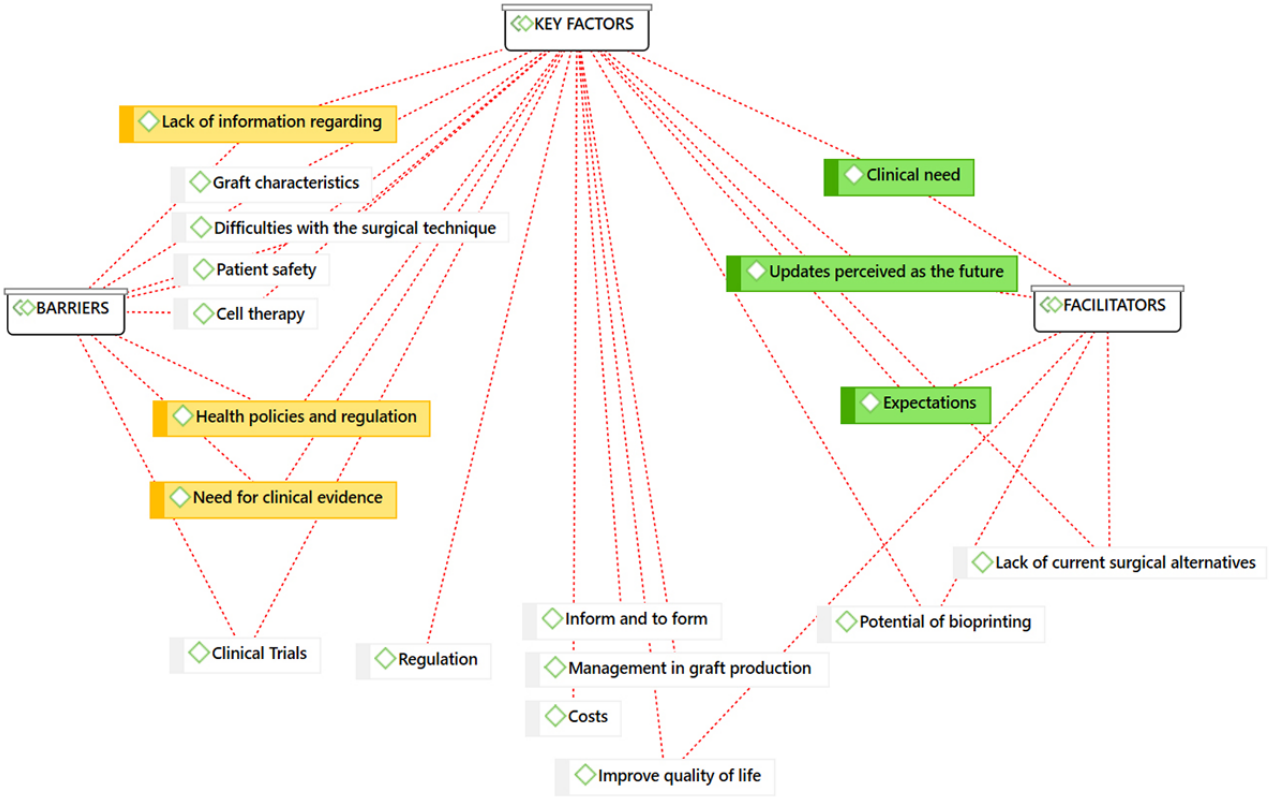
At the same time, participants emphasized that this technique had the ability to improve patients' quality of life significantly, either by alleviating their pain, improving their mobility, or by preventing lesions from developing into arthritis in younger patients. If these were to be accomplished with the new technology, surgeons expect the need for total prosthesis to diminish significantly.

Key Factors

Where barriers and facilitators meet, key factors emerge. Key factors function as the theoretical framework for the perspectives of orthopedic surgeons on bioprinted cartilage. In general, their belief is grounded on clinical need and expectations for effective solutions. Despite this, a reluctance to adopt the technology was detected among the interviewees, with reasons ranging from (conscious and unconscious) lack of information to clinical demands. Figure 4 offers a complex concept map, which is the first attempt to represent the stance of clinicians with an aim to help direct future research.

Apart from the elements present in both barriers and facilitators, two more factors were considered key factors and coded as such. They included costs and the identity of companies that would manage the product. It is impossible to address these uncertainties now; hence, they could not be labeled as either facilitators or barriers, only as relevant factors that need to be addressed.

Figure 4. Where barriers and facilitators meet, key factors emerge.



Discussion

Principal Considerations

As has been proven in a previous bibliographical review [20,21], the research and acquisition of bioprinted cartilage is still in a premature state. Other researchers have already highlighted that despite the growing number of solutions coming from tissue engineering that are being transitioned to clinical use, the success of considerably sized scaffoldings with personalized geometries is still a significant challenge. Therapies based on mesenchymal stem cells (MSC), despite having been successful in renovating the cartilage and alleviating pain, have not provided enough evidence on original hyaline cartilage restoration that would improve osteoarthritis in the long term.

The goal of this research is to understand how trauma surgeons perceive this situation and define main barriers and facilitators to develop strategies favoring the future implementation of bioprinted cartilage. The data collected and organized into either barriers or facilitators as detailed in our results will help future discussions focus on the most fundamental aspects of this technology.

One of the main needs identified is improving communication with orthopedic surgeons, particularly regarding 3D printing. The lack of knowledge was evident in two ways: conscious and unconscious. Of the two, the latter will be more difficult to address, as it requires further research to better identify the knowledge gaps. When conscious of their lack of knowledge, clinicians have no problem asking questions. However, the lack of knowledge was unconsciously displayed when assumptions were made regarding terms, techniques, or solutions leading to misinterpretation and confusion. To lead and conduct successful translational research, it is necessary to study and solve problems transversally. An unconscious deficit of knowledge was driven by reading publications or listening to conversations that dealt with cell therapy in a generic and unscientific manner. Thus, the lack of background knowledge was significant, resulting in misperceptions and unfounded reluctance in adopting the technology.

Furthermore, we discovered a lack of knowledge on current applications of 3D printing in medicine, with many of the interviewees having no knowledge of this facet. To address this issue, organization of specific multidisciplinary seminars to discuss the current applications of 3D printing in medicine should be undertaken. This could contribute to orthopedic surgeons becoming more proactive in the implementation of bioprinted cartilage grafts.

In parallel, efforts should be made to help promote an understanding of the fundamentals of cell therapy. This issue was identified as an unconscious knowledge gap. This was also observed in the case of gene therapy for cancer treatment [22]; participants were aware of the treatment but had no deep understanding of it. This was evident from the fact that they used cartilaginous cells provided by laboratories [23] but were reluctant to consider using bioprinted cartilage made of unknown-origin cells, or other cell therapies.

These findings highlight the evident need to develop formative strategies. These strategies would need to be based initially on the fundamentals of cell therapy, escalating toward the future possibilities this technology could offer. Thus, new channels of communication could be created in the medical community.

While it is important for surgeons to have basic knowledge regarding the future applications of cartilage grafting, it is equally important for researchers to recognize and acknowledge the practical needs of clinicians and strive to meet their expectations. Some of the factors that caused the orthopedic surgeons concern included issues such as viability, traceability, and durability. Tissue and skin banks for allografts have established their reliability by ensuring traceability and establishing manipulation standards. Orthopedic surgeons now demand the same degree of reliability from bioprinted cartilage [24].

In addition to the characteristics of the graft, this study has identified important factors that would help direct research in the initial stages. First, by focusing research on specific lesions, such as 1 or 2 cm lesions found in the knee or the ankle, clinicians would have access to a site that is easier to access and operate on. Second, younger patients should be established as the primary recipients of the graft, with the aim of avoiding long-term joint deterioration.

Another issue detected during this study was concern regarding the business model for producing bioprinted grafts. Orthopedic surgeons feared it may not align with current production models. This situation, coded as a key factor, is one of the main issues identified as a barrier in the implementation of this technique.

By analyzing the stance of orthopedic surgeons, at least two possible lines of action can be suggested. If production was handled by private companies, the main demands from surgeons would be for the pieces to be individually customized, with a short production-delivery timeframe. In this instance, the biosafety and tissue traceability could be controlled. Another issue that would need addressing is the cost of the graft. This model would also need to address the patent issue and comply with the ethical requirements and, more importantly, with the current regulations and legislation. The Spanish company Regemat is an example of this. They use Hoffa's fat pad and chondrocytes as described by Lopez Ruiz [25] and induced differentiation of autologous MSC to develop and commercialize cartilage.

Another possibility would be to establish public centers, possibly in a public-private collaboration model, that would have the human and technical resources necessary to produce their own 3D bioprinted pieces. The foundations for such a model already exist in hospitals where 3D printers are already in use. As mentioned above, these hospitals have trained staff who are already competent in the use of 3D printers for a wide variety of uses ranging from the printing of fractures, surgical planning, and creating customized guides for the patient. This system, which would be integrated into hospitals, would allow for constant communication between the medical and technical teams. The hospital as a meeting point ensures that as the technology becomes widely used, more potential applications will be detected, thereby improving the learning curve for both sides—the medical team exploring new and better applications for the technique and the engineering team designing context-specific solutions. This solution would mean bioprinting is the next logical step, born from the growing needs of all medical specialties.

Cell therapy has stirred a debate within the scientific community. Cell therapy can be individually customized, is expensive and innovative, and might help bring a change in health regulation and health care policies. Our research has shown that the demands for scientific evidence for bioprinting will be more stringent than what was required for previous techniques. This is the case of platelet-rich plasma, which has been used by doctors for more than 20 years despite the lack of evidence for its effectiveness [26], with information on clinical trial outcomes having only recently been published [27].

Communication, not only among medical professionals, but among policy makers and health care authorities, is essential to start a debate to define the level and form of evidence required. In this manner, one of the main barriers highlighted by orthopedic surgeons, namely the need for clinical trials, could be surmounted.

Limitations

This study needs to be interpreted in the context of its limitations. There are inherent limitations to the number of participants and the number of focus groups. Only the data extracted from the orthopedic surgeons' interactions is legitimate; however, it is their opinion that focuses the research in this context.

Conclusions

These study results are preliminary in nature and therefore they cannot be generalized without a broader demographic. However, the preliminary literature review confirms the lack of research on clinical applications of bioprinted cartilage. Orthopedic surgeons are willing to accept that this new technology has the potential to solve a clinical need and to recognize bioprinting as the technology of the future. However, clear scientific evidence is required before bioprinted cartilage can be used and a debate regarding the optimal business model will be necessary.

We also believe it is necessary to develop a communication strategy and a forum for multidisciplinary discussion to discuss the need for regulation and define the necessary scientific evidence that is required to promote the acceptance of grafts as a viable therapeutic option. From our perspective, this study serves as a first step in the clinical translation of bioprinting cartilage research.

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Authors' Contributions

The first author completed the field work and the analysis of the data obtained. The other authors contributed to the content, writing, and editing of the manuscript. All the authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

iPS: induced pluripotent stem
MSC: mesenchymal stem cells

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Original Paper

The Impact of Aging and Hand Dominance on the Passive Wrist Stiffness of Squash Players: Pilot Study

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Abstract

Background: Passive joint stiffness can influence the risk of injury and the ability to participate in sports and activities of daily living. However, little is known about how passive joint stiffness changes over time with intensive repetitive exercise, particularly when performing unilateral activities using the dominant upper limb.

Objective: This study aimed to investigate the difference in passive wrist quasi-stiffness between the dominant and nondominant upper limb of competitive squash players, compare these results with a previous study on young unskilled subjects, and explore the impact of aging on wrist stiffness.

Methods: A total of 7 healthy, right-side dominant male competitive squash players were recruited and examined using the Massachusetts Institute of Technology Wrist-Robot. Subjects were aged between 24 and 72 years (mean 43.7, SD 16.57) and had a mean of 20.6 years of squash playing experience (range 10-53 years, SD 13.85). Torque and displacement data were processed and applied to 2 different estimation methods, the fitting ellipse and the multiple regression method, to obtain wrist stiffness magnitude and orientation.

Results: Young squash players (mean 30.75, SD 8.06 years) demonstrated a stiffer dominant wrist, with an average ratio of 1.51, compared with an average ratio of 1.18 in young unskilled subjects. The older squash players (mean 64.67, SD 6.35 years) revealed an average ratio of 0.86 (ie, the nondominant wrist was stiffer than the dominant wrist). There was a statistically significant difference between the magnitude of passive quasi-stiffness between the dominant and nondominant wrist of the young and older squash player groups (P=.004).

Conclusions: Findings from this pilot study are novel and contribute to our understanding of the likely long-term effect of highly intensive, unilateral sports on wrist quasi-stiffness and the aging process: adults who participate in repetitive sporting exercise may experience greater joint quasi-stiffness when they are younger than 45 years and more flexibility when they are older than 60 years.

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KEYWORDS

wrist; exercise; aging

Introduction

Background

Joint stiffness is a biomechanical feature of human anatomy that is both essential and potentially detrimental to participation in sports, leisure activities such as music, and activities of daily living. Reduced joint stiffness may increase the risk of injury because of poor stabilization of joints and an inability to maintain joint postures [1,2]. Increased joint stiffness has been associated with reduced joint range of motion (ROM) and inflexibility, such as during the aging process [3,4], following surgical intervention [5], or because of abnormal muscle tone secondary to neurological injury or disease [6,7].which can cause both injury and functional limitations.

The term joint stiffness has various definitions depending on the discipline and nature of the research. In physical education, sports medicine, and allied health disciplines, joint stiffness is more commonly referred to as the flexibility, or ROM, of a joint or group of joints [8,9]. In the biomechanical literature, joint stiffness is referred to as the ratio of the change in joint torque to the change in joint angle [10]. Regardless of the definition of the term, joint stiffness is understood to be multidimensional, made up of (1) the elastic properties of noncontractile tissue (tendons, ligaments, and the joint capsule), (2) the elastic properties of intrinsic muscle cross-bridges, and (3) the reflex action of a muscle following change in length [11]. The different methods of assessment aim to distinguish between these components of joint stiffness, altering both the primary tissue structure under evaluation and the magnitude of joint stiffness reported. This study focuses on the measurement of passive joint quasi-stiffness, defined as the rate of change of resistance torque during a slow angular displacement of the joint, in the absence of muscle contraction [1,12].

Extensive research has been conducted on passive joint quasi-stiffness of the lower limb and the impact on gait [6,7], with less research focusing on the upper limb and the equally important impact on activities of daily living, leisure activities, and sports. Of the joints within the upper limb, the neuromuscular control of the wrist has been identified as being dominated by joint stiffness [13,14]. It is, therefore, of paramount importance that we develop our understanding of the properties and variables of passive wrist stiffness in different populations to better comprehend how stiffness impacts the planning and coordination of wrist movements by the neuromuscular system during functional and sporting activities.

Within the literature on wrist joint stiffness, there is large variability in the magnitude and orientation of passive joint quasi-stiffness, likely because of differences in study methodology (alignment and orientation of the starting position, ROM, number of degrees of freedom assessed, and the method of data analysis) as well as subject characteristics (including sex, hand dominance, participation in sporting and leisure activities, and age). Previous studies have investigated the impact of study methodology [15-17], sex [14-17], and hand dominance [17]. A recent study [17] demonstrated that there was increased passive wrist quasi-stiffness in the dominant upper limb compared with the nondominant upper limb of healthy young men and women. This finding suggests that there are biomechanical factors associated with increased use of the dominant upper limb that influence the passive stiffness of the wrist. To date, the impact of both participation in a highly unilateral sporting activity and aging on passive wrist quasi-stiffness has not been investigated, despite the vital function of the wrist in common sporting activities such as tennis, bowling, golf, badminton, and squash.

Objectives

Squash players were chosen as the target population for this study because of the highly repetitive, intensive, unilateral nature of the sport and for the vital role the wrist and forearm play in generating high racquet head speeds during the forehand and backhand stroke actions [18,19]. Research has demonstrated that exercise causes adaptations in the properties of muscle tissue such as muscle fiber size, type, and muscle cross-sectional area [20,21], which have been associated with changes in passive joint quasi-stiffness [1,22]. As increased mechanical stimulation of the wrist likely leads to adaptation in muscle tissue during competitive squash play, we hypothesize that (1) squash players will have a larger difference in wrist quasi-stiffness between the dominant (playing side) and nondominant upper limb, regardless of age, and (2) the orientation of wrist stiffness would be equivalent for all study participants. The purpose of this study was to further develop our understanding of joint stiffness by determining the impact of intensive unilateral exercise, in this case playing competitive squash, and the process of aging on wrist properties.

Methods

Recruitment

Volunteer competitive squash players were recruited with a study flyer posted on a local Web-based squash association newsletter. The inclusion criteria were as follows: (1) male, (2) aged 18 years or older, (3) no prior wrist surgery or injury, (4) English-speaking, and (5) a minimum of 5 years of playing experience. Only male subjects were recruited to reduce the risk of data variability, as previous work had demonstrated a difference in the magnitude and direction of wrist quasi-stiffness between the male and female sex [14-17]. Subjects were asked not to participate in any upper limb exercise in the 24 hours preceding their evaluation session to decrease the risk of reduced wrist ROM because of muscle swelling [11] and muscle thixotropic behavior [23] associated with eccentric wrist exercise. To ensure the study participants were competitive players, their squash skill level was recorded using the United States Squash Rating Algorithm (USSRA) [24]. The USSRA calculates a measure of each player's squash skill and ability using the data collected from all matches played in the last 45 months. Further details regarding the calculation of the algorithm can be found elsewhere [24].

Table 1. Subject demographics and age group allocation.

Group allocation	Young players				Older players		
	Subject 3	Subject 5	Subject 6	Subject 7	Subject 1	Subject 2	Subject 4
Age (years)[a]	31	42	26	24	61	72	61
Years of playing experience	20	25	12	10	37	53	20
Squash sessions/week (n)	5	2	4	4	3	3	4
US squash rating criteria by skill level	5.5	5	4.5	5.12	4.47	3	3.5
Hours post upper limb exercise	24	>48	>24	>48	24	24	>48

[a]Subject demographics were collected by interview before commencing the experiment.

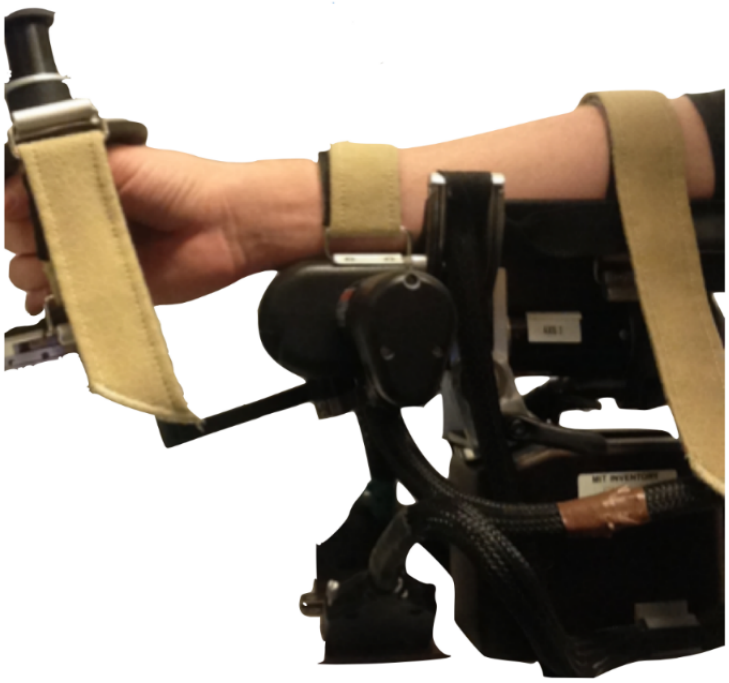
A total of 7 healthy male competitive squash players aged between 24 and 72 years (mean 43.7, SD 16.57) volunteered to participate (Table 1). All 7 subjects identified as right hand-dominant for squash play, with 1 subject (subject 3 in Table 1) identifying as ambidextrous (left-hand dominant for activities of daily living, but right-hand dominant during squash play). The sample subject group had a mean of 20.6 years of squash playing experience (range 10-53 years, SD 13.85), a USRSL of 4.2 (range 3-5.5, SD 0.94—possible ranking ranges from 2 to 6, with 6 being the highest ranking), and reported playing between 2 and 5 times per week (median=4, mode=4). A total of 4 subjects were enrolled in the young squash group (mean age 30.75, SD 8.06 years), and 3 subjects were enrolled in the older squash group (mean age 64.67, SD 6.35 years). The Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects approved the study, with all volunteers providing written informed consent before participation.

Data from 7 right-hand dominant males (mean age 28.57, SD 12.11, range 19-55 years) reported in the study by Durand et al [17] (using the same experimental set-up) were used to compare wrist quasi-stiffness of unskilled subjects with the subjects participating in this trial who participate in regular, intensive, unilateral upper limb activity.

Evaluation Method: Massachusetts Institute of Technology Wrist-Robot

Wrist quasi-stiffness was evaluated using a 3 degree of freedom Wrist Robot (Figure 1, InMotion 3.0, Interactive Motion Technologies, Watertown, MA, USA), described elsewhere [25]. The robot forearm support positions the wrist joint so it aligns with the rotation axes of the robot. The Wrist Robot generates torques and simultaneously records the angular displacement produced into wrist flexion-extension (FE) and radial-ulnar deviation (RUD) [25]. A strap was used to lock forearm pronation-supination of the robot to eliminate confounding forearm movements during the trial. A gravity compensator was included in the robotic set-up to reduce the influence of gravity on the data collected. The gravity compensator was constant for each direction and equivalent to the sum of an average hand mass and the robot handle mass.

Figure 1. Massachusetts Institute of Technology Wrist-Robot and experimental forearm, wrist, and hand position (excluding finger strap).



Experimental Procedure

Subject demographics were collected in the form of an interview (Table 1). The experiment commenced randomly with the left or right upper limb (using the MATLAB randi X function, MathWorks, Natick, 2016, MA) [26]. The reference position for the upper limb was in keeping with the set-up of Durand et al [17] and Drake and Charles [14] to allow accurate analysis and comparison of study results; the elbow was flexed to 30°, the third metacarpal was aligned with the forearm, and the wrist was positioned in 0° wrist extension and 7° of ulnar deviation (UD). Although previous studies have used an almost neutral RUD wrist position (0° along wrist UD), this study and Durand et al [17] deliberately selected 7° of wrist UD as this initial wrist position was more comfortable, allowing subjects to remain in a passive muscle state and avoid unwanted muscle activity. The wrist and forearm position was verified with goniometry [27]. Hand grip remained relaxed and the forearm in a neutral position by wrapping a strap over the fingers, securing the hand to the Wrist Robot handle. Subjects were instructed to remain relaxed throughout the experiment, which was monitored by palpating the muscle groups responsible for wrist FE-RUD and checking the data collected between trials. The robot applied a torque of up to 1.95 Nm to reach a predefined target (from 0-20° along each direction defined through the 2D FE-RUD space) at a predefined speed (between 0.1 and 0.2 rad/s to inhibit muscle reflexes). Data were collected at a rate of 200 Hz. Each trial consisted of 36 movements (inbound and outbound movements) along 12 equally spaced directions through the space defined by FE-RUD. The movements started in pure wrist extension for the right upper limb (pure flexion for the left side) and proceeded counterclockwise, with each of the 12 targets reached once. This cycle was repeated 3 times during each trial to reduce the influence of any artifacts (reflex or small muscle contraction). A trial was conducted on the left and right side before repeating the sequence a second time. Out of the 2 trials for each subject, the trial with the least data noise (unwanted muscle activity) on the left and right wrist was used in the data analysis.

Statistical Analysis

Torque and displacement data were processed using a customized program in MATLAB 2016b [26]. Data collected before commencing each trial of 36 movements were removed, knowing the time to complete each movement, the number of movements, and the acquisition frequency. The processed data were then applied to 2 different estimation methods, the fitting ellipse [16] and the multiple regression (MR) method [28], to obtain wrist stiffness magnitude and orientation among the 4 parameters commonly used (listed below) to characterize a stiffness ellipse [16,28]:

- Size: stiffness magnitude (ellipse surface [Nm/ rad]^2)
- Orientation: stiffness orientation (angle in degrees between radial deviation (RD) direction and ellipse major axis direction toward RD, counterclockwise angles are considered positive)
- Shape: the ratio of the major axis of the stiffness ellipse to the minor axis
- Equilibrium position: the offset of the ellipse center corresponding to the FE and RUD offset angles.

The fitting ellipse method (Figure 2) calculates the torque and angular displacement parallel and perpendicular to the direction of each of the 36 perturbations. Stiffness was then estimated (separately for outbound and inbound movements) by running a linear regression of the torque and the angle parallel to the perturbation direction. The mean stiffness values for the estimates of each of the outbound and inbound 36 perturbation directions were then used to fit a stiffness ellipse. Previous research indicates that the major weakness of the fitting ellipse approach is that it only considers the components of torque and angle parallel to the perturbation direction and does not include stiffness effects perpendicular to the perturbation direction. Of note, the fitting ellipse method allows for asymmetry of the elastic field with respect to the neutral position and is susceptible to data noise [17]. Although we fitted the stiffness values with a least square condition to keep consistent ellipse shapes, an excessive stiffness value along 1 direction will tend to stretch the ellipse and increase the size of the ellipse.

The MR method (Figure 2) determines the 4 elements of the stiffness matrix by multiple linear regression (using MATLAB's regress function [26]). Separate stiffness matrices were estimated for the inbound, outbound, and the composite of both movements. Each matrix was separated into the symmetric and asymmetric parts. Only the symmetric part of each stiffness matrix was displayed as a stiffness ellipse [28].

A 1-sample Kolmogorov-Smirnov test was used to confirm the normal distribution of the data. A 1-way analysis of variance was calculated to determine the statistical difference between the wrist quasi-stiffness of the left and the right arm in the young and older squash player groups and to compare the magnitude of the wrist quasi-stiffness and orientation of the 4 young squash players with the results of the 7 young right-handed dominant, unskilled male subjects [17]. The level of statistical significance for comparisons was set to $P<.05$. A Pearson r calculation was performed to determine the correlation between the magnitude of passive wrist quasi-stiffness in both the young and older squash groups and (1) age, (2) years of squash play, and (3) frequency of squash play.

Figure 2. (a) The fitting ellipse method, where variable τ represents torque, 'j' corresponds to 1 of the 12 directions considered through the FE-RUD plane, || means parallel to the wrist movement direction, and ⊥ means perpendicular to this direction. R_j is the rotation matrix for the jth direction, θ represents angular displacement, and 'K' represents quasi-stiffness [16]. (b) The MR method, where variable 'K' represents quasi-stiffness, 'FE' refers to flexion-extension, 'RUD' refers to radial-ulnar deviation wrist joint movement planes, τ represents torque, ∂ means partial derivative, θ represents angular displacement, 's' denotes the symmetric, 'a' represents the antisymmetric components of each stiffness matrix, and 'T' represents the transpose operation [28].

(a)

$$\begin{bmatrix}\tau_{j,\parallel}\\ \tau_{j,\perp}\end{bmatrix} = R_j \begin{bmatrix}\tau_{FE}\\ \tau_{RUD}\end{bmatrix}$$

$$\begin{bmatrix}\theta_{j,\parallel}\\ \theta_{j,\perp}\end{bmatrix} = R_j \begin{bmatrix}\theta_{FE}\\ \theta_{RUD}\end{bmatrix}$$

$$K_j = regress(\tau_{j,\parallel}, \theta_{j,\parallel})$$

(b)

$$K = \begin{bmatrix}K_{FE,FE} & K_{FE,RUD}\\ K_{RUD,FE} & K_{RUD,RUD}\end{bmatrix} = \begin{bmatrix}\frac{\partial \tau_{FE}}{\partial \theta_{FE}} & \frac{\partial \tau_{FE}}{\partial \theta_{RUD}}\\ \frac{\partial \tau_{RUD}}{\partial \theta_{FE}} & \frac{\partial \tau_{RUD}}{\partial \theta_{RUD}}\end{bmatrix}$$

$$\begin{cases}[K_{FE,FE}, K_{FE,RUD}] = regress(\tau_{FE}, [\theta_{FE}, \theta_{RUD}])\\ [K_{RUD,FE}, K_{RUD,RUD}] = regress(\tau_{RUD}, [\theta_{FE}, \theta_{RUD}])\end{cases}$$

$$K_s = \frac{K + K^T}{2} \text{ and } K_a = \frac{K\text{-}K^T}{2},\ K = K_s + K_a$$

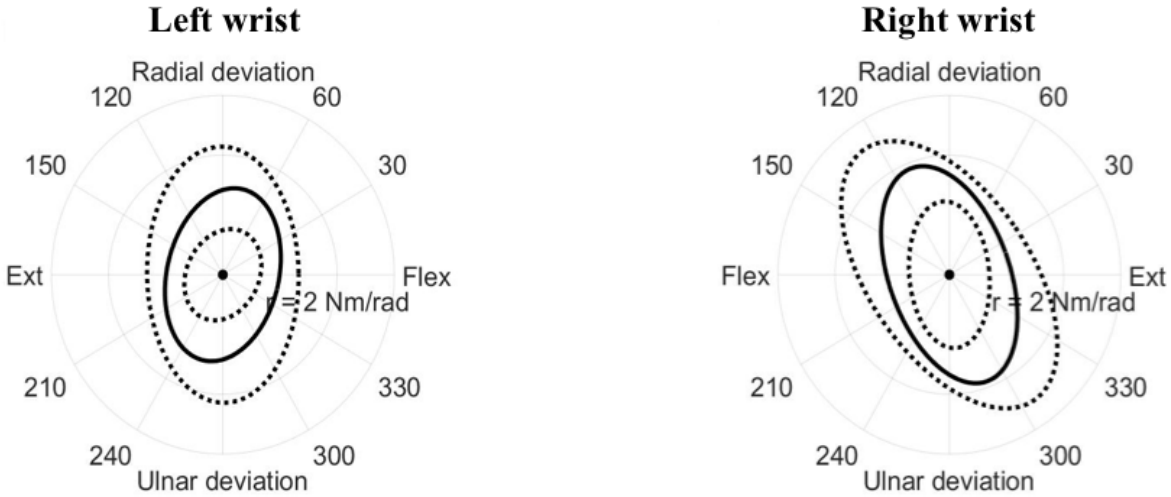
Results

Magnitude of Wrist Stiffness in Squash Players: Hand Dominance and Age Group Analysis

For the older adult group, the mean passive wrist stiffness magnitude of the left upper limb was 11.91 Nm/rad^2 (SD 1.26) and 9.99 Nm/rad^2 (SD 2.12) for the right upper limb. The ratio between right (dominant playing upper limb) and the left arm for the older adult group was 0.86. The older adult demonstrated a higher mean stiffness in the left (nondominant, nonplaying) upper limb (Figure 3). For the young adult group, the mean passive wrist stiffness magnitude of the left upper limb was 4.58 Nm/rad^2 (SD 1.39) and 6.75 Nm/rad^2 (SD 4.44) for the right upper limb. The ratio between right and left upper limb for the young squash group was 1.51. This playing group demonstrated a higher mean stiffness in the right (dominant playing) upper limb (Figure 4). There was a statistically significant difference between the magnitude of passive quasi-stiffness between the dominant and nondominant wrist of the young and older squash player groups (P=.004).

Figure 3. Mean passive quasi-stiffness ellipses (solid lines) and standard deviations (dotted lines) for the left and right wrist of the older adult squash player group (n=3).

Figure 4. Mean passive quasi-stiffness ellipses (solid lines) and standard deviations (dotted lines) for the left and right wrist of the young squash player group (n=4).



Magnitude of Wrist Stiffness in Young Adults: Unskilled and Squash Player Analysis

Results from the comparison of the 4 young squash payers (ratio right over left stiffness magnitude of 1.51) with the 7 young unskilled males (ratio right over left stiffness magnitude of 1.18) showed a stiffer dominant wrist for the squash players. There was no statistically significant difference between the young unskilled and the young squash player groups (P=.98).

Correlations: Magnitude of Wrist Stiffness and Subject Characteristics

The correlation between the passive wrist stiffness of all 7 players and subject characteristics revealed an interesting difference between the dominant and nondominant upper limb. There was a strong positive correlation between passive stiffness of the nondominant left wrist and age (R^2=0.87), whereas there was no clear correlation between passive wrist stiffness of the dominant right wrist and age (R^2=0.09) or years of squash play (R^2=0.01). When analyzing the correlation of the subject characteristics and the age subgroups, the young squash player group showed a strong positive correlation between passive wrist stiffness of the right wrist and the frequency of play (R^2=0.76). The older adult players demonstrated a strong negative correlation between passive wrist stiffness of the right wrist and the age of the player (R^2=0.88) and the number of years of playing experience (R^2=0.96).

Orientation of Wrist Stiffness: Unskilled and Squash Player Analysis

For the young unskilled group, the orientation of highest quasi-stiffness followed a “dart throwing” pattern, with a mean angle of 14.42° (SD 4.45) for the left wrist and a mean angle of –13.96° (SD 7.06) for the right [17]. For the young squash player group, the orientation of highest quasi-stiffness had a mean angle of 16.11° (SD 12.80) for the left wrist and a mean angle of –20.95° (SD 15.20) for the right. Both groups showed symmetric values for right and left wrists; however, a statistically significant difference was found between the unskilled and squash player groups (P<.001).

Discussion

Passive Wrist Quasi-Stiffness and Exercise

The magnitude of passive wrist quasi-stiffness of the young players confirmed the study hypotheses that competitive squash players demonstrate greater quasi-stiffness in the dominant playing upper limb compared with the nondominant upper limb. Although the ratio of dominant over nondominant wrist quasi-stiffness for young squash players compared with unskilled young subjects did not reach statistical significance, there was a trend favoring the squash player group. Studies investigating other sporting activities have shown that muscle strength, orientation of joint stiffness, and pattern of ROM between the playing and nonplaying upper limb do not consistently increase or decrease on the playing side. Klinge et al [29] studied the effect of strength training on flexibility and demonstrated that a 43% increase in isometric muscle strength resulted in a 25% increase in passive joint stiffness. Borsa et al [30] studied the difference in glenohumeral joint stiffness and ROM between the pitching and nonpitching upper limb in professional baseball players. Their results showed a difference in the ROM of the pitching and nonpitching upper limb but not a significant increase in passive stiffness on the pitching side. Indeed, the correlation between the measure of joint ROM and passive joint stiffness remains unclear. Some studies claim that joint ROM and passive joint stiffness (K) can be considered 2 components of the same phenomenon. Pando et al [15] demonstrated that the pattern of wrist stiffness was inversely related to the ROM ($K_{Radial\ Deviation} > K_{Ulnar\ Deviation} > K_{Extension} \sim K_{Flexion}$, whereas $ROM_{Radial\ Deviation} < ROM_{Ulnar\ Deviation} < ROM_{Extension} \sim ROM_{Flexion}$). However, in the study by Gleim and McHugh [31], an increase in ROM of a joint did not correspond with a decrease in passive stiffness of a joint or muscle. This study claimed that changes in ROM can be attributed to increased stretch tolerance without a change in stiffness magnitude [31].

There have been few studies, to the authors' knowledge, investigating the effect of exercise or sporting activities on passive wrist stiffness. Leger and Milner [11] investigated passive and active joint stiffness following wrist extensor muscle injury caused by a single session of intensive eccentric exercise. The study concluded that passive wrist stiffness (measured at a single neutral joint position) did not change following eccentric exercise-induced muscle injury. These findings suggest that this form of exercise does not cause mechanical changes to the noncontractile tissues in a neutral wrist position following a single session of such exercise. It is, therefore, likely that both differences in sporting activities as well as the biomechanics of joints will limit the comparison of our study results. Instead, an evaluation of the magnitude of quasi-stiffness in this study (of the young players), when compared with similar studies using unskilled subjects [15,17], reveals that passive wrist stiffness is slightly higher for competitive squash players. This trend in passive wrist stiffness is likely attributed to the greater cross-sectional area of the surrounding forearm muscles and tensile strength of the passive wrist structures (ligaments, tendons, and bone geometry), which are due to increased mechanical loading of the wrist during frequent, repetitive, and intensive squash play [32-35]. This conjecture is supported by the strong positive correlation (R^2=0.76) between the frequency of play and passive wrist stiffness in the young player group. The increased mechanical loading of the wrist associated with squash play may also explain the significant difference in the orientation of wrist quasi-stiffness between the unskilled and young squash playing groups. Nonetheless, as there is inconsistency in the orientation of wrist quasi-stiffness reported in the literature, it is possible that both differences in study subject's physical activities and study methodology contribute to the variance seen [14-17].

Influence of Aging and Exercise on Quasi-Stiffness

Although age-related increases in passive joint stiffness may seem clinically obvious, how exercise impacts passive joint stiffness in older adults has not been widely studied and results are inconsistent. Inconclusive results are likely because of variances in the joints evaluated, the study methodology, and the definition of flexibility and stiffness measurements. In research on flexibility, active older tennis players were shown to maintain shoulder flexibility on their playing side [36], whereas older soccer players were shown to have less flexibility in lumbar flexion and hip rotation than younger players [37]. Investigations into the effects of aging and immobility have shown that reduced physical mobility can be associated with increased passive stiffness. Lapier et al [38] and Gillette and Fell [39] found in animal studies that immobilization leads to increased intramuscular connective tissue and increased joint stiffness. In this study, the negative correlation between wrist stiffness on the dominant playing side and both the years of squash play (R^2=0.96) and age (R^2=0.88) in the older adult group strongly suggest that participating in high-intensity exercise could, in fact, slow or even prevent increases in joint stiffness during the aging process. This theory explains the higher stiffness magnitude on the nondominant (nonplaying) wrist in the older squash group and the significant difference in the magnitude of quasi-stiffness between the older and young squash players.

Changes to Muscle Fiber During Aging

The effect that squash play appears to have on the passive stiffness of the wrist with aging may partly be because of changes in the physiological properties of muscle fibers. The wrist flexor and extensor muscles are composed of approximately 50% type I and 50% type II muscle fibers in young adults aged 17 to 30 years [11,40]. Type II muscle fibers appear to be the most affected by aging, with reports of a 15 to 26% reduction in type IIa and IIb cross-sectional area and a preferential denervation of type II fibers between the age of 20 and 80 years [41]. The increasing proportion of smaller, slow-contracting type I muscle fibers with aging is thought to be an adaptive response to minimize fiber loss. The changes to type II muscle fibers and the increasing percentage of type I fibers are thought to be largely responsible for the reduced muscle mass, force generation of muscle tissue [41], and possibly the increased passive joint stiffness of older adults [42].

Type I muscle fibers have been reported to have greater passive stiffness, likely because of increased collagen concentration and cross-linking of collagen compared with type II muscle fibers [8,42]. Human and animal studies have demonstrated that an increase in type I muscle fibers leads to increased passive stiffness, whereas when physical exercise induces an increase in type II muscle fibers, there is a corresponding decrease in passive stiffness [8,42]. These observations might explain the pattern of passive wrist joint stiffness seen in the older squash playing group, where the left nonplaying wrist showed a higher passive stiffness (probably owing to an increased percentage of type I muscle fibers during the aging process) and the right dominant playing wrist demonstrating less passive stiffness (likely because of an exercise-induced relative increase or sparing of type II muscle fibers.)

Limitations

One must take this study with the appropriate caveats; several features of our study design limit the impact and generalizability of the results. Notably, the small sample size of this pilot trial significantly limits the power of the results. Other papers within this field of study have also reported small sample sizes ranging from 6 to 15 subjects [13-17]. The volunteer method of recruitment may have introduced self-selection bias, whereby the volunteer study subjects are not representative of the broader population that participate in squash or other unilateral upper limb sporting activities. Although the study recruited subjects with a wide age range, there were not enough subjects within each age group, and hence, for the most part, we only observed statistical trends favoring some of our conclusions. To reliably determine that there was a significant difference in wrist quasi-stiffness between the dominant (playing side) and nondominant upper limb of the older squash player group, a power analysis (GPower 3.1) indicates that (assuming an alpha value of .05, power of 0.80, and an effect size (f) of 0.32, calculated from the results of this pilot study) a total of 82 subjects would be required. Additional demographic data such as the duration of squash play, as well as the frequency of play per week, would better represent the subject's playing intensity and may enable more accurate characterization of the influence of playing intensity on passive joint quasi-stiffness. In addition, collecting data such as grip strength and electromyography would have provided further insight into the subject's muscle characteristics and muscle state during the trials to validate the measure of passive joint quasi-stiffness. Nevertheless, we believe our results provide additional information on a sparse landscape of limited literature on the impact of intensive unilateral exercise on passive joint stiffness. Indeed, the absence of comparative studies indicates that our study's findings are novel and potentially influential and that further research is required in this field.

Conclusions

This study provides a valuable initial insight into the possible effect that highly intensive, repetitive, unilateral sports may have over time on wrist quasi-stiffness and reducing the impact of the aging process. Further studies are required to investigate this relationship with a larger sample size and age group analysis. This field would also benefit from the study of passive wrist stiffness in young and older subjects who participate in intensive bilateral sporting activities such as upper limb weight or grip training to determine the magnitude and effect of changes in muscle fiber type across the lifespan. Our findings confirm that the evaluation of passive joint stiffness has relevance and far-reaching value in many fields, from sporting activities to the rehabilitation of the older adults, following surgical interventions, or those with neurological impairments.

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Conflicts of Interest

HIK is a co-inventor of several MIT-held patents for robotic therapy. He was the founder of Interactive Motion Technologies and Chairman of the Board (1998-2016). He successfully sold Interactive Motion Technologies to Bionik Inc. He founded 4Motion Robotics, Inc in 2017. TH is now employed by Bionik Inc, the company that purchased Interactive Motion Technologies.

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Abbreviations

FE: flexion-extension
MR: multiple regression
RD: radial deviation
ROM: range of motion
RUD: radial-ulnar deviation
UD: ulnar deviation
USSRA: United States Squash Rating Algorithm

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Original Paper

Determining the Accuracy of Oculus Touch Controllers for Motor Rehabilitation Applications Using Quantifiable Upper Limb Kinematics: Validation Study

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Abstract

Background: As commercial motion tracking technology becomes more readily available, it is necessary to evaluate the accuracy of these systems before using them for biomechanical and motor rehabilitation applications.

Objective: This study aimed to evaluate the relative position accuracy of the Oculus Touch controllers in a 2.4 x 2.4 m play-space.

Methods: Static data samples (n=180) were acquired from the Oculus Touch controllers at step sizes ranging from 5 to 500 mm along 16 different points on the play-space floor with graph paper in the x (width), y (height), and z (depth) directions. The data were compared with reference values using measurements from digital calipers, accurate to 0.01 mm; physical blocks, for which heights were confirmed with digital calipers; and for larger step sizes (300 and 500 mm), a ruler with hatch marks to millimeter units.

Results: It was found that the maximum position accuracy error of the system was 3.5 ± 2.5 mm at the largest step size of 500 mm along the z-axis. When normalized to step size, the largest error found was 12.7 ± 9.9% at the smallest step size in the y-axis at 6.23 mm. When the step size was <10 mm in any direction, the relative position accuracy increased considerably to above 2% (approximately 2 mm at maximum). An average noise value of 0.036 mm was determined. A comparison of these values to cited visual, goniometric, and proprioceptive resolutions concludes that this system is viable for tracking upper-limb movements for biomechanical and rehabilitation applications. The accuracy of the system was also compared with accuracy values from previous studies using other commercially available devices and a multicamera, marker-based professional motion tracking system.

Conclusions: The study found that the linear position accuracy of the Oculus Touch controllers was within an agreeable range for measuring human kinematics in rehabilitative upper-limb exercise protocols. Further testing is required to ascertain acceptable repeatability in multiple sessions and rotational accuracy.

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KEYWORDS

upper extremity; kinematics; physical medicine and rehabilitation; validation studies; virtual reality

Introduction

Current gaming and virtual reality platforms [1] that use motion-controlled interfaces offer an affordable and accessible method of tracking human kinematics. However, given that consumer-grade platforms are originally intended for playing video games and to immerse players in virtual environments, their tracking performance should be evaluated before they are employed as tools for biomechanical or clinical analysis [2]. Previously tested rehabilitation protocols using commercial

gaming technology such as Wii Motes (Nintendo Co, Ltd, Kyoto, Japan) to provide positional feedback for trunk compensation [3] or a Kinect (Microsoft Corporation, Redmond, United States) to measure range and speed of motion for upper-limb exercises [4,5] have shown potential to be used as rehabilitation tools that could provide quantifiable changes in clients' kinematic motor abilities to therapists. Other studies using accelerometers to track patterns in functional upper-limb movements were able to capture differences similar to those measured by clinical scales [6] and found benefits from objective quantitative evaluations of changes in motor ability during therapy regimens, which can be collected from in-game progress reports [7]. In addition, success has been found in translating kinematic upper-limb metrics to clinical Fugl-Meyer scoring [8] and in detecting exercise repetitions via kinematic monitoring for telerehabilitation and at-home programs [9]. Current clinical assessments for upper-limb motor function, such as the Fugl-Meyer Assessment and Wolf Motor Function Test, only provide low-resolution point-scores rated qualitatively by therapists, and kinematic analysis of upper-limb motion has been reported to be a useful addition to these clinical assessments [10]. When measuring range of motion in a clinical setting, the goniometer is considered a gold-standard clinical measurement tool used by therapists [11]. However, only static joint angles can be measured, and typically with some visual estimation and multiple testers [12].

One of the latest (released December 2016) devices to be developed for interacting with virtual environments is the Oculus Touch (Oculus VR, LLC, Menlo Park, CA, United States) controller set. The controllers are peripheral accessories of the Oculus Rift virtual reality headset and are employed to track users' hand movements. Their tracking system employs a proprietary algorithm that collects data from infrared sensors via constellation tracking [13] and inertial measurement units (IMUs). Given that the controllers are wireless, lightweight, low-cost devices that can be used to track a user's hand position and orientation in 3-dimensional (3D) space, they could have the potential to be employed in rehabilitative and biomechanical motion-tracking applications. At the time of this study, there was no sufficient information about the tracking performance of the controllers provided by the manufacturer, and there is currently a lack of scientific papers employing a systematic approach to test their potential application as tools for motion-tracking data capture. As a result, in this study, we evaluated the tracking accuracy of the Oculus Touch controllers to present a preliminary evaluation that could be informative to the biomechanical and rehabilitation research community. The specific aim of the experiment was to quantify the relative positional accuracy of the Oculus Touch controllers in 3 spatial dimensions. As the controllers are intended for hand-held motion control, the evaluation setup was centered around the movement size for standing/sitting upper-limb reaching tasks.

Methods

Technical Setup

An Oculus Touch controller (Figure 1), 2 Oculus Sensors, an Oculus Rift headset, and a computer running Windows 10 (Microsoft Corporation) were employed in this study.

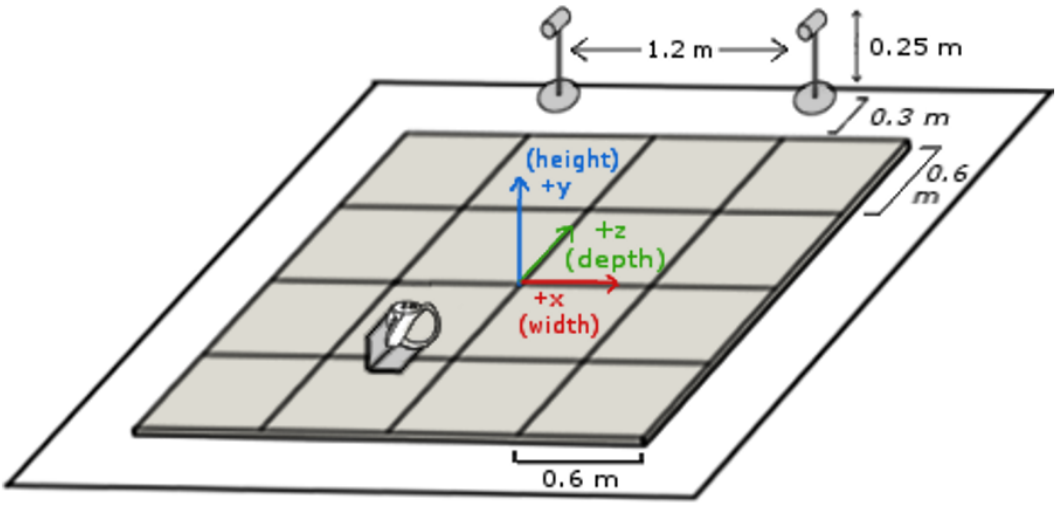
A custom computer application was developed in Unity 2017 (Unity Technologies, San Francisco, United States) to capture and log the controller's position during the experiment. The data capture was performed at the headset's native frequency of approximately 90 Hz , using the Unity OVR Plugin package to access controller data. The virtual environment was set up over a 2.4 m x 2.4 m play-space in the x-z plane to be within the recommended manufacturer play area. This space consists of 16 commercial 600 mm square force/torque plates professionally installed on a subfloor of auto-levelling epoxy and flat to within 0.5 mm (Figure 2). The y-axis was only bounded by the camera sensors' field of view limitations.

To ensure consistency, the Oculus Sensors were placed on the floor at 0.3 m along the front edge of the space and 1.2 m apart, equidistant from the centre line, for the entire experiment. The sensor heads were manually leveled and visually aligned to have parallel, front-facing fields of views. Both the sensors and controllers maintained an initial y-position of 0 at the floor—this would be equivalent to placing the sensors at table height and the controllers at hand height.

All measurements were taken by securing the right-hand Oculus Touch controller to a flat L-shaped jig (Figure 2) and resting it on the floor for 5 seconds. Initial calibration of floor height and play-space size and orientation was done through the official commercial Oculus setup client.

Figure 1. The right-side Oculus Touch controller. Left: front view. Right: top-down view.

Figure 2. The experimental setup and coordinate frame. The play-space was divided into 16 squares.



Experimental Procedure

Measurements were taken along each of the 3 spatial axes (x: width, y: height, z: depth) in a single session. The x and z axes were measured in increments of 5, 10, 50, 150, 300, and 500 mm steps relative to a recorded 0 value. The estimate for a 500 mm largest step was attributed to an approximate lower arm and hand length from human anthropometric data in Huston [14].

This length should replicate the size of a simple outward reach from the elbow. Each set of steps was taken from the zero line of each axis in both the positive and negative direction and then taken in the positive direction at +600 mm and in the negative direction at –600 mm along the same axis (Figure 3; left). Graph paper with millimeter unit markings was used to define the step sizes to the relative 0 point of each set. The graph paper step sizes were verified using a Mitutoyo 500-196 digital calipers, accurate to 0.01 mm, visually aligned to the edge of the unit markings within the third significant digit. A ruler with half-millimeter unit markings was used for steps larger than 150 mm. The bottom left corner of the jig was used as an origin for the 3 axes with respect to the controller. The x and z axes edges were aligned with the graph paper visually. The L-shaped jig was checked for orthogonality using a calibrated 90-degree ruler in all 3 directions before its use. To test the repeatability of the L-shaped jig alignment on graph paper, the controller was moved at least 300 mm away from and then toward a single point near the centre of the play-space on each axis 3 times.

In the x-axis, 4 sets of steps were taken at 4 different depths for a total of 16 sets of steps to measure the accuracy of the controllers over the play-space area (Figure 3). The same configuration was used for the z-axis but using 4 sets of steps along 4 different x-axis values, 600 mm apart.

Figure 3. Left: A top-down visual representation of the expected spacing of the data points in the x-axis. Right: The x-z points at which the y step sets were taken.

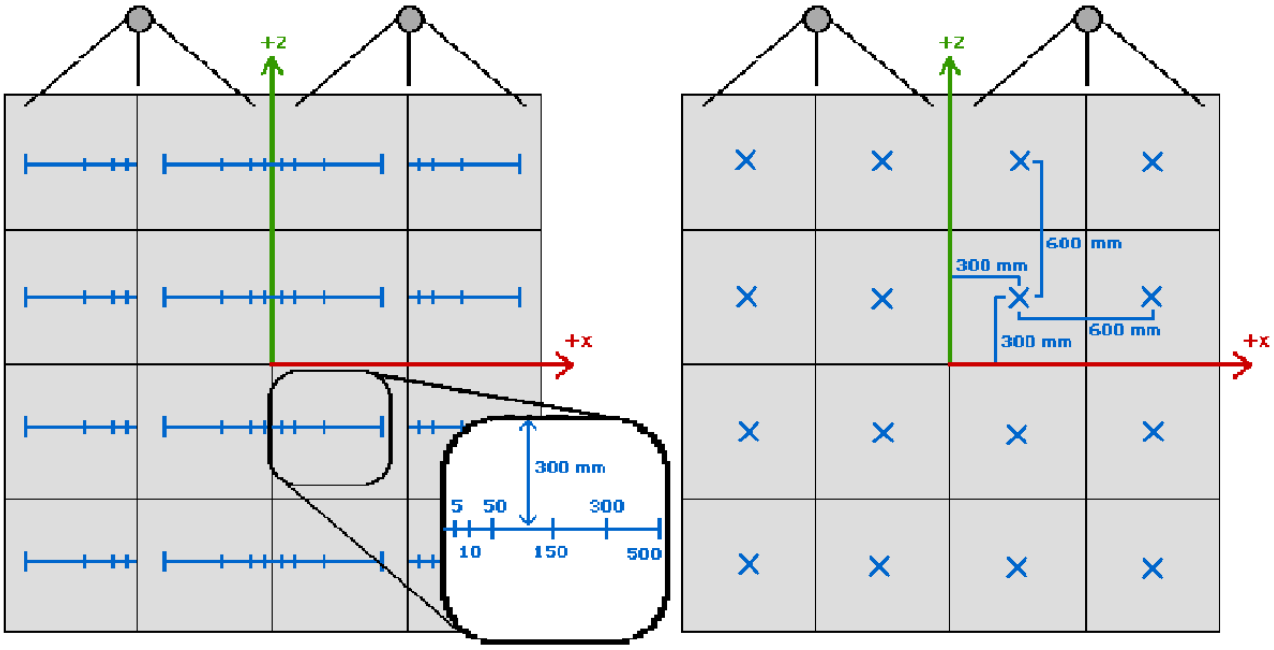
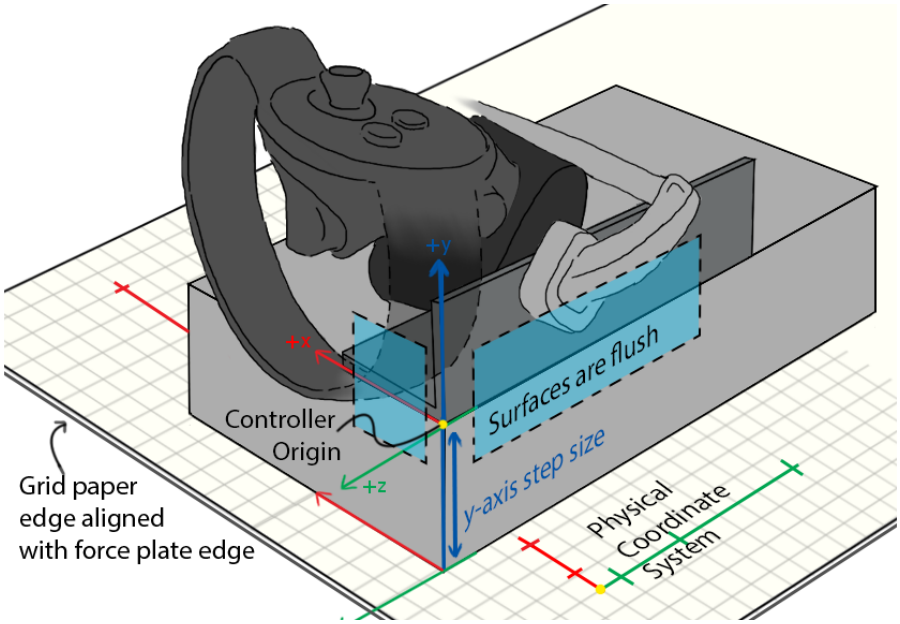


Figure 4. Close-up of the Oculus Touch controller in the L-shape jig over an aluminium block used to measure y-axis steps. Both controller (system) and graph paper (physical world) axes are represented and were aligned visually during the experiment.



The 16 y-axis step sets were taken 600 mm apart from each other in the x-z plane starting 300 mm from the 0 line in each perpendicular axis in the x-z plane. This was the approximate centre of each of the 16 tiles seen in Figure 3 (right). The y steps were measured by placing the controller and jig on level aluminum blocks of specific heights, which were measured using zeroed, calibrated digital calipers accurate to 0.01 mm. The L-shaped jig was used as a physical origin point and axes and was aligned with the top left corners of the aluminum blocks (Figure 4).

The aluminum blocks were chosen to allow the y-axis step sizes to approximately match the same x and z step sizes, and had heights of 6.23, 12.56, 50.82, and 152.5 mm. The x and z positions were monitored and recorded but not analyzed for alignment accuracy.

Data Analysis

To remove motion artifacts from pressing the buttons on the controller to start and stop the data recording, the first 1.5 seconds (135 samples) were removed and the next 2 seconds (180 samples) were used as the sample data for each measured point. After those 2 seconds, the rest of the data recording (approximately 1.5 seconds or 135 samples) was also discarded, regardless of length. The data were averaged to calculate the measured value at each point.

For each sample point, the 3D position of the controller was measured. The variation was calculated for each data point and used to determine the static precision of the system. The position error for each point was calculated by subtracting the measured displacement (Euclidean distance) by the expected step size. The Euclidean distance was used to account for any misalignment of the Oculus tracking coordinate system with respect to the physical grid. The error values were then averaged to generate values for expected displacement error in a specific area of the play-space as well as for a specific step size over the entire play-space. The percent error was calculated to normalize the error to the step size.

Results

Positional Accuracy

The average and percent errors for all step sizes in the x, y, and z directions are presented in Tables 1 and 2.

The largest absolute error was found to be 3.5 mm in the z-axis for a step size of 500 mm, which normalizes to a 0.7% error. The largest normalized error was found to be 12.7% for the smallest step of 6.23 mm in the y-direction. The largest percent errors for the x and z axes were 4.7% and 3.5%, respectively, also at the smallest step size (5 mm).

Table 1. Position error for different step sizes at all areas of the defined play-space measured with 0.01 mm accuracy using digital calipers. The percent error was calculated using nonrounded values of error in millimeter.

Directional axis and step size (mm)	Error	
	Average (SD), mm	Average percent error (SD %)
x		
5.00	0.23 (0.19)	4.7 (3.9)
10.00	0.25 (0.18)	2.5 (1.8)
50.00	0.39 (0.29)	0.8 (0.6)
150.0	0.76 (0.50)	0.5 (0.3)
z		
5.00	0.17 (0.15)	3.5 (3.1)
10.00	0.25 (0.22)	2.5 (2.2)
50.00	0.28 (0.22)	0.6 (0.4)
150.0	0.72 (0.46)	0.5 (0.3)
y		
6.23	0.79 (0.62)	12.7 (9.9)
12.56	0.48 (0.82)	3.8 (6.5)
50.82	0.41 (0.62)	0.8 (1.2)
152.5	0.93 (1.10)	0.6 (0.7)

Table 2. Additional position error for larger step sizes at all areas of the defined play-space measured with ruler and graph paper markings. The percent error was calculated using nonrounded values of error in millimeter.

Directional axis and step size (mm)	Error	
	Average (SD), mm	Average percent error (SD %)
x		
300.5	1.5 (1.0)	0.5 (0.3)
500.5	2.5 (1.0)	0.5 (0.3)
z		
300.5	2.0 (1.0)	0.7 (0.3)
500.5	3.5 (2.0)	0.7 (0.4)

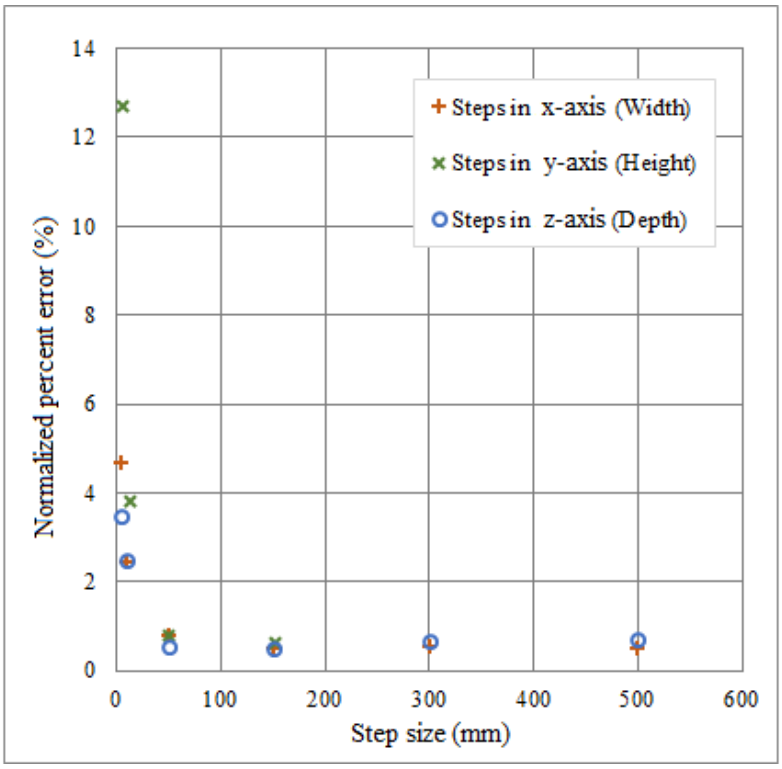
When the average percent error was calculated for each step size across the entire play-space, it was found that the error decreased nonlinearly with increasing step size (Figure 5).

Step sizes with values of ≤10 mm had an accuracy error greater than 2%. Normalized error averages in step sizes larger than >10 mm were fairly uniform.

The variation was calculated for static data points at the 16 different locations in the play-space and averaged across all points to find an average noise value of ±0.036 mm (x: ±0.025 mm, y: ±0.024 mm, z: ±0.055 mm). The single-point repeatability test found that the controller was able to return to the same x-y-z point with an output measurement variation slightly above the average noise value (x: 0.080 ± 0.546 mm, y: 0.088 ± 0.063 mm, z: 0.044 ± 0.326 mm).

To investigate how accuracy varied over the entire play-space, the displacement and percent error were averaged over each area set. These average errors over the play-space area for x, y, and z are presented in Multimedia Appendix 1 as exploratory analysis to see if there were any patterns in accuracy based on distance away from the Oculus sensors. A large error (14.0%) occurred in 1 area of the y-axis measurements. This was a result of a 2 mm error at a 6.23 mm step, resulting in a large normalized value of approximately 40% despite being a small error in absolute distance (millimeters). No distinct pattern of position accuracy based on x-z location in the play-space was observed.

Figure 5. Percent error for different step sizes. No values were calculated for 300 mm and 500 mm in the y-axis as the largest aluminum block used matched the 150 mm step size.



Discussion

Principal Findings

The study team found a maximum positional accuracy across measured step sizes less than 150 mm for the Oculus Touch controller of 0.76 ± 0.50 mm in the lateral x-axis, 0.72 ± 0.46 mm in the anteroposterior z-axis, and 0.93 ± 1.10 mm in the vertical y-axis direction. Larger step sizes found lower positional accuracies of 2.5 ± 1.0 mm in the x-axis and 3.5 ± 2.5 mm in the z-axis. The largest error in percent when normalized to step size (12.7 ± 9.9%) was found in the smallest step size in the y-axis set at 6.23 mm.

The error values found are considered within an acceptable range of error for the measurement of biomechanical movement as the human perception of the just noticeable difference (JND) even for fine motor function (finger distance/position) is larger than this value (13.0% for young subjects and 16.1% for older persons [15]). In addition, in a different study [16], it was reported that the JND of the fully extended human shoulder when moved passively was found to be 0.8º. Using a 50th percentile female arm length of 702 mm [14], a 0.8º change in joint angle would cause an arc length of 9.8 mm, which is larger than both the average noise and accuracy error of the system. Therefore, the error in relative distance should not be noticeable to the user.

In studies on the accuracy of visual assessments of angular joint positions done by physical therapists and other health professionals, it was determined that joint positions could only be determined with an error of approximately 5º within the referenced radiometry measurement [17] of wrist angle and 7.4º in shoulder abduction compared with goniometry of nonmoving subjects [18]. Measurement of glenohumeral range of motion using a goniometer was reported to have an SE between 4.4 to 9.9º [19]. Moreover, the Oculus Rift headset has a visual field of view of 100º and a resolution of 2160x1200 pixels [20]. This results in a 0.046º change in the object edge to show up as a single pixel change. With a noise level of 0.069 mm as an arclength, it is expected that visual jitter would not occur until the controller is less than 8.59 mm away from the user in the headset's point of view.

It was found that although normalized percent error decreased as step size increased, the absolute error (millimeter) was found to be largest when the largest step was measured. This could be the effect of an inherent scaling phenomenon found in the Oculus sensor tracking, which uses infrared image processing as 1 of its main sources of position tracking for the Oculus Touch controllers.

We expected that the outer edges of the defined play-space would provide areas with the largest error; however, no discernable pattern was found to occur over the x-z plane. This provides evidence to support a consistent accuracy of the controllers within the documented [21] x-z field of view of the Oculus Sensors. That is, regardless of where in the play-space a user might stand, a reach of 500 mm outwards from the body would be measured sufficiently accurately.

Comparison With Prior Work

On the basis of the results from this study, the Oculus Touch controllers should be an adequate motion tracking alternative for biomechanics applications, as similar low-cost, commercially available systems that have been employed to measure joint movements, such as the Kinect V1 and V2, have displacement accuracies on the order of centimeters [22,23]. A previous study

evaluating the tracking accuracy of the Oculus Rift head-mounted display found similar accuracy values for the larger step sizes [24]. On the other hand, more expensive and complex motion capture systems such as the Vicon-460 (Vicon Motion Systems Ltd, Oxford, United Kingdom) with submillimetric accuracy [25] allow researchers to measure movements with higher accuracy. In addition, wearable inertial sensors were able to quantify upper-limb positioning within 1 mm when custom sensor algorithms were applied [7]; however, wearable research-grade systems trade ease of use and commercial availability for higher accuracy. For kinematic tracking that does not require submillimetric accuracy, such as for monitoring changes in gross motor upper-limb movements over time in a rehabilitation program [26], for training neural networks to detect the number of repetitions during rehabilitative exercises [9], or in cases where there would otherwise be no quantitative measures [8], the Oculus Touch controllers could provide a cost-effective alternative. Comparison with the Oculus Touch controllers by using other tracking tools simultaneously during upper-limb exercises may provide better insight into which level of accuracy is optimal for different use cases, such as for automated repetition counting as opposed to for measuring joint angles for digital goniometry. In cases where the tracking technology is used to facilitate virtual environments for engaging upper-limb exercises, a higher position accuracy may provide better visual fidelity to movement in the real world, and therefore, better transfer of improved motor functions from game tasks to real-world tasks [27].

Limitations

Occlusion of some of the controllers' infrared light-emitting diodes could have occurred when placing the controllers close to the floor, which might have increased the measured error. Moreover, as the system requires an initial calibration of the user's approximate height, this also could have acted as an additional source of error. As a result, future studies should investigate the accuracy of the system away from the floor, as well as the accuracy of the controller's 3D orientation measurement, as we only measured position error in this study. Reproducibility of the measurements made by the Oculus system should also be investigated by having multiple experimenters perform the same procedure and by comparing measurements from different tracking sessions. Standardized measurement system analysis procedures should be followed in terms of the number of repetitions used as listed in analysis of variance gage repeatability and reproducibility documentation [28]. Dynamic conditions should also be evaluated before use in clinical kinematic analysis to assess the interaction between IMU sensor drift and camera sensor correction while in motion. A limitation of the Oculus Touch controllers is that it is only capable of measuring the position and orientation of a single point as a proxy for hand position. Future studies should directly compare the Oculus Touch absolute point-position with a professional marker-based motion-tracking system to ensure the elimination of error because of the use of visual and physical measuring tools. These absolute point-position studies should also evaluate larger step size accuracies to encompass bigger movements. Additional studies could include the evaluation of inverse kinematic algorithms that employ the hand and head positions (from headset) to generate a model of the user's arms [29,30]. This would allow direct comparison against other devices that digitally measure goniometric angles.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Exploratory results of accuracy based on x-z location: displacement in millimeters (left) and in percent (right) accuracy error for the Oculus Touch controller in the x (top), y (centre), and z (below) directions. Error is represented by the width of the circle for each step set area, however the circle size scale was magnified for visualization purposes and it is not to scale with the rest of the chart. Standard deviation is shown in parentheses.

[PNG File, 232KB - biomedeng_v4i1e12291_app1.png]

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Abbreviations

3D: 3-dimensional
IMU: inertial measurement unit
JND: just noticeable difference

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Review

The Effects of Titanium Implant Surface Topography on Osseointegration: Literature Review

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Abstract

Background: A variety of claims are made regarding the effects of surface topography on implant osseointegration. The development of implant surfaces topography has been empirical, requiring numerous in vitro and in vivo tests. Most of these tests were not standardized, using different surfaces, cell populations, or animal models. The exact role of surface chemistry and topography on the early events of the osseointegration of dental implants remains poorly understood.

Objective: The aim of this study was to consider the major claims made concerning the effects of titanium implant surface topography on osseointegration. The osseointegration rate of titanium dental implants is related to their composition and surface roughness. The different methods used for increasing surface roughness or applying osteoconductive coatings to titanium dental implants were reviewed. Important findings of consensus were highlighted, and existing controversies were revealed.

Methods: This paper considered many of the research publications listed in Medical Literature Analysis and Retrieval System Online and presented in biomedical research publications and textbooks. Surface treatments, such as titanium plasma spraying, grit blasting, acid etching, alkaline etching, anodization, polymer demixing, sol-gel conversion, and their corresponding surface morphologies and properties were described.

Results: Many in vitro evaluations are not predictive of or correlated with in vivo outcomes. In some culture models, increased surface topography positively affects proosteogenic cellular activities. Many studies reveal increase in bone-to-implant contact (BIC), with increased surface topography modifications on implant surfaces.

Conclusions: Increased implant surface topography improves the BIC and the mechanical properties of the enhanced interface.

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KEYWORDS

implant interface; TPS; acid etching; alkaline etching; anodisation; polymer demixing; sol gel

Introduction

The elusive dream of replacing missing teeth with an artificial analogue, which is as close to its natural predecessor, has been a part of dentistry for thousands of years. The coincidental discovery of the tenacious affinity between living bone and tissues, termed as osseointegration, propelled dentistry to a new age of reconstructive dentistry. Branemark et al [1] started the era of implantology. Since then, this method still remains popular and reliable, with only shape and surface of the titanium implants having changed [2-4]. Interactions between implant biomaterials and biological environments occur at interfaces, and they are affected by the nature of the biomaterial, such as its surface chemistry and energy, roughness, and topography. These parameters play a role during implant integration in bone tissue, and they consequently play a role for osseointegration [5-7]. Osteogenesis at the implant surface is influenced by several mechanisms. A series of coordinated events, including

cell proliferation, transformation of osteoblasts, and bone tissue formation might be affected by different surface topographies. There is a clinical impression that the amount of bone-to-implant contact (BIC) is an important determinant in the long-term success of dental implants. Consequently, maximizing the BIC and osseointegration has become a goal of treatment, which is enhanced by implant surface roughness. The first generation of successfully used clinical titanium implants, which were machined with a smooth surface texture, now approach 50 years in clinical use. The second generation of clinically used implants underwent chemical and topographical modifications, usually resulting in a moderately increased surface topography [8]. The implant surface plays an important role in biological interactions for 2 reasons. First, the surface of a material generally differs in terms of composition and morphology, from the body of the material. These differences are because of molecular rearrangements and surface reactions and contamination. Second, materials may or may not release toxic or biologically active substances. Thus, the properties of a surface guide the biological response [9-11]. The significant challenge in implantology is the design of biomaterials that actively promotes a faster and more improved osseointegration process while avoiding undesirable tissue responses. This requires selective control of interactions at the tissue-implant interface, the site of a series of complex events that depend on synergistic parameters, including surface chemistry. This review focuses on the different surfaces and methods that aim to accelerate the osseointegration of dental implants. The physical and chemical properties of implant surfaces are discussed in relation to their biological and clinical behavior. This literature review also aims to elucidate implant surface topography and obtain a perspective regarding the topography of the implant surface, which could be beneficial to implant surgery when implemented in practice

Methods

Overview

Surface properties of oral titanium implants play decisive roles for molecular interactions, cellular response and, bone regeneration. It is increasingly recognized that interactions between biomaterials and host tissues are controlled by nanoscale features. Cells grow on nanostructured extracellular matrices, and biological events, such as signaling and cell-substrate interactions, occur at the nanometric level. Nanometer-scale surface features can increase the surface energy, thereby increasing the wettability of blood and the spreading and binding of fibrin and matrix proteins. This in turn favors cell attachment and tissue healing, particularly directly after implantation. It also directly influences cellular proliferation, differentiation, alignment, and, finally, osseointegration [10,12-18]. Currently, several techniques are commonly used to modify the smooth surface topography of dental implants to create nanosurface topography. Some techniques comprise adding matter to the implant surface, creating a dented surface (convex profile), and they are called additive techniques to increase the surface area and provide a more complex surface macrotopography, for example, titanium plasma spraying (TPS). Conversely, other techniques comprising eliminating matter from the titanium surface, creating pits (concave profile), are known as subtractive or ablative techniques, altering the microtopography or texture [19]. One or several of these methods are used to produce either an isotropic surface (ie, with surface asperities that are randomly distributed so the surface is identical in all directions) or an anisotropic surface (ie, surface with a directional pattern). The surface treatments are suggested to improve the capacity of anchorage into bone [20]. The additive methods employed the treatment in which other materials are added to the surface, either superficial or integrated, and they are categorized into coating—TPS, plasma-sprayed hydroxyapatite (HA) coating, alumina coating, and biomimetic calcium phosphate (CaP) coating—and impregnation. The common subtractive techniques are large-grit sands or ceramic particle blasts, acid etch, and anodization. Textbox 1 shows the ways through which surface roughness of dental implants can be obtained.

Textbox 1. Methods to obtain surface roughness.

- Mechanical modifications
  - Roughening of implants by titanium plasma-spraying
  - Roughening of implants by grit blasting
- Chemical modifications
  - Roughening of implants by acid etching
  - Roughening of implants by alkaline etch
  - Roughening of implants by anodization
  - Roughening of implants by sol gel
  - Roughening by polymer demixing
- Antibiotic coatings
- Stem-cell therapies and surface modification
- Shot peening/laser peening
- Photofunctionalization
- Biomolecular coatings
- Self-assembled monolayer in nanotextured titanium
- Fluoride-modified implant surfaces

Mechanical Modifications

Roughening of Implants by Titanium Plasma Spraying

This method comprises injecting titanium powders into a plasma torch at high temperature [21]. The titanium particles are projected onto the surface of the implants, where they condense and fuse together, forming a film about 30 μm thick. The thickness must reach 40-50 μm to be uniform [7]. Borsaria et al [22] compared the biological response of osteoblast-like cells with titanium surfaces with different roughness levels, and they concluded that the new ultrahigh roughness and dense coating provided a good biological response. In a preclinical study using pigs, the bone/implant interface formed faster with a TPS surface than with smooth-surface implants [7].

It has been shown that this 3-dimensional topography increased the tensile strength at the bone/implant interface. An extensive and close contact between the implant and the host bone surfaces is the condition that maintains primary stability and avoids excessive interfacial micromotion during bone healing, which may be detrimental to the osseointegration process. Ong et al [23] studied the bone interfacial strength and bone contact length at the plasma-sprayed HA and TPS implants in vivo, where noncoated titanium implants were used as controls. The interfacial strength between bone and TPS-coated implants was suggested to be governed by the bone ingrowth into the roughened titanium surfaces, thereby providing a mechanical bone-implant interlock, whereas the interfacial strength between bone and HA-coated implants was suggested to be attributed to bone apposition on HA surfaces.

Several techniques were proposed to adhere HA to titanium implants, but only the plasma spraying coating technique has been successfully used on commercial implants [24].

Roughening of Implants by Grit Blasting

Blasting is a technique that leads to the creation of a porous layer on the implant surface achieved through the collision with microscopic particles, such as ceramic, alumina, titanium oxide, and CaP particles [7]. The ceramic particles are projected through a nozzle at high velocity by means of compressed air. Depending on the size of the ceramic particles, different surface roughness can be produced on titanium implants. The thickness of the porous layer can be modulated by the granulometry of the particles [25]. Wennerberg et al [26-30] demonstrated in a rabbit model that grit blasting with different sizes of titania (TiO_2) or Al_2O_3 particles altered the commercially pure titanium topography and resulted in a similar enhancement of bone formation at the implant. These studies also demonstrated that specific surface modifications increased the biomechanical interlock of the implant with bone when measured with a torque device. TiO_2, when used as a blasting material, showed interesting results in experimental studies, being associated to a significant enhancement of bone-to-implant contact when compared with machined surfaces [31]. CaPs, such as HA, beta-tricalcium phosphate, and mixtures, have also been considered for blasting materials. These materials are biocompatible and osseoconductive. They are resorbable, leading to a clean-textured, pure titanium surface. Manoa et al [32], to achieve better osteoconductivity, used the blast coating method of spraying apatite powder on the surface of titanium implants. Apatite powder–coated implants generally showed a more rapid bone response and good osteoconductivity than noncoated implants. The rough surface created by blasting has

been demonstrated to stimulate osteoblastic gene expression, as well as to enhance bone formation and bone-implant fixation, in a word, osseointegration [33,34]. Although an associated inflammatory response was reported [35], the overall success rate was satisfactory, with the majority of implants yielding good osseointegration and stability at 1 year after surgery [25]. Among the range of available materials, alumina is one of the most commonly used for blasting.

Chemical Modification

Roughening of Implants by Acid Etching

The combination of strong acids is effective in creating a thin grid of nanopits on a titanium surface [25], ranging from 0.5 to 2 μm in diameter. Etching with strong acids, such as HCl, H_2SO_4, HNO_3, and particularly HF, is needed to attack titanium for creating rough surfaces [7]. Etching is then stopped by adding water. The recovered disks are washed further with ethanol in an ultrasonic bath for 20 min and dried [36 **]**. Variola et al [36] demonstrate that by varying etching parameters, such as solution composition, temperature, and exposure time, it is possible to modify the topography, oxide thickness, and wettability of commercially pure titanium. Thus, chemical oxidation with H2SO4 (conc)/H2O2 (aq) solutions is an efficient tool to achieve various physical and chemical configurations on this implant surface. Yi et al [37] have shown that controlled chemical oxidation of titanium using a mixture of H2SO4/H2O2 yields a nanotextured surface. The resulting nanotopography significantly influences the very early stages of in vitro osteogenesis. Such an early effect is needed to control the healing cascade from the very start. They also showed that the treated titanium substrate becomes highly porous and has a surface comprising nanosized pits, which have average diameters and fractal dimensions ranging between 20-22 nm and 1.11-1.17 nm, respectively. Atomic force microscopy revealed a 3-fold increase in surface roughness. The thickness of the oxide layer on the treated titanium surface is estimated to be ~32-40 nm [21].

HF is known to show a high ability to dissolve the passivation layer, mainly comprising TiO_2, on titanium-based materials. Therefore, a mixture of HF and HNO3 has been also used to create surface structures at the microlevel [33,38]. Moreover, it has been shown that fluoride incorporation into the created surface structures induces an enhanced osteoblastic differentiation, and it is favorable to the osseointegration of implants [39]. However, fluoride contaminations are known to have an ambivalent influence on the response of the host tissue [40]. Furthermore, dual acid etching with HCl and H2SO4 heated above 100°C has produced surface topography that is able to attach to fibrin scaffold and promote adhesion of osteogenic cells [21]. Various clinical studies have shown acid-etched (AE) implants to be successful in humans, with radiological evidence suggesting improved bone apposition rates compared with machined implants.

Roughening of Implants by Alkaline Etch (Sodium Hydroxide, Potassium Hydroxide, and $NaFl_2$)

Sodium hydroxide (NaOH) treatment catalyzes the production of titanium nanostructures outward from the titanium surface [41]. Treatment with an NaOH solution results in a sodium titanate hydrogel layer converted in an amorphous sodium titanate layer, with heat treatment at 600°C. Titanate gel layer allows HA deposition. This behavior has also been seen with other metals, such as zirconium and aluminum [42]. Titanium oxide nanotubes chemically treated with NaOH accelerated HA crystal growth in a simulated body fluid (SBF). Both chemical and topography changes are imparted [41,43].

Roughening of Implants by Anodization

Anodization is one of the most commonly used techniques to create nanostructures with diameters of less than 100 nm on titanium implants [44]. Voltage and direct current (galvanic current) are used to thicken the oxide layer among the implant surface. The titanium substrates serve as the anode in the process, whereas an inert platinum sheet provides the cathode. The anode and cathode are then connected by copper wires and linked to a positive and negative port of a 30 Volts/3 Amperes power supply, respectively. Diluted hydrogen fluoride (either at 0.5 wt% or 1.5 wt%) is used as electrolyte. Subsequently, a strong acid dissolves the oxide layer, creating a pattern that follows the convective lines of the galvanic current. Therefore, through the regulation of voltage and density, it is possible to control the diameters of nanotubes and the gap between them [25]. Kim et al [45] concluded that desired porosity and surface roughness can be achieved by adjusting the anodization conditions, such as voltage, solution concentration, and current density. By anodic oxidation, it is possible to get amorphous or crystalline oxide, depending on the applied voltage and electrolyte used [13,45]. Ercan et al [46] postulated that anodization can create novel nanotubular structures that can influence the concentration and conformation of adsorbed proteins to alter cellular interactions. Various studies have shown that in comparison with conventional titanium, the anodized nanotubular titanium showed increased osteoblast adhesion, osteocalcin production, alkaline phosphatase activity, and fibronectin adsorption [47,48]. It is also shown that osteoblasts are well spread, and they increase deposition of calcium-containing minerals on anodized nanotubular titanium [49]. Anodized surfaces result in a strong reinforcement of the bone response, with higher values for biomechanical and histomorphometric tests in comparison with machined surfaces [7]. A higher clinical success rate was observed for the anodized titanium implants in comparison with turned titanium surfaces of similar shapes [50]. A total of 2 mechanisms have been proposed to explain this osseointegration: mechanical interlocking through bone growth in pores and biochemical bonding [51,52]. Modifications to the chemical composition of the titanium oxide layer have been tested with the incorporation of magnesium, calcium, sulfur, or phosphorus. It has been found that incorporating magnesium into the titanium oxide layer leads to a higher removal torque value compared with other ions [7,52].

Roughening of Implants by Sol Gel (Titania, Calcium Orthophosphates, Hydroxyapatite, and Silica Coatings)

Sol gel is a technique widely used to deposit surface coatings on the dental implants, such as TiO_2, calcium orthophosphates ($CaPO_4$), HA, Silica, and TiO_2 [53-56]. The sol-gel technique

involves the evolution of inorganic nanoscale networks in a continuous liquid phase through the formation of colloidal suspension, which is followed by gelation of the sol. In a typical sol-gel process, a colloidal suspension, or a sol, is formed from the hydrolysis and polymerization reactions of the precursors, which are usually inorganic metal salts or metal organic compounds, such as metal alkoxides. Complete polymerization and loss of solvent leads to the transition from the liquid sol into a solid gel phase. Thin films can be produced on a piece of substrate by spin coating or dip coating. A wet gel will form when the sol is cast into a mold, and the wet gel is converted into a dense ceramic, with further drying and heat treatment. A highly porous and extremely low-density material called an aerogel is obtained if the solvent in a wet gel is removed under a supercritical condition. Ceramic fibers can be drawn from the sol when the viscosity of a sol is adjusted into a proper viscosity range. Ultrafine and uniform ceramic powders are formed by precipitation, spray pyrolysis, or emulsion techniques. Under proper conditions, nanomaterials can be obtained [57-59].

Titania Coating

TiO_2 coatings on titanium have been used to improve the corrosion resistance of titanium. In practice, the very thin (at most, several tens of nanometers) oxide film on the titanium surface, which is formed in an aqueous environment, plays a decisive role in determining the biocompatibility and corrosion behavior of the titanium implant [60,61]. As the corrosion resistance is known to increase with the thickness of the oxide layer [61-63], many attempts have been made to form a thick TiO_2 layer on the titanium substrate, using various methods, such as anodization, thermal oxidation, and the sol-gel process.

Calcium Phosphate Coating

CaP coatings provided titanium implants with an osteoconductive surface. Following implantation, the dissolution of CaP coatings in the periimplant region increased ionic strength and saturation of blood, leading to the precipitation of biological apatite nanocrystals onto the surface of implants. This biological apatite layer incorporates proteins and promotes the adhesion of osteoprogenitor cells that would produce the extracellular matrix of bone tissue. Furthermore, it has been also shown that osteoclasts, the bone resorbing cells, are able to degrade the CaP coatings through enzymatic ways and create resorption pits on the coated surface. Finally, the presence of CaP coatings on metals promotes an early osseointegration of implants with a direct bone bonding as compared with noncoated surfaces. Finally, the presence of CaP coatings on metals promotes an early osseointegration of implants with a direct bone bonding as compared with noncoated surfaces. The challenge is to produce CaP coatings that would dissolve at a similar rate than bone apposition to get a direct bone contact on implant surfaces [61].

Roughening of Implants by Polymer Demixing

Polymer demixing is receiving particular attention, as it is a method that can develop topographies over a large area by a relatively cheap manufacturing method. By controlling the polymer concentration and the proportions of the polymers, different topographies can be produced. These can be pits, islands, or ribbons of varying height or depth. The ratio of the polymers used varies the topography shape, and the concentration of polymer in the casting solution changes the feature sizes [62]. A 2-polymer mixture is spin cast so that phase separation occurs, resulting in topographies distributed across the surface, with geometry determined by choice of polymers, solvent, substrate, and spin casting parameters, with cell response shown to vary with topography geometry. It can control not only the topography's pattern but also the scale of such topography within nanoscale (10-100 nm). Features created using this technique have a somewhat disordered spatial arrangement; yet, very precise control can be achieved in the vertical scale. However, nanometric features created by polymer demixing often tend to exhibit larger micrometric structures in 1 or more planes, and they can exhibit different chemistries in addition to topography. This technique has proved to increase adhesion, proliferation, cytoskeleton deviant, and gene expression on nanosurface created on titanium [59,63,64].

Chemical Vapor Deposition

Chemical vapor deposition is a process involving chemical reactions between chemicals in the gas phase and the sample surface, resulting in the deposition of a nonvolatile compound on the substrate [65]. The substrates are heated at high temperature to cause the gases to decompose, resulting in deposition. Vapor deposition processes usually take place within a vacuum chamber. If no chemical reaction occurs, this process is called physical vapor deposition; otherwise, it is called chemical vapor deposition. In chemical vapor deposition processes, thermal energy heats the gases in the coating chamber and drives the deposition reaction. Thick crystalline TiO_2 films with grain sizes below 30 nm, as well as TiO_2 nanoparticles with sizes below 10 nm, can be obtained with this method [66,67]. Surfaces created using this technique promote the adhesion of osteoblasts while minimizing the adhesion of fibroblasts [68]. Implant topography used to enhance the tissue-abutment interface remains largely unexplored. It should be noted that the currently available implants differ in their micron-level topography, their design, and their bulk material composition. It may be difficult to derive specific conclusions from the aggregate data regarding surface topography alone. However, for each example of current implant surfaces of available implants and cell culture, histological and clinical data suggest that surface modification offers incremental advantages to clinical problems where rapid bone accrual at the implant surface provides solutions.

Antibiotic Coatings

Antibacterial coatings on the surface have been studied as a possible way to prevent surgical-site infections. Gentamycin, along with the layer of HA, can be coated onto the implant surface, which may act as a local prophylactic agent, along with the systemic antibiotics in dental implant surgery. It was seen that the bacterial adhesion by Streptococcus mitis and Actinomyces oris can be restricted by acidic pH and aerobic atmosphere [69].

Stem-Cell Therapies and Surface Modification

Surface treatment of titanium screw-shaped implants creates a nanopattern that has been demonstrated *in vivo* to be associated with an enhanced osteogenesis. Several studies confirmed the observation, stating the promotion of stem cells' growth, provided by oxidative nanopattering. Furthermore, the most suitable nanoarrangement of TiO_2 nanotubes was with a diameter of 15 nm in a vertical alignment and was associated with a high spreading and differentiation of rat mesenchymal stem cells (MSCs) into the osteogenic lineage. Notably, 15 nm roughly correspond to the predicted lateral spacing of integrin receptors in the flourapatitecomplexes. In adults, the osteoblast is derived from a bone marrow stromal fibroblastic stem cell, termed the MSC, a nonhematopoietic multipotent stem-like cell vital for the osteogenic process capable of differentiating into both osteoblastic and nonosteoblastic lineages, thus enhancing the bone commitment and osseointegration [69-71].

Shot Peening/Laser Peening

Shot peening is similar to sand blasting, where the surface is bombarded with small spherical particles, each particle on coming in contact with the surface causes small indentations or dimples to form. Laser peening involves the rise of high-intensity (5-15 GW/cm^2) nanoscale pulses (10-30 ns) of a laser beam striking a protective layer of paint on the metallic surface. These implants demonstrate a regular honeycomb pattern with small pores [71].

Photofunctionalization

UV treatment of dental implant surfaces enhances bioactivity and osseointegration by altering the TiO_2 on the surface. By promoting interactions of cells and proteins to the implant on a molecular level, UV light is believed to enhance the osteoconductivity. UV treatment reduces the degree of surface hydrocarbon and increases surface energy and wettability by converting hydrophobic implants to superhydrophilic. UV light has been suggested to raise the level of protein absorption and cellular attachment to titanium surfaces, and it has been shown to restore bioactivity caused by age-related degradations. UV treatment is simple and cost effective for all types of titanium surfaces [72,73].

Biomolecular Coatings

The biomolecular coatings that can be used are the following: (1) bone morphogenic proteins (BMP), (2) non-BMP growth factors, (3) peptides, and (4) extracellular matrix. The surface-specific adsorbed biofilm determines cell adhesion, as proteins act as contact for the attachment of cells. This is accomplished by means of integrins, which are specific transmembrane receptors that bind to adhesive proteins on the biomaterials' surface and to components of the cytoskeleton through their extra and intracellular domains, respectively. In general, the biocompatibility of bone-replacing implant materials is closely related to osteoblast adhesion onto their surface. Osteoblast attachment, adhesion, and spreading will influence the capacity of these cells to proliferate and differentiate itself upon contact with the implant. These latter processes are quintessential for the establishment of a mechanically solid interface, with complete fusion between the implant surface and bone tissue without any intervening fibrous tissue.

Self-Assembled Monolayers on Nanotextured Titanium

The recent development of nanomaterial science raised a large interest in understanding the influence of nanoscale properties of materials on the behavior of biomolecules. In particular, it was shown that cellular adhesion can be governed by selective nanostructuring of biomaterials [74]. Self-assembly of molecular monolayers is another powerful approach to modify surface properties. Thiol-based self-assembled monolayers (SAMs) on metals, mostly on gold, have been extensively studied and used as model systems for a variety of applications. In general, these highly ordered SAMs can alter surface electronic levels, hydrophobicity, and adhesive properties, and they provide the surface with chemical functional groups. For oxide surfaces, a variety of molecules, including alkyltrichlorosilanes, phosphonates, and carboxylic acids, can be grafted on the surface, although the resulting films are generally not as well ordered as alkanethiols on gold. A recent interest has emerged for organic functionalization of the native oxide surfaces of tantalum, titanium, and related alloys in connection with their wide use as biocompatible materials, particularly in implants. For this purpose, phosphoric acid–terminated alkyl chains were shown as a good candidate for building SAMs on such materials because of their strong chemical bonding to surface oxides. However, similar functionalization of commercial titanium metal, which is more relevant to fabrication of bioimplants, leads to lower contact angles [66].

Flouride-Modified Implant Surfaces

The element fluoride was selected as a surface modification agent because of its specific qualities both in contact with calcified tissues and also in contact with titanium. Fluoride was known to have a particular affinity for calcified tissues, and it had proven an effect as a prophylactic agent against dental caries by binding to calcium forming calcium fluoride and fluorapatite, leading to an increased stability of the HA structure and resistance against acid attach [67].

The calcium-binding capacity of fluoride has also been successfully used in the treatment of systemic bone diseases, such as osteoporosis. Systemic treatment with fluoride was reported to give an increased trabecular density and further an induced calcification of bone, leading to a stronger bone, with improved load-bearing capacities and improved fracture resistance. There were indications in the literature that fluoride acted primarily on osteoprogenitor cells or undifferentiated osteoblasts, and fluoride thus had an effect at the cellular level, in addition to a physicochemical effect. It was reported in studies that fluoride treatment of bone triggered acute increases of intrinsic calcium levels, further indicating a cellular effect of fluoride [75]. A surface modification of titanium implants with fluoride incorporated into the superficial TiO_2 layer could thus lead to an implant with an improved bone response compared with nonmodified titanium implants. Studies were therefore initiated to establish a method for modifying titanium with the use of fluoride to create an implant intended to have improved biological properties. The nanoscale roughness created by the fluoride modification may add a further bone-promoting effect

to the already seen by the microstructure because of the blasting. A unique nucleating effect is demonstrated by fluoride-modified titanium, in the case when the implant is immersed into a liquid saturated with respect to calcium and phosphate, it attracts these ions to the surface, and crystals of CaP start to grow [76].

Results

Coating the implant surfaces with rhBMP-2 and recombinant human vascular endothelial growth factor I65 (rhVEGFI65) affects osseointegration. On testing the effect of coating, there were 5 different groups of implants:

1. AE surface (control group);
2. CaP coated surface (CaP group);
3. CaP bearing incorporated rhBMP-2 (BMP group);
4. CaP bearing incorporated rhVEGFI65 (VEGF group); and
5. CaP bearing incorporated rhBMP-2+rhVEGFI65 (BMP+VEGF group).

On osseointegration, it was seen that the BMP and BMP+VEGF groups showed significant enhancement in bone volume density compared with the AE control group. All implants with CaP coating demonstrated significantly enhanced BIC rates compared with the AE controls at 2 weeks. However, the BMP+VEGF group did not significantly enhance BIC at 4 weeks. It was concluded that the biomimetic CaP-coated implant surfaces, with both BMP and VEGF, enhance bone volume density but not BIC [77].

Microstructured microrough surface topography implants provided by the grit-blasting/acid-etching process were further biofunctionalized using HA, bioactive peptide, or any bioactive substance. When (1) microstructured+HA+a low concentration of bioactive peptide (20 µg/mL), (2) micro-structured+HA, (3) microstructured, and (4) microstructured+HA+a high concentration of bioactive peptide (200 µg/mL) were compared, implants with 200 µg/mL peptide had the highest mean value of direct BIC. In addition, bone density analysis revealed that implant surfaces with 20 µg/mL peptide provided a higher adjacent bone density when compared with the other groups. Nevertheless, the differences among the groups were also not statistically significant. The authors concluded that biofunctionalization of the implant surface might interfere in the bone apposition around implants, especially regarding the aspect of bone density [78].

When a dual AE surface (minimally rough) had significantly higher rabbit-reverse torque (RTQ) values than when grit blasted (moderately rough) and plasma sprayed (rough) values were assessed to analyze the effect of coarse surface roughness, it was seen that coarse surface roughness had no benefit [79,80].

In recent years, studies on submicron, micron, and coarse roughness properties have been presented. It seems that all 3 layers play an important role in overall osseointegration, with each layer addressing bone formation at different time points. In vitro studies have evaluated the surface topography effects on bone formation through osteoconduction, including the steps of protein absorption, fibrin clot retention, and platelet interaction. For example, enhanced surface topographies, because of blasting or acid etching, displayed significantly greater fibrin retention forces than machined surfaces. Microtopographic surfaces, defined as those exhibiting features in the scale range of platelets (≤3 µm), displayed greater platelet activation than smoother surfaces. The new T3 implant (BIOMET 3i) has a surface addressing different aspects of osseointegration and periimplant health. The coronal aspect of the implant has a microtopography similar to the fully etched OSSEOTITE implant, comprising submicron features superimposed on 1-3 µm pitting, overlaid on a minimally rough surface topography (Sa<1.0 µm). From the base of the collar to the apical tip, the T3 implant has greater roughness. The resulting trilevel surface comprises submicron features of CaP nanoparticles superimposed on 1-3 µm pitting, overlaid on a moderately rough surface topography (Sa ~1.4 µm). The apical surface is designed to enhance osseointegration. As such, the included surface features have been researched to assess their potential impacts on de novo bone formation and the strength of the resulting bone-to-implant interface at different time points: nanoroughness to initiate osseointegration, double acid-etchedfor the next osseointegrative time point, and course micron features for long-term bone locking. Preliminary clinical results are promising in different bone qualities and locations. However, further follow- up is needed before definitive conclusions can be drawn about this implant surface.

Furthermore, it is seen that fluoride-modified titanium implants increase the expression of Runt-related transcription factor 1 (RUNX-2), osterix, type I collagen, and bone sialoprotein and increases *alkaline phosphatase* activity. In addition, fluoride modification augments the thrombogenic properties of titanium, promoting fibrinogen activation and rapid coagulation, resulting in a less dense fibrin clot that could promote osteoblast migration to the implant surface in vivo [81].

Discussion

Surface characteristics play a special role in the biological performance of implants. Mechanical properties, such as Young's modulus, and fatigue properties are mainly determined by the bulk of the material and chemical and biological interactions between the material and the host tissue. They are closely associated with the material surface properties. These interactions include early events, such as binding of water molecules, ions, and biomolecules, as well as mineralization at the implant surface. The original surface is thus a result of these early interactions with a conditioning layer, on which the cells will eventually interact. This is regarded as one of the factors that will determine the tissue regeneration around the implant [8]. It is a generally held and very widely supported principle that implants that have a roughened surface are much more likely to rapidly osseointegrate than implants with a smooth-machined surface, with the optimal roughness being in the range of 1-1 OpM. This may be because of implants with smooth surfaces being more susceptible to fibrous encapsulation than implants with roughened surfaces [82]. Fibrous encapsulation is the formation of a poorly vascularized collagenous capsule around the implant, which results in the failure of osseointegration. There are a number of factors that can cause fibrous encapsulation, including a sustained inflammatory response, lack of vascularization at the implant

site, and low levels of osteoblast migration or attachment to the implant surface [83]. The ultimate result of fibrous encapsulation is that the tissue does not attach directly to the implant surface, leaving a space between the fibrous capsule and implant, which fills with fluid. This fluid-filled space provides an ideal environment for bacterial infiltration and a subsequent infection, which leads to bone resorption via a sustained inflammatory response.

Roughened surfaces also have a thicker titanium oxide layer, which is a reactive layer of surface particles thought to have a dynamic effect on surrounding tissues, encouraging attachment. There is a broad consensus that rough implant surfaces have superior osseointegrative potential than smooth implant surfaces. However, there is a broad range of methods to create roughened titanium surfaces, and there has been much discussion in the literature about which of these methods creates surfaces optimized for osseointegration. Surface roughness can be divided into 3 levels depending on the scale of the features: macro, micro, and nanosized topologies. The macrolevel is defined as one which has topographical features in the range of millimetres to tens of microns. This scale is directly related to implant geometry, with threaded screw and macroporous surface treatments giving surface roughness of more than 10 microns. The microtopographic profile of dental implants is defined as one where surface roughness is in the range of 1-10 um. This range of roughness maximizes the interlocking between mineralized bone and the surface of the implant [7,26,84]. At the nanoscale, a more textured surface topography increases the surface energy. Nanotopography might also directly influence cell proliferation and differentiation, as it has been suggested that nanopatterning can modulate cell behavior [25,61,85-88]. Repetitiveness and homogeneity are key parameters to define the nanostructure of an implant surface, but these are difficult to quantify and are considered as qualitative morphological parameters. If nanostructures are not clearly visible (no patterns, no particles, and insignificant texture) or not homogeneous and repetitive, the surface should be considered as nanosmooth. Grit blasting is one of the most common methods by which titanium dental implants are roughened. The increased osseointegration was confirmed by Rasmusson et al [89], who investigated the osteogenic properties of titanium grit-blasted surfaces. Wennerberg et al [7,26,30] also demonstrated with a rabbit model that grit blasting with TiO_2 or Al_2O_3 particles gave similar values of BIC, but it drastically increased the biomechanical fixation of the implants when compared with smooth titanium. These studies have shown that the torque force increased with the surface roughness of the implants while comparable values in bone apposition were observed. Nevertheless, Aparicio et al [34] highlighted some features related to alumina blasting for dental implants that could compromise osseointegration, such as particle detachment during the healing process and absorption by the surrounding tissues. The use of HA to roughen implant surfaces has been reported to result in similar rates of bone apposition around implants as other techniques, but HA has the advantage of being resorbable *in situ*. However, several in vitro and in vivo studies [7,26,30,89] suggested that grit-blasted titanium surfaces encourage osteoblast differentiation and, by extension, osseointegration. Cells from both osteoblast cell lines and primary mandibular bone from various species grown on grit-blasted titanium surfaces have been reported to increase expression of osteoblast specific messenger RNA and proteins, as well as increase mineralization compared with cell grown on smooth surfaces. Similarly, grit-blasted microimplants in humans have been shown to increase bone apposition compared with smooth-machined edges [90].

Another titanium implant surface treatment that has been reported to increase the chances of osseointegration is acid etching. Acid etching is often used in conjunction with grit blasting in implant manufacture. Cho et al [91] postulated that chemical acid etching alone of the titanium implant surface has the potential to greatly enhance osseointegration without adding particulate matter (eg, TPS or HA) or embedding surface contaminants (eg, grit particles). Several investigators [92] have reported that grit particles can remain impregnated in the implant material, and they are potentially a causative agent in observed tissue breakdown. Their study indicated that rough AE implants achieve greater resistance to reverse torque removal than machined-surface implants, which infers that chemically acid etching implant surfaces has higher strengths of osseointegration than machined-implant surfaces [91]. Lima et al [93] designed a study to measure implant osseointegration using 3 different surface treatments. fiber mesh, grit blasting, and acid etching, and they concluded that overall, AE surfaces demonstrated greater mean osseointegration than fiber mesh surfaces. A study conducted by Bana et al [94] indicates that etching with concentrated sulfuric acid is an effective way to modify the surface of titanium for biological applications. Guo et al [68] compared the osteoinductive and bone-specific gene expression in cells adherent to TiO_2-grit-blasted versus TiO_2 grit-blasted and HF-treated (TiO_2/HF) commercially pure titanium implant surfaces. They concluded that as a marker of osteoinduction, the increased levels of RUNX-2 in cells adherent to the TiO_2/HF surfaces suggest that the additional HF treatment of the TiO_2 grit-blasted surface results in surface properties that support adherent cell osteoinduction. Etching with strong acids has been shown to cause hydrogen embrittlement of titanium, which can cause microcracks on the surface, potentially undermining the structural integrity of the implant and ultimately leading to implant failure. Nevertheless, AE implants have a proven clinical track record, and they are still in use [95]. Plasma surface coating of HA or titanium is one of the most effective methods in developing these surface depositions, thus enhancing the surface roughness. A metastable CaP solution provides excellent bioactivity of the HA/YSZ/Ti- 6Al-4V composite coating, which has the ability to induce bone-like apatite nucleation and growth on implant surface. HA coatings promote better cell proliferation. According to Liu et al [96], the bonding strength of HA on titanium alloys decreased long hours of immersion time in the SBF. After an immersion in the SBF, the HA coatings became weak because of the intermellar or cohesive bonding degradation in the coating. However, Knabe et al [97] found that a plasma-sprayed titanium surface exhibits the highest surface roughness compared with a deep profile surface structure (the surface was acid etched and grit blasted), and in an *in vitro* test, the HA coating has less bone contact compared with other surface modifications. Some reports showed that the mechanical

properties of HA can be significantly improved by the addition of yttria-stabilized zirconia. HA coatings reinforced with zirconia possessed better performance in bond strength and dissolution behavior of the titanium implants. Over the same period (4 weeks after SBF immersion), the HA/YSZ/Ti-6Al-4V composite coating showed a reduced tensile strength by ~27.7% compared with the pure HA coatings with ~78.8% [98]. It has been reported that more new bone is formed, and new bone grows more rapidly into pores of the surface of alkaline-modified plasma-sprayed implants, and this may be beneficial to reduce clinical healing times and consequently improve implant success rates. Kim et al [60] concluded that the HA layer was employed to enhance the bioactivity and osteoconductivity of the titanium substrate, and the TiO_2 buffer layer was inserted to improve the bonding strength between the HA layer and titanium substrate, as well as to prevent the corrosion of the titanium substrate. The sol-gel approach was favored because of the chemical homogeneity, high surface area in single step, fine grain size of the resultant coating, the low crystallization temperature, and mass producibility of the process itself [60]. Cordioli et al [79] reported no benefits by increasing coarse surface roughness at 5 weeks in an RTQ model, specifically demonstrating that a dual AE surface (minimally rough) had significantly higher RTQ values than grit-blasted (moderately rough) and plasma-sprayed (rough) surface. These findings are consistent with those of Klokkevold et al [80], who measured reverse torque (RTQ) for dual AE and moderately rough-surfaced implants 1 month after placement in rabbit tibias. The latter study included additional time points for testing reverse torque and showed that the rougher-surfaced implants had significantly higher RTQ results at 2 and 3 months after placement. The authors attributed the higher RTQ to the moderately rough surfaces' increased depth of topography and subsequent void volume, which permitted additional bone ingrowth for mechanical interlocking. In recent years, studies on submicron, micron, and coarse roughness properties have been presented. It seems that all 3 layers play an important role in overall osseointegration, with each layer addressing bone formation at different time points. In vitro studies have evaluated the surface topography effects on bone formation through osteoconduction, including the steps of protein absorption, fibrin clot retention, and platelet interaction. Becker et al [99] investigated bone formation onto sand-blasted and AE (control group), chromosulfuric acid surface–enhanced (CSA group), and recombinant human BMP-2 (rhBMP-2) biocoated CSA—BMP-A group: noncovalently immobilized rhBMP-2 (596 ng/cm2); BMP-B group: covalently immobilized rhBMP-2 (819 ng/cm2)—implants after placement in the mandibles and tibiae of dogs. After 4 weeks of healing, BIC values appeared to be highest for the BMP-B group, followed by BMP-A, CSA, and the control in both the mandible and the tibia. Wikesjo et al [100] studied whether adsorbing rhBMP2 onto a titanium porous oxide (TPO) implant surface might increase or accelerate local bone formation and support osseointegration in the posterior mandible (type II bone) in dogs. A similar study conducted by Wikesjo et al to evaluate local bone formation and osseointegration in the posterior maxillae (type IV bone) was analyzed in 8 adult monkeys. The authors concluded that rhBMP-2–coated TPO surfaces enhanced local bone formation in type IV bone in a dose-dependent fashion in nonhuman primates, resulting in significant osseointegration.

Nikolidakis et al [101] examined the effect of transforming growth factor beta 1 (TGF-beta 1) on the early bone healing around dental implants installed into the femoral condyle of goats. The authors concluded that a low dose of TGF-beta 1 has a negative influence on the integration of oral implants in trabecular bone during the early postimplantation healing phase. Schouten et al [102] investigated the effect of implant design, surface properties, and TGF-beta 1 on periimplant bone response, an extensive improvement of the bone response to titanium implants can be obtained by adding an electrosprayed CaP coating. The supplementation of a 1 µg TGF-beta 1 coating has only a marginal effect. The cellular response to fluoride-modified titanium implants has been assessed in different osteoblast cellular models using MSCs from different origin, primary cultures of osteoblasts, nontransformed clonal cell lines (MC3T3-E1), or osteosarcoma cell lines (MG63). The different cellular models, time-point of the analysis, or implant production might explain the differences in the reported results. Thus, although some studies have reported increased proliferation on fluoride-modified titanium implants, others failed [103,104]. In solution, fluoride has been proved to stimulate bone cell proliferation, but its effect varies according to the stage of differentiation of the cells; thus, the fluoride ion acts primarily on osteoprogenitor cells or undifferentiated osteoblasts rather than on more differentiated osteoblasts. In addition, some studies find higher cell adhesion in fluoride-modified titanium implants compared with control; other studies found no differences. In this regard, it is important to include the importance of the surface topography when discussing the number of cells attached on the surfaces, as the modification of titanium surface with HF is influenced by HF concentration, the exposure time, and the initial surface topography. In the same line, differences in the results of gene expression analysis might also be explained by differences in the roughness or chemical composition of the surfaces used in the different studies.

Thus, the future of dental implantology should aim to develop surfaces with controlled and standardized topography or chemistry. Different methods have been described to modify or embellish titanium substrates by mechanical and chemical methods. Modification of titanium endosseous implant surfaces enhances interfacial bone formation measured as BIC. The future of dental implantology should aim at developing surfaces with controlled and standardized topography or chemistry. This approach is the only way to understand protein, cell, and tissue interactions with implant surfaces. These therapeutic strategies should ultimately enhance the osseointegration process of dental implants for their long-term success.

Conflicts of Interest

None declared.

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Abbreviations

AE: acid-etched
BIC: bone-to-implant contact
BMP: bone morphogenic protein
CaP: calcium phosphate
CSA: chromosulfuric acid
HA: hydroxyapatite
MSC: mesenchymal stem cell
NaOH: sodium hydroxide
RTQ: rabbit-reverse torque
RUNX-2: Runt-related transcription factor 1
SAM: self-assembled monolayer
SBF: simulated body fluid
TGF-beta 1: transforming growth factor beta 1
TiO_2: titania
TPO: titanium porous oxide
TPS: titanium plasma spraying
VEGF: vascular endothelial growth factor

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