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Wearable Sensors in Syncope Management

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Syncope is a common disorder with a lifetime prevalence of about 40%. Implantable cardiac electronic devices, including implantable loop recorders (ILR) and implantable cardioverter-defibrillators (ICD), are well established in syncope management. However, despite the successful use of ILR and ICD, diagnosis and therapy still remain challenging in many patients due to the complex hemodynamic interplay of cardiac and vascular adaptations during impending syncopes. Wearable sensors might overcome some limitations, including misdiagnosis and inappropriate defibrillator shocks, because a variety of physiological measures can now be easily acquired by a single non-invasive device at high signal quality. In neurally-mediated syncope (NMS), which is the most common cause of syncope, advanced signal processing methodologies paved the way to develop devices for early syncope detection. In contrast to the relatively benign NMS, in arrhythmia-related syncopes immediate therapeutical intervention, predominantly by electrical defibrillation, is often mandatory. However, in patients with a transient risk of arrhythmia-related syncope, limitations of ICD therapy might outweigh their potential therapeutic benefits. In this context the wearable cardioverter-defibrillator offers alternative therapeutical options for some high-risk patients. Herein, we review recent evidence demonstrating that wearable sensors might be useful to overcome some limitations of implantable devices in syncope management.

MeSH Keywords: **Biosensing Techniques • Death, Sudden, Cardiac • Syncope • Syncope, Vasovagal**

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Background

Syncope is a common disorder with an enormously high lifetime prevalence of about 40% [1,2]. It is defined as a transient loss of consciousness attributable to global cerebral hypo-perfusion, further characterized by rapid onset, brevity, and spontaneous recovery [2]. Therapeutic options are often limited [3]. In this context, neurally-mediated syncope (NMS) is by far the most common cause of transient loss of consciousness but diagnosis can be challenging in some patients [4]. In patients with recurrent syncope of unexplained origin, implantable loop recorders (ILR) are now well established as a diagnostic tool as outlined in the guidelines of the European Society of Cardiology [3]. However, these implantable cardiac electronic devices currently do not monitor hemodynamic parameters beyond heart rate and rhythm. Importantly, it is now evident that the circulatory adjustments resulting in hypotension often occur just prior to a sudden loss of consciousness [1,5]. This opens up new avenues to predict syncope even before symptoms become manifest. NMS prediction by early and noninvasive measurement of the underlying circulatory adjustments would protect patients from syncope-related falls and accidents. Advanced signal processing in combination with the integration of these systems in wearable sensors have paved the way to develop novel approaches for early detection of impending syncopes. The avoidance of even a small routine surgical procedure is another advantage of wearable multi-sensor systems. This has an important impact on quality of life, especially in younger patients.

In contrast to the relative benign NMS, in arrhythmia-related syncopes, especially in structural heart disease, immediate therapeutic intervention by electrical defibrillation is often mandatory. This is important because these syncopes often have a rapid onset with a high risk of sudden cardiac death. In these patients immediate termination of a ventricular tachyarrhythmia by electrical defibrillation is often lifesaving. Therefore, the implantable cardioverter-defibrillator has become the therapy of first choice for a large number of patients with heart failure who have an impaired left ventricular ejection fraction [3]. However, in patients with a transient risk of arrhythmia-related syncope, ICD and accompanying risks, including device infections, lead defects, and traumatizing inappropriate shocks, might outweigh their potential therapeutic benefits [6]. For these patients the wearable cardioverter-defibrillator (WCD) has become a second therapeutic option besides implants, translating wearable sensors into clinical practice [6,7]. Herein, we review recent evidence and future perspectives indicating that wearable sensor technologies open up new avenues beyond implantable cardiac electronic devices in the management of patients with syncope.

Syncope Prediction

The high incidence and prevalence of syncope and related morbidity underpin the necessity of an early detection of an approaching syncope. In NMS this is important in diagnostic as well as in therapeutical settings. Since pharmacological and interventional therapies are limited, acute syncope prediction would prevent falls in these patients. The prediction of potentially life-threatening arrhythmia-related syncopes is especially important in patients with structural heart disease to prevent sudden cardiac death. The hemodynamic interaction of various systems, including vascular- and heart rate/rhythm-related parameters, underscores the need for multimodality of wearable sensor systems, which are addressed here.

Neurally-mediated syncope

The triggering mechanisms of NMS are complex and incompletely understood [8]. During the development of NMS, postural-dependant venous blood pooling sets off a cascade of autonomic reflexes [9,10]. The resulting neurally-mediated hemodynamic adaptations [11,12] typically result in a decline in blood pressure (BP) and a change (decrease or increase) in heart rate (HR) [13]. Hemodynamic studies indicate that vasodilatation is the most common reproducible phenomenon occurring just prior to the onset of dizziness or a sudden loss of consciousness [2,14]. Several approaches, predominantly based on HR and/or BP, have been proposed to acutely predict syncope, with mixed results as discussed elsewhere in detail [15–20]. Several groups demonstrated that the combination of HR and BP analysis improves NMS prediction [1,13,21]. However, to detect impending NMS early on, continuous BP measurements are needed. This approach, however, is not yet technically feasible in an ambulatory setting. In recent years we [1,22,23] and others [24–26] have been working on algorithms, taking into account photoplethysmogram (PPG) morphology features, towards a better characterization of patient status in different settings. In line with previous studies, we found that pulse wave characteristics are useful to characterize BP changes [22,27]. In this context, the pulse arrival time (PAT) is a simple and reliable parameter to characterize blood pressure changes (Figure 1). PAT is defined as the time between the R peak in the electrocardiogram and the onset of the pulse wave in the periphery [1]. In particular, it has been demonstrated that a pertinent relation of PAT measures with systolic BP can be observed shortly before syncope, when PAT starts to steadily increase [23]. This might explain the predictive power of PAT to detect critical events related to BP regulation failures based on this simple and easy measure [28]. After having investigated a wide range of male and female patients (age: 18–80 years) with and without various cardiovascular diseases, we found that PAT changes preceding syncope appear to be relatively homogenous. However, larger

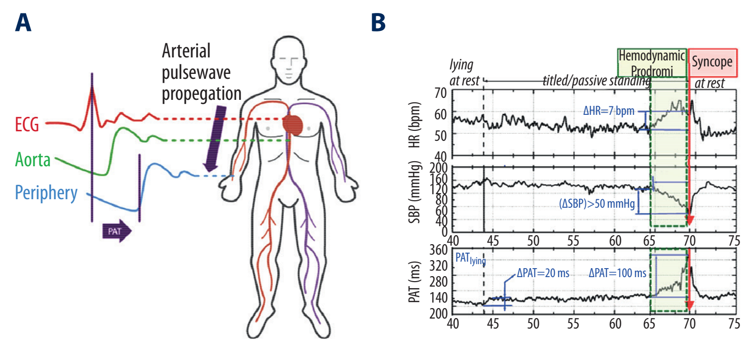


Figure 1. Pulse arrival time for neurally-mediated syncope prediction. (**A**) Illustration demonstrating the pulse arrival time (PAT) reflecting the arterial pulse wave propagation. The PAT is defined as the time between the R peak in the electrocardiogram and the onset of the pulse wave in the periphery. A Photoplethysmogram (PPG) and a single-lead electrocardiogram (ECG) are used for PAT calculation. (**B**) Example showing hemodynamic adaptations preceding syncope during head-up tilt table testing. Note the relationship between the increase in systolic blood pressure (SBP) and the decrease in PAT while heart rate (HR) is increasing.

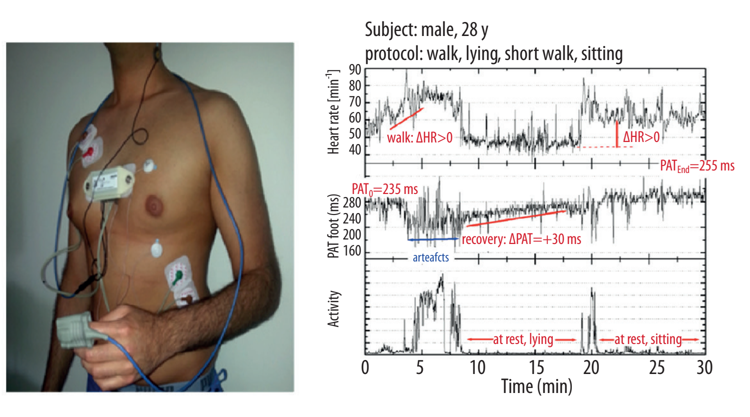
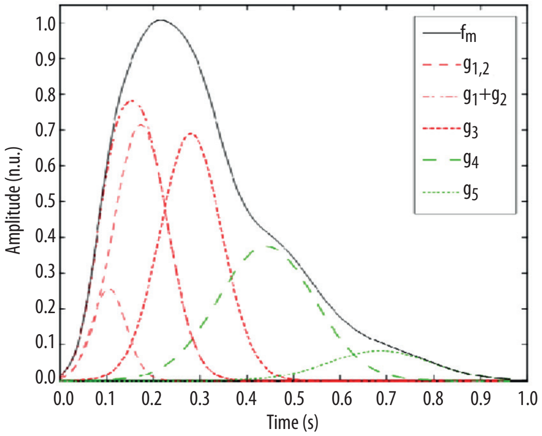


Figure 2. Body-worn sensor system for neurally-mediated syncope prediction. Left panel: patient with the modified Sensatron device using an electrocardiogram and the photoplethysmogram for syncope prediction. Right panel: Example showing signals (heart rate, pulse arrival time [PATfoot], and patient activity [activity]) in a patient during walking, sitting, and lying, from a series of investigations in unsupervised scenarios illustrating the complexity of such a measurement. For Details see [1,22,23,29].

patient numbers are needed to clarify the impact of age-dependent and pathophysiological changes in cardiac and vascular function. Because PAT includes (1) the pre-ejection period and (2) the microvascular circulation (PPG from finger/ear/forehead), it appears to be useful in reflecing acute changes in BP, but might be limited in characterizing arterial stiffness in the context of acute syncope prediction. Importantly, PAT has, in general, a complex relation to systolic BP and HR that is rather difficult to interpret unless detailed context information is available [29]. However, since electrocardiogram (ECG) and PPG can be easily and comfortably acquired synchronously, these measures suggest a range of interesting applications in NMS diagnostic as well as training procedures (Figure 2) [30]. In patients undergoing head-up tilt table testing, we developed a syncope warning system and demonstrated the feasibility of PAT-based syncope prediction in patients without any evidence of heart rhythm disorders, including bundle branch block, atrioventricular block, or tachyarrhythmias [1]. A prospective study testing our previously developed algorithms [1,31] for NMS prediction in patients undergoing head-up tilt table testing and orthostatic self training, addressed the predictive value of this syncope warning system in a larger patient population (NCT01262508).

Arrhythmia-related syncope

In contrast to the almost always relatively benign NMS, arrhythmia-related syncopes often occur very fast without any prodromal symptoms [2]. Ventricular tachyarrhythmias are most common in this context. Affected patients have an increased risk of sudden cardiac death due to the sudden loss of cardiac output within seconds after the initiation of arrhythmias. ICD have been shown to protect patients at high risk for ventricular tachycardias from sudden cardiac death. However, defining a high-risk patient is still challenging. While the risk of death from early post-myocardial infarction is large, clinical trials have failed to demonstrate a mortality benefit from the early use of implantable defibrillators. Moreover, many patients are only transiently at high risk, limiting the value of an ICD in this population. This especially holds true for patients with various causes of transient heart failure. For high-risk patients with arrhythmia-related syncope who are not candidates for



$$f_m(t,\beta_j)=\Sigma_{j=1}^{5} g_j(t,\beta_j),\ \text{for}\ \beta_j=\{a,b,c\}$$

$$g_j(t,\beta_j)=a_j\,e^{\frac{-(t-b_j)^2}{2c_j^2}}$$

Figure 3. Characterization of hemodynamics using decomposition of the PPG signal into its forward and reflection waves. Upper panel: Representation of the multi-Gaussian model of a PPG pulse and individual Gaussian functions corresponding to the main forward wave and consequent reflection at the arterial pathway. The positions of the characteristic waves (here called Wa, Wb, Wc, Wd, and We waves) can provide insight about the locations of the individual components of the PPG pulse. Lower panel: Formulation of a proposed 5-Gaussian model. The parameters aj, bj, and cj correspond to the amplitude, location, and length, respectively, of the Gaussian function j. Here, the first 2 Gaussians correspond to the ventricular ejection and the third Gaussian is related to the first pulse reflection at the junction between the thoracic and abdominal aorta. The fourth and fifth Gaussians derive from the reflection at the juncture between the abdominal aorta and common iliac arteries and minor reflections and re-reflections in the systemic structure, respectively.

an ICD, the WCD has become an important therapeutical alternative [6,7]. Whether wearable defibrillators reduce mortality in (1) heart failure patients who are not candidates for an ICD (ClinicalTrials.gov: NCT01326624), or (2) after a myocardial infarction (NCT01446965) is currently under investigation [6].

Wearable Sensor Systems

Wearable sensors in neurally-mediated syncope management

The feasibility of integrating a syncope warning system into a body-worn network was the first step in conducting hemodynamic studies in patients with syncope. Based on a standard electrocardiogram, use of a PPG and an accelerometer enable hemodynamic changes to be characterized in syncope patients in standardized settings. A prototype device has been created (Figure 2). Current research focuses on more robust feature extraction approaches, since standard PPG signals are prone to artifacts.

During standardized diagnostic procedures (e.g., head-up tilt table testing), PPG-derived signals have been found to provide representative parameters for left ventricular and peripheral vascular performance [32,33]. Characterization of hemodynamics using decomposition of the PPG signal into its forward and reflection waves has been investigated (Figure 3). In this context, a novel algorithm for assessment of left ventricular ejection time from the PPG waveform has been introduced. We propose the use of Gaussian functions to model both systolic and diastolic phases of the PPG beat and consequently determine the onset and offset of the systolic ejection from the analysis of the systolic phase 3rd derivative. The results achieved by the proposed methodology revealed better estimation of left ventricular ejection time, and similar correlation with the echocardiographic reference, as compared with previously proposed algorithms.

The PAT methodology is based on hemodynamic surrogate measures, which are also sensitive to patient activities such as posture changes that are not necessarily related to blood pressure variations. The impact of posture on the PAT measure and related hemodynamic parameters such as the pre-ejection period in well-defined procedures has been characterized [29]. Additionally, the PAT of a monitored subject has been investigated in an unsupervised scenario illustrating the complexity of such a measurement. Our results show the failure of blood pressure inference based on simple calibration strategies using the PAT measure only. However, there are opportunities to compensate for the observed effects towards the realization of wearable cuff-less blood pressure monitoring devices. These findings emphasize the importance of accessing context information in personal healthcare applications, where vital sign monitoring is typically unsupervised. The presence of motion artifacts in PPG signals is one of the major obstacles in the extraction of reliable cardiovascular parameters in real time and continuous monitoring applications [34]. Recently, a novel algorithm for motion artifact detection, which is based on the analysis of the variations in the time and period domain characteristics of the PPG signal, has been introduced [22,34,35]. The extracted features are ranked using a feature selection algorithm (NMIFS) and the best features are used in a Support Vector Machine classification model to distinguish between clean and corrupted sections of the PPG signal. The results achieved show that period domain features play an especially important role in the discrimination of motion artifacts from clean PPG pulses.

In this connection, the Sensatron is a multi-sensor device that records an ECG, an impedance cardiogram (ICG), near-infrared

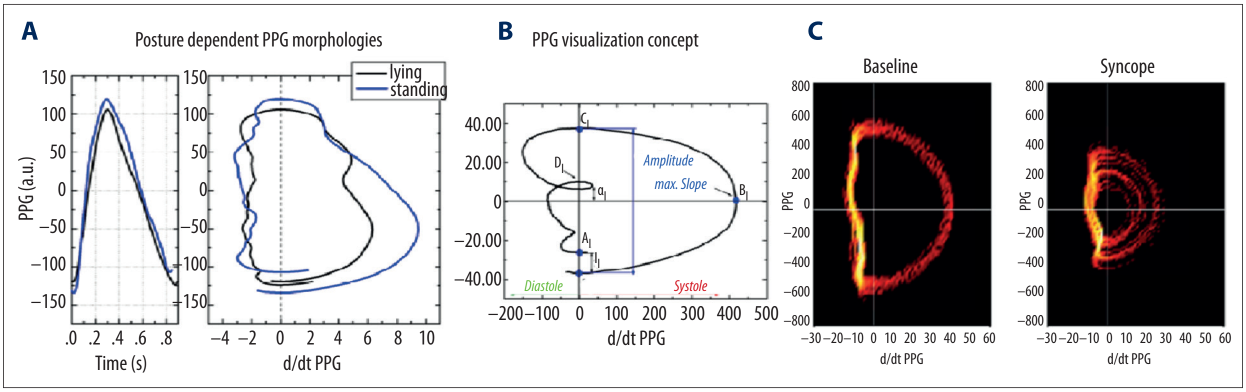


Figure 4. Phase-Space Representation of PPG Signals as Visualization Concept. (**A**) Comparison of 2 PPG acquired in lying and sitting posture with accompanying morphology changes. (**B**) Basic concept for the visualization of the PPG signal, where the PPG signal is plotted versus the derivative of the PPG. Characteristic points (A, B, C, D) for a single complete sequence i are marked. Additionally, it is indicated that the beginning of the cardiac cycle does not coincident with the beginning of the systolic cycle, which refers to a low-frequency modulation of the PPG (e.g., caused by respiration effort). (**C**) Histograms calculated for the states "basal" (Baseline) and "impending faint" (Syncope). This approach seems more intuitive than the classical time-amplitude representation of the waveforms and can be used to extract templates to compare different patient states. For details see text.

PPG, infrared PPG, and a thoracic inductive plethysmogram, as well as recording sound signals from 2 thorax locations. Up to three 3-axis acceleration sensors at the thorax, arms, or legs provide information on posture and movements. Data are stored on a memory card and can be wirelessly transmitted via Bluetooth. The design already takes into account an easy and planned adaptation to home monitoring scenarios for integration into functional textiles [35,36]. A first textile prototype was created within the "HeartCycle" project by "ClothingPlus" in Oy, Finland.

In addition, a novel visualization concept for PPG signals has been developed (Figure 4). This approach enables quick evaluation of PPG amplitude and amplitude oscillation, PPG slopes, and the existence of a local minima and maxima during the diastolic phase. This might be useful because morphological changes in the PPG during blood pressure break-down have been found. Our approach is based on a phase-space representation of the raw or pre-processed PPG signals, where basically the PPG signal is plotted versus the derivative of the same PPG sequence. The PPG signal is displayed based on this concept of a PPG pulse (i) until the next pulse (i+1). The beginning of the systolic phase (point Ai) appears at the lowest y-value at the zero-crossing of the x-axis, whereas the diastolic phase starts at the highest y value again at the zero-crossing of x (point Ci). The difference of the highest and lowest y-value (at point Ci and point Ai) represents the amplitude of the PPG. A zero-crossing during the diastolic phase indicates a fully developed dicrotic notch within the signal. The maximum slope during the systolic segment (point Bi) can be easily extracted and coincidences in this example with the zero-crossing of y, which is in general not the case.

Pre-processing steps include filtering, artefact detection and removal, optional normalization, and the noise-reduced calculation of the derivative. A storage unit is used to compare PPG signals acquired at different time segments (e.g., during a procedure). The current data processing and visualization prototype is based on Matlab. In addition, the rate of changes of heart rate, stiffness and reflection indexes, pre-ejection period, left ventricular ejection time, PAT, and pulse transit time parameters change preceding syncope. Preliminary evidence indicates that integration of these hemodynamic surrogate measures into existing syncope prediction algorithms reduces the number of false-positive event detections.

Wearable sensors in arrhythmia related syncope

The WCD is available for selected patients at increased risk for tachyarrhythmia-related syncope (Figure 5) [6,7]. The WCD is produced by a single manufacturer, ZOLL Lifecor Corp., Pittsburgh, PA, and received U.S. Food and Drug Administration approval in 2002 [37]. The WCD consists of 2 main components: the garment and the monitor. In recent years the WCD has been found to have robust ECG sensing and defibrillation capabilities [6,7]. The system uses 3 defibrillation electrodes, as well as 4 capacitive electrodes for long-term ECG monitoring (Figure 6). If a ventricular tachyarrhythmia is detected and therefore the risk for syncope is high, a vibration plate generates tactile notification as the first of a series of alarms [6]. Simultaneous activation of the 2 patient response buttons offers the possibility to withhold defibrillator discharge as long as the user is conscious. ECG recording of events and daily use are transmitted and stored by an internet-based information system [7]. The efficacy of the algorithm has been reviewed through a retrospective analysis of appropriate shocks, inappropriate shocks, and arrhythmia detections during a 1-year period [38]. The authors found that by incorporating a patient responsiveness test, as well as features

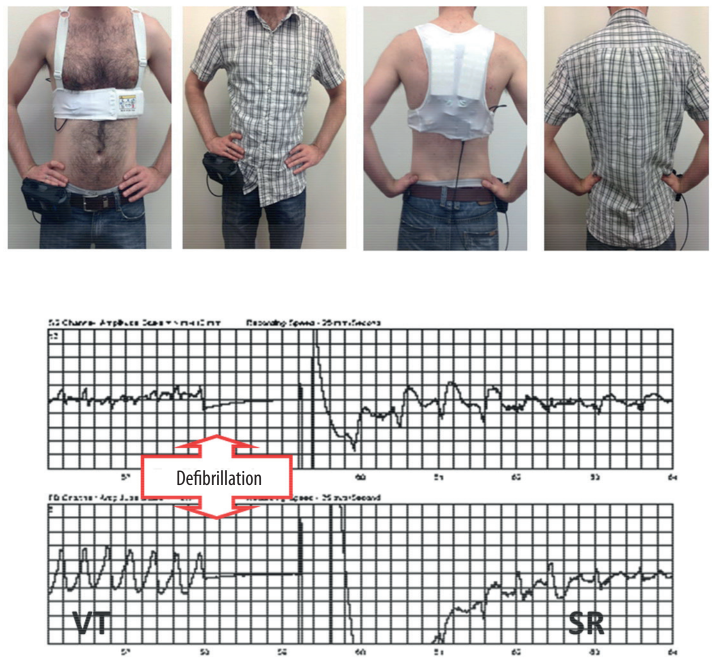


Figure 5. Wearable cardioverter-defibrillator (WCD) to treat ventricular tachyarrhythmia-related syncope. Upper panel: Example demonstrating a body-worn WCD (LifeVest System) in an anterior and posterior view without and with shirt. Lower panel: 2-lead electrocardiographic example showing termination of a ventricular tachycardia (VT) after defibrillation by the WCD restoring stable sinus rhythm (SR) following a syncope without prodromal symptoms.

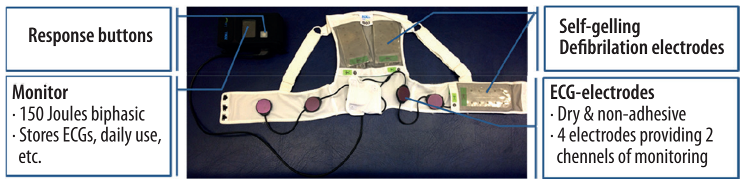


Figure 6. Wearable cardioverter-defibrillator (WCD) with related sensors. The WCD consists of 2 main components: the garment and the monitor. Two large posterior and 1 apical self-gelling defibrillation electrodes, as well as 4 (43×10 mm) non-adhesive capacitive dry tantalum oxide electrodes for long-term ECG monitoring, are integrated into the garment. The ECG-sensing electrodes provide 2 leads for electrocardiographic analysis. Defibrillation gel is emitted from gel capsules between the defibrillation electrodes and the skin immediately prior to shock delivery, lowering the electrode-skin interface impedance. In addition, this gel prevents skin irritation related to shock delivery. Incorporated into the system is a vibration plate to generate tactile notification when ventricular tachyarrhythmia is detected. The monitor unit contains a battery, a biphasic defibrillation module (capacitors and high-voltage converter), a digital signal processor for ECG analysis, an LCD display, and the patient response buttons to withhold defibrillator discharge. The latter is important in patients who do not experience a loss of consciousness despite arrhythmia detection. Also integrated into the monitor unit is a speaker for audible alarm and voice messages following the vibration alarm. For additional details see [6].

that eliminate or reduce signal interference common to external ECG electrodes [39], the WCD detection algorithm has a low risk of inappropriate shocks. In a retrospective analysis of about 100 patients at the University of Duesseldorf (unpublished), we found an even lower rate of inappropriate defibrillation in patients using the WCD, resulting in high patient satisfaction.

Conclusions and Future Perspectives

Predicting the most common cause of transient loss of consciousness – neurally-mediated syncope – is feasible by ECG- and PPG-based wearable multi-sensor systems. Miniaturized devices for ambulatory pulse arrival time measurement are on the horizon and might improve syncope warning systems in the future. Syncope prediction by PAT may also be realized in ambulatory blood pressure devices, which are extremely prevalent today in clinical practice. The option to use PAT for assessment of arterial stiffness is already available in some models of such devices. How the concept from HUTT can be translated to ambulatory settings is a topic of our ongoing research. Integration of recently presented algorithms (including parameters for left ventricular function) and peripheral vascular performance (including pre-ejection period, pulse transit time, and reflection indexes) in such wearable devices might additionally improve syncope management. For patients with structural heart disease who are at risk for potentially life-threatening tachyarrhythmias and related syncopes, the wearable cardioverter defibrillator has been found to be a relatively novel therapeutic option to prevent sudden cardiac death, and it is currently under investigation in randomized controlled trials. Since syncope is a highly complex entity representing the interplay of various systems, including vascular and heart rate/rhythm-related hemodynamics, the multimodality of wearable sensor systems may prove to be useful in various settings in and out of hospital. These include syncope management units, dedicated units for the treatment of complex ventricular arrhythmias, and home monitoring of patients with heart failure. In conclusion, wearable sensor technologies open up new diagnostic and therapeutical possibilities in the management of patients with syncope.

Conflicts of interest

The authors declare no conflict of interest.

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