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Unobtrusive acquisition of cardiorespiratory signals

Available techniques and perspectives for sleep medicine

The acquisition of physiological signals commonly requires sensors that are attached to the body. Depending on the measurement principle, electrodes, optical sensors, or (electro-)mechanical sensors are applied.

Polysomnography (PSG) captures a number of physiological signals by variable measurement principles and sensors (see ◘ Table 1). PSG and the corresponding sensors yield far-reaching statements on sleep, sleepiness, and attention. However, the systems used, i. e., the cabling and the sensors, imply a major reduction in patients' comfort and can significantly affect patients' sleep. Moreover, regarding many potential out-of-hospital applications in the context of sleep, sleepiness, and attention, PSG and the accompanying sensors are not applicable at all. Polygraphy uses a simplified setting compared to PSG (see ◘ Table 1). It is mainly used for screening purposes and is intended to be operable by patients at home, without the support of medical personnel. Polygraphy primarily directs cardiorespiratory function. Amongst other things, polygraphy allows detection of apnea and can provide information on continuous positive airway pressure therapy (CPAP) therapy. It can also be used to analyze heart rate (HR) dynamics, e. g., to estimate sympathetic activity. However, even polygraphy requires sensors attached to the skin, which disturb patients' comfort and might affect normal sleep. The self-application sometimes causes errors and said sensors can get misplaced, yielding corrupted measurements. Concerning long-term use, i. e., signal acquisition every night over longer periods, the comfort of current sensors is too low to be widely applied. Moreover, for applications without a clinical background, e. g., driver monitoring, even the simplified setup of polygraphy is not applicable, as a finger clip is not practicable.

Over the past years, various systems and techniques for unobtrusive acquisition of physiological signals, mostly directed at cardiorespiratory function, have evolved [4, 33]. The term "unobtrusive" thereby denotes non-contact or minimal-contact application, i. e., no sensor has to be attached to the body—neither directly, e. g., electrodes, nor integrated into clothing. The developments reflect the high demand for convenient means to monitor physiological signals and growing technical possibilities concerning hardware and software. Most of the proposed systems and methods were not specifically designed for sleep medicine. However, as they provide information on cardiorespiratory function, the ongoing developments open up novel opportunities even for sleep medicine.

This work provides an overview of techniques for unobtrusive acquisition of cardiorespiratory signals. We describe basic concepts, give examples of realizations, present the evaluation of available systems in the context of sleep, and discuss further opportunities and require-

Table 1 Signals which are typically recorded during polysomnography and polygraphy. Italics indicate information related to cardiorespiratory function. Given sensor principles represent common realizations. Note that varying setups can be used (particularly in polygraphy)

Signal/contained information	Recording technique	Typically done by polysomnography?	Typically done by polygraphy?
Brain function	Electroencephalogram	Yes, 3–6 channels	No
Eye movements	Electrooculogram	Yes, 2 channels	No
Chin muscle tone	Electromyogram	Yes, 2–3 channels	No
Leg muscle tone	Electromyogram	Yes, 2 channels	Optional
Behavior	Infrared video	Yes, 1 channel	No
Body movements	3D accelerometer	Yes, 1 channel	Optional
Body position	3D accelerometer	Yes, 3 channel[a]	Yes, 3 channel[a]
Heart function	*Electrocardiogram*	*Yes, 1–3 channels*	*Optional*
Pulse rate	*Finger photoplethysmogram*	*Yes, 1 channel*	*Yes, 1 channel*
Oxygen saturation	*Finger oxymetry*	*Yes, 1 channel*	*Yes, 1 channel*
Oronasal air flow	*Pressure transducers/thermocouples/thermistors*	*Yes, 1–2 channels*	*Yes, 1–2 channels*
Thoracic/abdominal respiratory effort	*Piezoelectric/inductive plethysmographic belts*	*Yes, 2 channels*	*Yes, 2 channels*
Snoring	*Microphone/from air flow sensor*	*Yes, 1 channel*	*Yes, 1 channel*

[a]A single sensor provides 3three-dimensional information, i. e., 3 channels

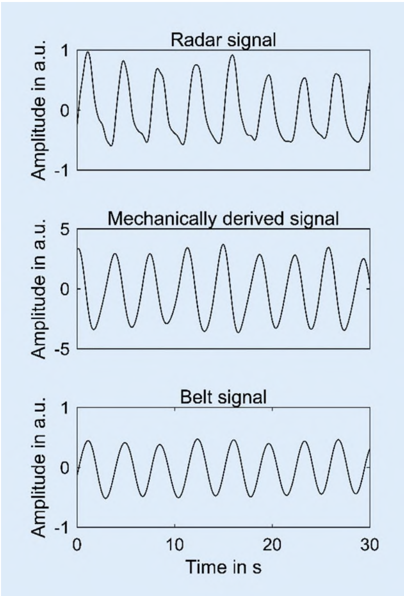

Fig. 1 ▲ Acquisition of respiratory function upon exploring respiratory rate by radar (*top signal* recorded using a bistatic 868-MHz mat-integrated Doppler radar) and by a mechanical sensor (*middle signal* recorded using a mat-integrated piezoelectric foil) compared to a reference signal recorded by a piezoelectric respiratory belt (*bottom*)

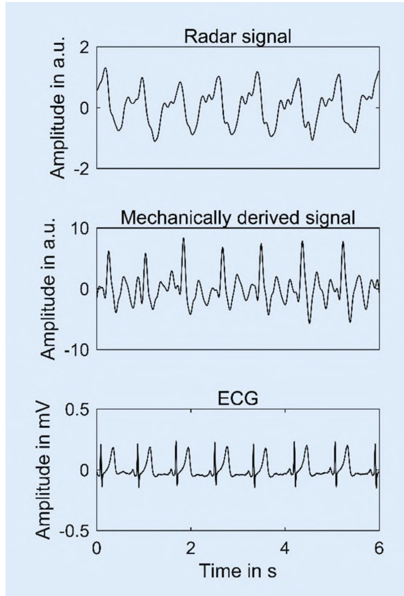

Fig. 2 ▲ Acquisition of cardiac function upon exploring heart rate by radar (*top signal* recorded using a bistatic 868-MHz mat-integrated Doppler radar) and by a mechanical sensor (*middle signal* recorded using a mat-integrated piezoelectric foil) compared to a reference recorded by a conductive electrocardiogram (*ECG; bottom*)

ments. Our aim is twofold: on the one hand, we want to review available techniques concerning their clinical applicability; on the other, we aim to provide sleep physicians with an insight into novel opportunities for signal acquisition, in order to stimulate considerations regarding novel applications of these techniques in the context of sleep, sleepiness, and attention.

Physiological background

According to different sensor principles, unobtrusive acquisition of cardiorespiratory signals exploits certain effects caused by cardiorespiratory function.

Regarding cardiovascular function, such effects comprise an electric effect, mechanical effects (movements and changes in tissue compositions), and a thermal effect. Electrical excitation of the heart results in dynamic electromagnetic fields inside the body and on its surface (electrical effect). Mechanical effects are intrathoracic and peripheral. Intrathoracic effects relate to the ejection of blood from the heart into the larger arteries, causing changes of intrathoracic properties and superficial movements. Such movements are distinctively present at the chest, but also apply to the whole body. Peripheral effects mean the blood supply to the body and superficial perfusion, which induce local movements and changes in superficial tissue properties. Finally, due to peripheral perfusion, thermal effects occur, which can be measured superficially.

Even respiratory function causes mechanical and thermal effects. Mechanical effects comprise changes in intrathoracic properties as well as superficial movements, which again are present at the chest, but apply to the body as a whole as well. Thermal effects are reflected in temperature differences around the mouth and nose that occur due to inhalation and exhalation.

Unobtrusive cardiorespiratory monitoring techniques

Mechanical assessment

Biomedical background. Mechanical methods exploit superficial movements induced by intrathoracic effects of cardiovascular (denoted as ballistocardiography) and respiratory function. Mechanical methods require physical coupling to the body surface and use force, pressure, and acceleration sensors [2, 16, 25]. As such sensors don't have to be attached directly to the body but, e. g., can be integrated into furniture, mechanical assessment allows for an unobtrusive assessment. Different technical realizations of mechanical sensors are feasible, e. g., electromechanical film sensors or piezoelectric sensors.

Mechanical methods can derive information on both respiratory and cardiovascular function at the same time. To distinguish between the two, frequency-selective filters are applied, which exploit the fact that effects due to respiration occur at lower frequencies than cardiovascular effects. **Figs. 1 and 2** contain examples of mechanical recordings from the back of a person lying down.

Current state. Ballistocardiographic measurements date back to the 19th century. Today, mechanical assessment is a widespread technique including some commercial solutions, e. g., EarlySense System (EarlySense, Ramat Gan, Israel). Sensor elements have been used in daily life equipment, such as chairs and beds [5]. Concerning bed usage, applications on top and under the mattress have been described, and a couple of works have already applied the sensor principle in sleep studies (e. g., [12, 16]).

Appraisal. Compared to other unobtrusive techniques, mechanical assessment often shows higher signal-to-noise ratio and allows extraction of not only an averaged HR, but also the beat-to-beat HR in many cases. Concerning respiration, mechanical methods typically derive a single signal comprising the joint respiratory movements of abdomen and thorax. Beyond cardiorespiratory function, mechanical sensors can record patients' activity, thus providing additional valuable information for overnight sleep recordings.

Radar-based assessment

Biomedical background. Similar to mechanical assessment, radar-based methods exploit movements induced by intrathoracic effects of respiratory and cardiac function. Different to the mechanical assessment, no physical coupling is required. Radar-based approaches make use of electromagnetic radiation in the range of classical radar frequencies (100 MHz to 100 GHz). Despite different possible configurations, in all cases a radar signal is applied to the body using an antenna and the reflected (or rarely transmitted) signal is detected by the same (monostatic radar) or another antenna (bistatic radar). Typical realization concepts of the antennas include planar (patch) antennas and horn antennas. The resulting signal is related to motion of the body surface and/or boundary layers inside the body.

Doppler radar-based systems take advance of a narrow bandwidth and the direct proportionality of boundary layer motion and receiver signal phase shift for a constant wavelength. Their main differentiator is the used carrier frequency, which ranges from 433 MHz up to 232 GHz, with a strong cluster at 2.4 GHz. Frequencies lower than 24 GHz penetrate the body for several centimeters (and reach the heart with less than 868 MHz), while all higher frequencies carry only information about the motion of the body surface. Most commonly in Doppler radar-based systems, the signal is sent continuously and processed using an I/Q-demodulator, which allows determination of attenuation and phase shift. Contrary to the Doppler concept, ultra-wideband (UWB) radar sends short (nanosecond) pulses of signal packets resulting in a wideband spectrum. The reflected signal packet pattern is modulated by motion of all reflection layers in its runtime characteristics.

Similar to mechanical assessment, today's systems usually derive information on respiratory and cardiac function simultaneously by applying a digital filtering technique. **Figs. 1 and 2** provide examples of acquired radar signals.

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Abstract

Over the past years, various systems and techniques enabling unobtrusive/minimally obtrusive acquisition of physiological signals have evolved. These systems and techniques open up novel opportunities for sleep medicine. This work provides an overview of unobtrusive systems and techniques to monitor cardiorespiratory function. We present basic principles of mechanical, radar-based, optical, and electrical measurements, and present concrete examples focused on how such systems and techniques can be used for sleep medicine. This work demonstrates the high potential of unobtrusive acquisition. Furthermore, it highlights the need for a standardized evaluation of the available techniques and demonstrates the demand for sleep-specific developments of available techniques in interdisciplinary collaborations.

Keywords

Cardiac function · Respiratory function · Unobtrusive monitoring · Non-contact signal acquisition · Sleep monitoring

Kontaktlose Erfassung kardiorespiratorischer Signale. Verfügbare Verfahren und Perspektiven für die Schlafmedizin

Zusammenfassung

In den letzten Jahren wurden verschiedene Systeme und Verfahren entwickelt, die es ermöglichen, kontaktlos bzw. minimal kontaktgebunden physiologische Signale zu erfassen. Die aktuellen Entwicklungen eröffnen für die Schlafmedizin neue Möglichkeiten. In dieser Arbeit wird ein Überblick über kontaktlose Techniken zum Monitoring der kardiorespiratorischen Aktivität gegeben. Die Autoren stellen die Grundlagen mechanischer, radarbasierter, optischer und elektrischer Messverfahren vor und geben konkrete Beispiele mit einem Fokus darauf, wie eine Nutzung für die Schlafmedizin aussehen kann. Es zeigt sich, dass die heutigen Systeme vielversprechende Möglichkeiten der Signalerfassung bieten, hinsichtlich zukünftiger Anwendungen allerdings eine standardisierte Evaluation verfügbarer Techniken und Weiterentwicklungen für den spezifischen Bedarf der Schlafmedizin in interdisziplinären Zusammenarbeiten erforderlich ist.

Schlüsselwörter

Herzfunktion · Atemfunktion · Patientenfreundliches Monitoring · Kontaktlose Signalerfassung · Schlaf

Current state. The first publications in this field date back to the 1970s. Over the past years, radar-based approaches have seen a revival in research activities due to the availability of highly-integrated low-noise signal processing circuits. Even in sleep medicine has radar found its application. The antennas can be applied externally or mat integrated. Some commercial products for registration of vital signs during sleep are now available. One of these is XeThru technology (Novelda, Norway) to assess respiratory movements during sleep. Recent dedicated external sleep monitoring radar research systems, like DoppleSleep [20] and the hybrid approach WikiSpiro [18], work in the antennas' far field and are realized at higher frequencies. They monitor thoracic surface motion for extraction of average respiratory rate and HR at a distance. Mat-integrated sensors such as in [10] use lower frequencies and are often realized in a bistatic manner with two or more flat patch antennas. These short-range sensors work in the antennas' near field and effectively register a mixture of body surface motion and pulsation of structures inside the body.

Appraisal. Radar provides ideal application conditions with nearly no specific

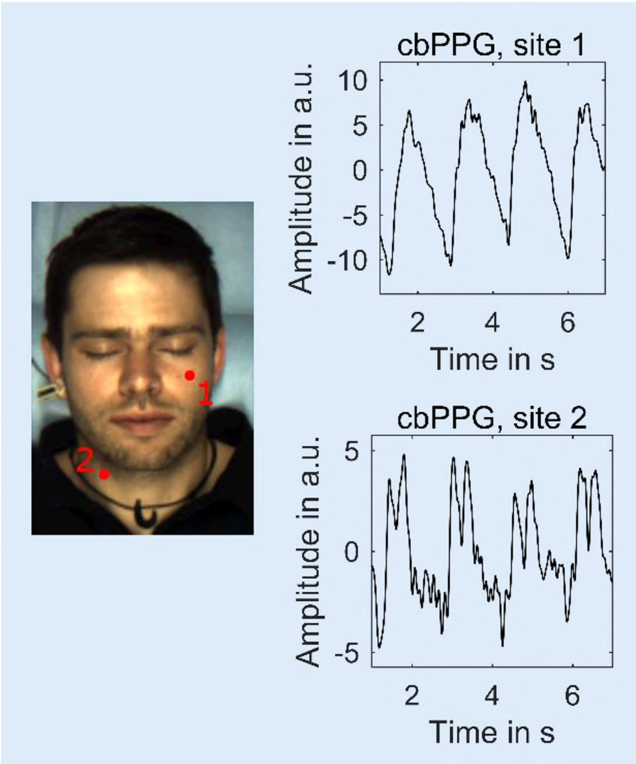

Fig. 3 ◂ Varying morphologies of the camera-based photoplethysmography (*cbPPG*) upon exploring heart rate recorded at different measurement sites. The signals are extracted from the green channel of a 10-bit RGB camera (UI-5240-CP-C, IDS Imaging, Germany) recorded at 100 frames/s

demands. Due to restricted signal quality, beat-to-beat HRs are not available in many cases, but rather only averaged HRs. Regarding respiration, radar typically registers abdominal and thoracic respiratory movements, and can't distinguish between them. However, Kagawa et al. used two Doppler radars to distinguish respiratory movements at the abdomen and chest at the same time, showing the possibility of a separate assessment [11]. Similar to mechanical sensors, even radar can provide additional information on activity. A further potential of radar-based measurements lies in the possibility to penetrate into the body. As stated before, lower frequencies penetrate the body for several centimeters, thus providing intrathoracic information. Such information relates to physiological activity, which otherwise needs ultrasound methods to be revealed and is of high interest. However, whether or how to use such information remains open.

Optical assessment

Biomedical background. Optical assessment makes use of camera systems that act in the visible and near-infrared range. By analyzing video recordings, the technique exploits variations of brightness in predefined regions of interest (ROI) induced by cardiac and respiratory function.

Concerning acquisition of HR, the underlying mechanisms are still under debate. Different factors can contribute to camera-based acquisition. Firstly, the varying blood volume, i. e., peripheral perfusion, at the measurement site is believed to alter light absorption. In analogy to conventional photoplethysmography, some researchers assumed a "direct" effect of light absorption by blood [9, 30] (which led to the frequently used terms camera-based photoplethysmography, cbPPG, or photoplethysmographic imaging). Others suppose an "indirect" effect, assuming that underlying blood vessels alter tissue properties by deformation. Secondly, ballistocardiographic effects due to blood ejection, which leads to movements of the whole body, alter the light absorption. Said effects cause movements of the recorded measurement site, which affect the intensity of reflected light. Thirdly, local displacements, i. e., superficial tilting due to movements of larger vessels, are likely to affect optical measurements. ◘ Fig. 3 shows an example of a measurement at two measurement sites. Strong variations in signal morphology, particularly in areas where a high mechanical impact is expected, give evidence of the existence of a local effect.

All mechanisms provide information on HR. Which one is most dominant to an optical measurement depends on various factors, including the recorded measurement area, the wavelength used, and the applied processing scheme.

Information on respiratory function can be derived from optical recordings as well. In this case, mechanical effects, namely movements induced by respiratory function, are exploited [23, 32]. To separate the information, which relates to respiratory and cardiac function, filtering is applied or different ROIs are used (see ◘ Fig. 4).

Current state. The first use of cameras to monitor physiological variables was described by Hülsbusch and Blazek in 2002 [9]. Using cameras to acquire physiological signals is today an emerging field. Thereby, wavelengths in the visible and near-infrared range, as well as different combinations of wavelengths, are used [26, 30]. Most of the available works are directed at image and signal processing techniques to make the camera-based acquisition more robust in conditions of varying illumination and movements. While existing studies typically consider healthy subjects, only a few studies have so far addressed clinical use of the technique (e. g., [7, 21, 26]). Despite widespread research activities in the field, commercial systems for camera-based monitoring are rare. Oxecam (Oxehealth, Oxford, Great Britain) is one commercial solution.

Use of optical systems to acquire physiological signals in the context of sleep is not common so far. Application of the technique for sleep monitoring requires use of near infrared (i. e., non-visible) light to avoid disturbing the patient. ◘ Fig. 4 shows an own implementation to record information on cardiac and respiratory function during sleep optically. The shown system was set up at the Sen-

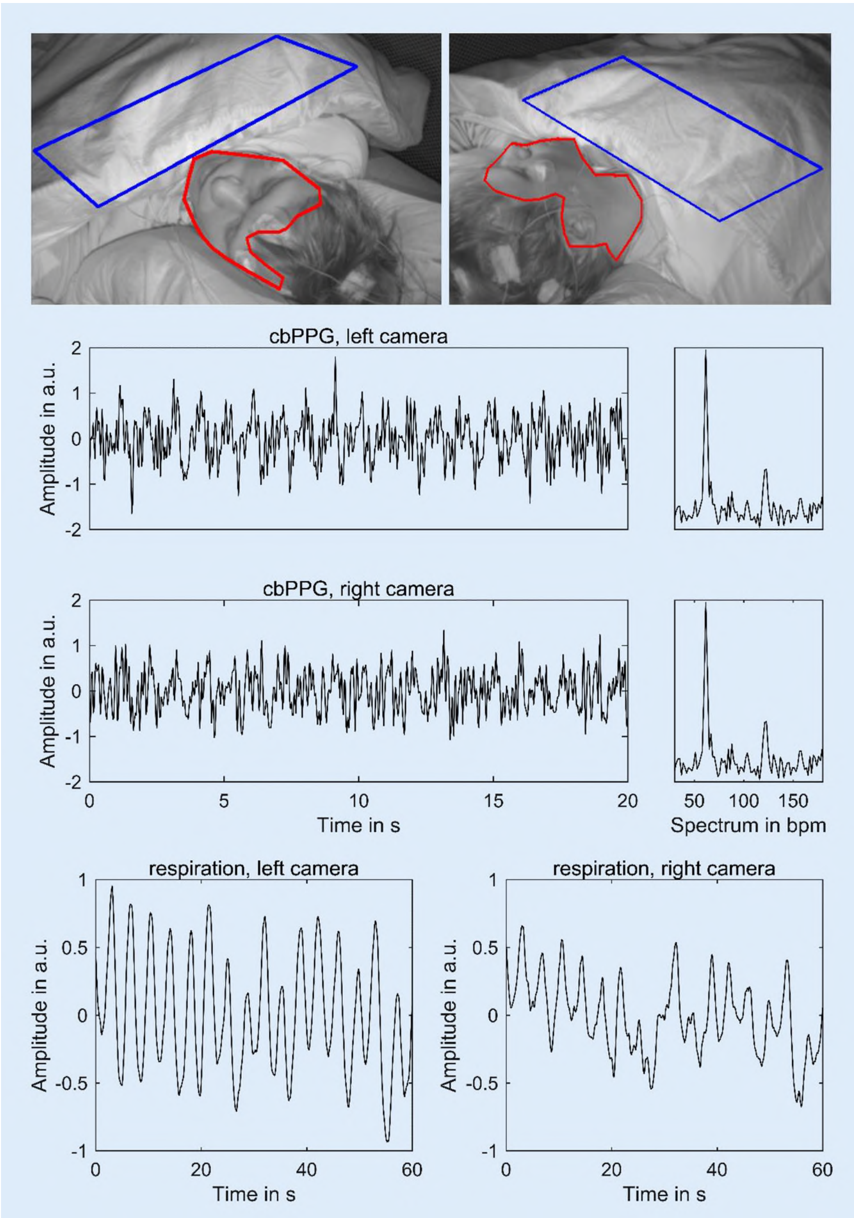

Fig. 4 ▲ Acquisition of information on cardiac and respiratory function during sleep using near-infrared cameras (UI-5240CP-NIR-DL, IDS Imaging, Germany). The photos show the regions that were evaluated to assess heart rate (*HR*; *red*) and respiratory movements (*blue*). Though hardly visible in the time domain, mean HR can be easily extracted from the camera-based photoplethysmography (*cbPPG*) spectra (*second* and *third row*, *second column*). Respiratory movements are clearly visible in the time domain, but differences in signal quality are evident

sory-Motor Systems Lab of ETH Zürich and proved the technical feasibility.

Appraisal. Due to restricted signal quality, beat-to-beat HRs are not available in many cases, but rather only averaged HRs (as can be deduced from ◻ Fig. 4 in contrast to ◻ Fig. 3). Concerning respiration, due to coverage of the thorax and abdominal region, a differentiated statement on the origin of respiratory movements will usually not be possible, but rather only a joint assessment is feasible. Another drawback arises from the technique's sensitivity to occlusion. However, optical assessment is of particular interest as further sleep-relevant parameters can be derived from optical recordings. For example, cameras can provide information on oxygen saturation (e. g., [23]) and other physiological parameters like vasomotor function [24].

Electrical assessment—capacitive electrocardiography

Biomedical background. Capacitive electrocardiography (cECG) acquires the electrical activity of the heart. The coupling to the subject is established capacitively and does not require any galvanic contact, i. e., no electrodes have to be attached to the skin. However, although the bioelectrical signal is equivalent to the standard conductive ECG, the electrical field at the body surface is indirectly measured via the displacement current in the electrode [8, 22].

While the measured signal is equivalent to standard ECG, achieving a comparable signal quality is demanding in terms of instrumentation. ◻ Fig. 5 shows the electrical equivalent front-end circuit of a cECG measurement system. The coupling capacitance C_c characterizes the coupling between the subject and the electrodes. The electrodes possess an input impedance (R_{in}, C_{in}), which is adapted by an impedance converter because the input impedance must be much larger than the source impedance imposed by C_c to avoid signal attenuation [22]. The capacitive voltage divider formed by C_c and C_{in} acts as a high-pass filter, which crucially affects the lower cutoff frequency of the system, thus implying high requirements on the electrode capacitance [8, 22]. The required large input impedance also increases the influence of external interferences [15]. Because of the lacking galvanic contact between subject and measurement system, common mode interferences are likely to occur, which can cause non-usable signal segments. Active reference potential control known from standard ECG recording, e. g., by driven-right-leg/driven-seat, can help to suppress AC common mode interferences caused by differing coupling capacitances C_c [8]. Even decreasing the electrode size decreases the coupling capacitance, while minimizing common mode interference [13].

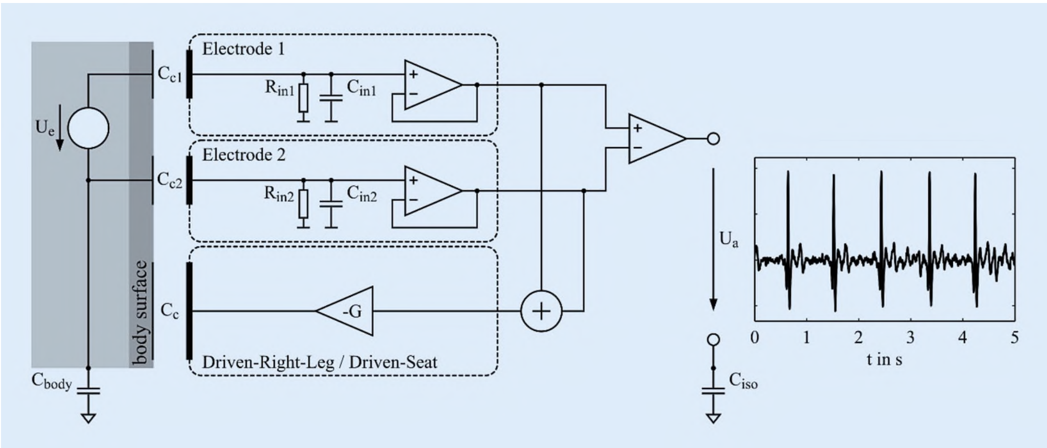

Fig. 5 ◀ Electrical equivalent front-end circuit of a capacitive electrocardiography (cECG) measurement system (adapted from [4, 8, 22]) with a sample cECG excerpt recorded using a cECG seat cushion

Assessment of respiratory function by cECG systems is not common. However, similar to using conductive ECG, methods known as ECG-derived respiration should be applicable, i. e., amplitude modulations, and fluctuations in RR intervals can be exploited [19].

Current state. Measurement of a cECG was first demonstrated using insulated electrodes in 1967. The field of cECG did not grown until the 2000s, when new applications of the cECG addressing long-term and everyday ECG monitoring were presented, e. g., by integrating capacitive electrodes into different kinds of seats (e. g., car seats [27]). Even in sleep medicine, the use of cECG was considered. Lim et al. [15] used eight aluminum-shielded cECG electrodes with the reference level measured through a large conductive textile ground sheet all covered by a cotton sheet. Fully flexible electrodes of highly conductive textile material in a bedsheet with cotton bedcover were used, e. g., in [13]. Today, some commercial solutions for cECG are also available, e. g., from Capical GmbH (Braunschweig).

Appraisal. Highly accurate results concerning HR extraction, even beat-to-beat HR, reflect the large achievements in cECG in recent years. The analysis of beat morphology as a further potential of cECG remains, however, challenging. As respiration must be derived "indirectly", the recorded respiration is suitable to assess respiratory rate but difficult to interpret. A disadvantage of cECG concerning sleep monitoring is its sensitivity to patient position, because not lying on the back may be troublesome.

Other techniques

Another camera-based approach to monitor respiration uses the Kinect camera (Microsoft, Redmond, WA, USA). It records distances and movements that directly relate to respiration [1, 31]. Even infrared cameras can provide information on cardiac and respiratory function by exploiting the thermal effects of both [14, 17]. Information on respiratory function can be derived either directly by detecting exhaled air [17], or indirectly by monitoring the mouth or nasal area [14]. However, particularly concerning acquisition of HR, the infrared-based measurement is much more expensive, as high-quality cameras have to be used. Other, less popular systems to acquire cardiorespiratory signals comprise electric or magnetic impedance methods, acoustic methods, and laser-based methods (see [4] for details).

Evaluation of available techniques for sleep medicine

A number of studies applied the presented unobtrusive methods in the context of sleep. However, the majority of works only evaluate the feasibility of signal acquisition during sleep. Few works based exclusively on mechanical and radar-based sensors, but no optical or electrical methods, go further and foster an evaluation with a clinical background in the field of sleep medicine.

Weinreich et al. [29] showed SleepMinder (Resmed, San Diego, CA, USA), a radar-based system, to classify sleep apnea–hypopnea syndrome (SAHS) at a cutoff of apnea–hypopnea index (AHI) = 15/h with a sensitivity, specificity, positive predictive value, and negative predictive value of 96, 88, 87, and 95%, respectively (N = 54). Kagawa et al. [11] found a correlation of 94% between respiratory disturbance index (RDI) from PSG and radar measurements. When classifying SAHS using the RDI at a cutoff of AHI = 15/h, Kagawa et al. yielded a sensitivity, specificity, positive predictive value, and negative predictive value of 96, 100, 100, and 88%, respectively (N = 35). Zhao et al. [28] combine information on HR and respiratory rate, both gained using a mechanical sensor, to classify SAHS. They yielded a sensitivity and positive predictive value of 89 and 90%, respectively (N = 42). These results are very promising and suffice for clinical requirements.

Besides classifying SAHS, some works aimed at sleep staging based on unobtrusive sensors. De Chazal et al. [6] evaluated the ability of a radar-based system to distinguish sleep from awake states. The proposed algorithm uses information on activity and respiration. Overall, they yielded a kappa of 38%/45%/30% (considered as "fair agreement") and an error in total sleep time of 8.2%/19.0%/27.6% for all subject/low AHI subjects/high AHI subjects. Kortelainen et al. [12] pursued sleep staging using information on HR and activity based on a mechanical sensor. Distinguishing wake, rapid eye movement (REM), and non-REM (NREM) sleep, the researchers yielded a kappa value of 44%. Apart of being very coarse compared to clinical sleep staging, even the yielded accuracies do not suffice for clinical needs and further work is required in this regard.

However, as said before, most researchers who have proposed unobtrusive sensors do not foster a clinical evaluation at all, but restrict themselves to proving the feasibility of signal acquisition. Thereby, different metrics are in use (e. g., HR correct detection rates or correlations between tracings of HR or respiratory rate versus a gold standard). Moreover, the used data heavily differ in composition and extent. Such characteristics hinder meaningful comparisons between different approaches and constitute a substantial problem with respect to the application of unobtrusive techniques.

Discussion

General assessment of available techniques

Various systems and techniques exist to acquire cardiorespiratory signals unobtrusively. Such techniques typically do not provide all signals/information required by standard PSG or polygraphy. In their current state, the unobtrusive techniques thus cannot replace current systems equivalently. Consequently, they cannot be used in all clinical situations in which the current systems are used. However, these systems provide information on cardiorespiratory function and some works have already demonstrated their suitability for certain clinical situations. As Bianchi et al. [3] and Penzel et al. [19] highlight, with the wide opportunities for analyzing cardiorespiratory signals for sleep assessment, further successful use cases can be expected. Besides sleep assessment, applications for sleepiness and fatigue in daily life become feasible by unobtrusive sensing and should be pursued in the future.

The most relevant drawbacks of unobtrusive techniques are a low signal-to-noise ratio and a high susceptibility to artifacts. A combination of unobtrusive methods is tempting to increase the robustness of unobtrusive sensing (sensor data fusion). Beyond making unobtrusive measurements more robust, the fusion of sensor data is also suitable for increasing the explanatory power of unobtrusive measurements, e. g., by determining the pulse wave delay from multimodal unobtrusive measurements.

Practical conclusions for sleep medicine

The presented unobtrusive techniques

- make physiological assessment more convenient,
- can, in their current state, not replace polygraphy equivalently but provide related information,

- allow for new daily life applications in the context of sleepiness and attention, e. g., driver monitoring,
- suffer from a lack of standardized evaluation.

Further studies should
- derive more information available from unobtrusive sensors to meet diagnostic requirements,
- strengthen the cooperation of sleep medicine and technical groups,
- foster concrete applications using unobtrusive sensing,
- carry out a standardized evaluation of available techniques,
- systematically investigate the added clinical value.

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Compliance with ethical guidelines

Conflict of interest. S. Zaunseder, A. Henning, D. Wedekind, A. Trumpp, and H. Malberg declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from all individual participants from whom identifying information is included in this article.

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