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CLINICAL PROJECT

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Minimally invasive detection of sleep apnoea and effects of nCPAP therapy: a proof-of-concept study

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1. Background

Basic concepts: from anatomic architecture to ventricular function

According with the model of a helical myocardium, described for the first time by Turrent and Guasp in the 1954 (1), cardiomyocytes are functionally divided in an upper-basal loop, where they are disposed circumferentially, and in an apical-loop where they are arranged in a right-handed and left-handed helices to form a vortex at the apex. This figure-8 configuration, along with interactions between cardiomyocytes, is responsible for the complex beat-to-beat mechanical motion of the heart: a global counter-clockwise twist during the pre-ejection phase, a vigorous counter-clockwise apical twist during ejection and a clockwise apical untwist during the isovolumic phase (2), in order to boost the blood mass into the main vasculature with a helical mouvement. Changes in LV pre-load, after-load (3) and contractility (3-5) affect LV twist mechanics.

Recording the beat-to-beat blood velocity and heart-induced chest wall motions: ballistocardiography and seismocardiography

In the late 1887, Gordon assumed that the body moves with each heart beat (6). Nowadays, we can confirm Gordon's hypothesis and state that the micro-movements of the body are due to the blood ejection velocity into the ascending aorta (7, 8). These "cardiogenic body movements" can be measured by the mean of ballistocardiography (BCG), which measures the displacement, velocity and acceleration of the body in response to the displacements of the heart and blood in the main vasculature (9); and the seismocardiography (SCG) which assesses the micro-vibrations produced by the heart contraction and blood ejection into the vascular tree which are transmitted to wall chest, where they are recorded (10).

Because of the advent of more performant imaging technologies, such as bi-dimensional and tri-dimensional echocardiography and cardiac resonance, BCG and SCG are not used anymore nowadays (11).

Experimental application of BCG and SCG

A large body of studies exists on the potential applicability of BCG and SCG in clinical practice. For instance, SCG records changes in the ventricular wall motion and compliance after an ischaemic event to a similar extent than an ECG (12), and when combined with an ECG, the accuracy of detecting physiologically significant coronary artery disease is greater than with an ECG recording alone (13). BCG was successfully used in automatic detection of atrial fibrillation (14), and to predict adverse clinical outcome in patients with heart failure (15).

Apart from the clinical setting, BCG and SCG have been used to analyse cardiac function in a microgravity environment. The first 3D-BCG recordings were made during the 4th expedition on the Saluyt-6 orbital station by the Soviets (16), as well as during the Spacelab mission in 1993 (17). 3D- BCG was also used to assess cardiac function (pre-ejection period (PEP)) and left ventricular ejection time (LVET)) on 5 healthy volunteers during the European Space Agency parabolic flight campaigns (18).

SCG and BCG signals: from parameters recording to biological interpretation

The SCG records the base-to-apex rotational movements transferred to the chest wall in the form of micro-vibrations. Several parameters of biological interest can be derived from SCG signals, especially the amplitude and temporal signals. The amplitude signals are related to left ventricular pressure (19), stroke volume and aortic blood pressure (20). Temporal signals provide information about ventricular function: namely a) PEP, a marker of cardiac contractility, b) LVET, c) the PEP/LVET ratio, a heart rate independent parameter and d) the isovolumic relaxation time (IVRT), which reflects the cardiac performance during the diastolic phase of the cardiac cycle (21). The BCG records also several waveforms, three of which are likely

of main importance for sleep apnoea monitoring: namely the "I", "J" and "K" waves (7, 8). These waves are elicited by the ventricular contraction which occurs after the QRS complex on the ECG. They represent the body movements in response to the cardiac blood ejection (22). Should the thoracic aorta be simplified into an ascending and a descending tube, on whom blood pressure and volume flow rate forces act in opposite directions, then the BCG waveforms represents the sum of those forces (8). Various cardiovascular parameters can be estimated from the BCG signal, and are shortly presented below. The J wave of the BCG represents the point of highest amplitude in the BCG waveform; heart rate can be determined by the time interval between consecutive J peaks, the J-J intervals (23). Various algorithms can assess heart rate from BCG signals (24-28). Also, heart rate variability, a non-invasive tool to assess cardiac sympathetic and parasympathetic modulation (29), can be calculated from BCG peak intervals, without the need of RR interval calculations obtained from ECG recordings. Changes in BCG waveforms amplitude are related to stroke volume (SV) and cardiac output (CO) modifications in healthy subjects (30, 31). Finally, similarly to SCG, BCG measurements provide an estimation of the PEP (32, 33), and the LVET which indicates the percentage of the cardiac cycle devoted to ejection as compared to ventricular filling (34, 35).

Sleep disordered breathing and their cardiovascular impact: why detect them?

Sleep apnoea syndrome is a common chronic respiratory disease characterised by cyclic airflow cessations during sleep. Clinically, they are classified in three entities: obstructive, where the airflow cessation is due to upper airways collapse; central, where the airflow cessation arise from a central lack in driving to the breathing muscles with no compensatory respiratory efforts; mixed, characterised by an initial central event followed by an obstructive one. Nowadays, up to 24% of men and to 9% of women aged 30 to 60 years disclose already an asymptomatic and underdiagnosed sleep disorder breathing (SDB) (36). Its current high prevalence will supposedly increase in the future years, as a result of the obesity pandemic in an ageing population. SDB is a potential cardiovascular risk factor (37). A patent causal relationship between SDB and cardiovascular disease has not been clearly established until now, but several chronic patho-physiological mechanisms could make sense in supporting such a link. Intermittent hypoxaemia, due to cycled upper airway collapse, is responsible for abnormal sympathetic activation (38), endothelial dysfunction (39), oxidative stress (40) and inflammation (41), all of which are related to cardiovascular illnesses, especially hypertension (42), atherosclerosis (43), cardiac arrhythmias (44), heart failure (45), and coronary artery disease (46). SDB is, likewise, positively correlated with an increased morbidity and mortality in the cardiovascular population (47, 48) and seems to be an independent predictive factor in cardiovascular mortality after an acute coronary syndrome (49).

Moreover, the classical profile of patients at risk of having SDB (obese subjects, Pickwickian syndrome) has changed in the past year, so that there are new categories of patients who should be evaluated for sleep apnoea, above all those with cardiovascular co-morbidities (50).

Sleep disordered breathing and kino-cardiography: a new and promising tool for unobstrusive recording of SDB and its impact on the cardiovascular system.

Complete laboratory polysomnography (PSG) is the gold standard to diagnose SDB (50, 51). However, it is an expensive, time-consuming and uncomfortable tool, limiting its wide-spread use despite the high frequency of SDB in the general population. However, considering the high prevalence of SDB in the general population and the change in the profile of patients at risk of SDB and then, who should be evaluated for, there is growing interest in the research of alternative strategies to reach the most of patients at possible. A number of home sleep testing devices has been proposed over years to screen patient at risk of SDB, but according to the guidelines, they are NOT recommended for patients with cardiovascular comorbidities (50). Moreover, the devices available nowadays do not provide any information on the direct impact of the apnoea on the cardiovascular system.

Nevertheless, taking into account the high prevalence of SDB and the limited accessibility of expensive sleep testing *on one side* and, *on the other side,* the marked recent technological advances in SCG and BCG technologies *as well as* the peculiar hemodynamic characteristics of sleep apnoea episodes, we wish to test

the hypothesis that modern SCG and BCG recordings can provide an highly accurate assessment of sleep apnoea, and evaluate the effects of nCPAP therapy.

There are several reasons to believe that the implementation of recent improvements in SCG-BCG will allow a precise quantification of such sleep-related events:

1) The cyclic pharynx collapses during sleep are associated to brain arousal, intrathoracic pressure swings (the so called 'Mueller – manoeuvres'), and intermittent episodes of hypoxaemia and re-oxygenation (45). When respiration resumes, the cardiac output faces a markedly increased peripheral sympathetic activity, leading to sudden rises in systemic blood pressure, and reflex reductions in heart rate, while the opposite occurs during the periods of respiratory collapse. As explained above, these changes are likely to induce marked modifications in the amplitude and temporal recording assessed by SCG recordings, as well as in the "I", "J" and "K" waves obtained from the BCG.
2) Previous studies which tested if BCG can detect sleep disturbances are encouraging, despite using remote techniques: Da Woon et al. used an unobtrusive polyvinylidene fluoride film sensor on a bed mattress to record BCG signals in a selected group of 10 OSA patients and 10 controls (52, 53). They calculated heart rate (HR) and heart rate variability (HRV) from J-J BCG interval and detected awakening periods in OSA patients with an accuracy of 97%. *The authors could however not determine why sleep was fragmented with this technique*. Zaho et al. also used a micro-movement sensitive bed mattress in subjects with a BMI < 35 kg/m² and no other concomitant cardiorespiratory disease (54). HRV was also retrieved from J-J BCG interval. However, *only selected periods of sleep were analysed for sleep-breathing events, a surrogate marker for obstructive, but not central apnoea*. Detection of these events was nevertheless achieved with a sensitivity of 98%, a specificity of 94%, and an accuracy of 98% (55). Last, Dehkordi et al. showed that it was possible to distinguish between central and obstructive events by recording acceleration from the suprasternal notch, the thorax and the abdomen (56). The subjects investigated were however *only normal volunteers* who performed several voluntary breaths hold in the presence of an oral nasal flow detector.
3) The unique expertise of our research team is that we are capable to record SCG and BCG signals in 3 dimensions (57, 58), both linearly and rotationally (16-18). While the above mentioned studies (52-56) assessed BCG changes only in a horizontal plane (x and y axis), which is not representative of the complex cardiac mechanic, we are capable to record these changes in a third anteroposterior dimensions (z axis). This is important because of the anterior-posterior direction of the aortic arch. In addition, as emphasized in the introduction of this research proposal, an important component of the body reaction to the heart movements is rotational, which we are capable to record in 3 dimensions. Overall the combined SCG and BCG 3D-linear and 3D-rotational signals represent 6 degrees of freedom (DOF) while past BCG had only 2-DOF. For simplicity, this 6 DOF signal combination will be designated as Kino-cardiography (KCG) recordings in this research proposal. We anticipate that the unique KCG properties will considerably increase our detection capability of obstructive and central apnoea, as compared to previous studies.

2. Aims and hypothesis tested

The main hypothesis tested in our study is that KCG provides sensitive and accurate measures of obstructive and central apnoea as compared to state-of-the-art polysomnography. Our secondary hypotheses are related to modifications in the SCG and BCG parameters during the apnoea and the effects of nCPAP therapy: we believe that the KCG signals are profoundly affected by the apnoea and they are reversed to the normal baseline with the CPAP. These hypotheses will be tested through a series of studies in normal volunteers and patients.

1-MAIN HYPOTHESES:

Group A. After a fine tuning period of the KCG signal post processing to maximise the sensitivity and specificity of voluntary apnoea detection in health subjects, we will start the first validation study. In 46 healthy volunteers, a computer program will generate random instructions of periods of normal breathing, voluntary end-expiratory breathing cessations periods (as surrogate of central apnoea) and Muller's manœuvre (as surrogate of obstructive apnoea). Meanwhile, the KCG will record the above-mentioned parameters. The number and duration of voluntary central and obstructive apnoea will be assessed in the KCG recordings, not knowing how many were actually generated by the computer program. We will also record the ECG, heart rate, beat to beat non-invasive blood pressure (Finometer), humeral blood pressure (Dinamap), ventilation, end-tidal CO_2 (AD instruments), O_2 saturation (Nellcor), cardiac output (CO) (Philips).

Group B. In patients suspected of sleep apnoea and admitted to the sleep unit of the Erasme hospital to perform sleep test as required by their medical condition, we will simultaneously record KCG and PSG and qualitatively compare the data. Bland-Altman plots will analyse the agreement between the sleep recordings obtained with the two methods. Peculiar attention will be paid to the accuracy of the detection of obstructive *versus* central *versus* mixed apnoea, of awakenings, and of the time spend in bed. In this second phase of the study, we plan to record these parameters only in selected patients, who will not disclose marked abnormalities which could hamper the reliability of the KCG recordings, namely moderate or severe valvular disease, permanent atrial fibrillation or frequent premature contractions, atrio-ventricular conduction disturbances, medications which reduce heart rate and heart rate variability (beta blockers, anti-arrhythmic drugs, calcium blockers, …), cardiac rhythm driven by a pace maker, heart failure of any origin, neurological diseases responsible for abnormal movements (restless leg syndrome, Parkinson disease, ataxia …).

Group C. In patients with a diagnosis of OSA, we will determine if KCG is capable to reliably assess the efficacy of the nCPAP therapy in comparison to simultaneous PSG recording. Ongoing adjustment in CPAP therapy pressure during the night, and its effect on cardiovascular haemodynamic assessed by the KCG, will be taken into account as well. The capability of the technique to detect changes in sleep quality will be tested both *within* subjects (before vs. after nCPAP therapy in the same patient) as well *among* the subjects investigated. The same restriction in the recruitment of the subjects of group B will be applied for the present group.

Group D. After validation of the three previous steps, we plan to extend the recordings on 100 unselected consecutive patients who will undergo PSG recordings because of complains of sleep apnoea. This will validate the clinical usefulness of KCG recording for the detection of sleep apnoea even in patients with multiples co-morbidities.

2-SECONDARY HYPOTHESES

We will test the hypothesis that the apnoeic events profoundly affected the KCG signals (PEP, LVET and PEP/LVET ratios). These parameters are affected by changes in cardiac pre- and after- load and sympathetic activity on myocardial contractility. Similarly, we plan to test the hypothesis that the isovolumic relaxation time (IVRT), an index of diastolic performance during the cardiac cycle, will be altered during the obstructive apneas, because marked variation in intrathoracic pressure result in large increases in LV transmural gradient and thereby reduce LV compliance. CPAP therapy should markedly reduce the nighttime variability in these parameters.

We will also asses the R-J interval which is related to blood pressure and determine if this parameter rises during the apneas and arousals when sympathetic activity is increased. Determination of the J-J intervals and the corresponding HRV, which is under strong autonomic control, should also present distinct changes in OSA patients, as compared to subjects receiving efficacious nCPAP therapy.

Last, breathing effort variations will be assessed. This refers to the mechanical interaction between respiration and KCG signals when sleep apnea occurs, independently from an autonomic nervous modulation of heart rate variability: when the obstructive apneic event occurs, the airflow decreases, which result in a

breathing effort thereafter. We will test the hypothesis that theses respiratory abnormalities are readily detectable by the KCG.

3. Methods

Study design and recruitment, expertise of the research group

Study A is an interventional pre-study on voluntary breath holding on healthy subjects. The parameter taken into consideration for sample size calculation in this group is the total (linear and rotational) systolic kinetic energy of the SCG (S_sys_kin) and the rolling ratio between the mean value and the standard deviation of this parameter: H = Mean(S_sys_kin) / Std(S_sys_kin). H discriminated voluntary obstructive apneas from episodes of normal respiration in a healthy volunteer (H = 1.1627 and 0.2308, respectively). The sample size is determined according to: 2·(Zalpha + Z1-beta)2·sigma2 / Delta2, where alpha = 5% is the accepted error, leading to Zalpha = 1.96 (2-sided); beta = 95% is the power of the study, leading to Z1-beta = 1.64; sigma is the estimated standard deviation of H; delta is the estimated effect of obstructive sleep apnea on H in patients. Sigma (Hbaseline) = 0.1247 was obtained by H determinations on a group of healthy subjects who were breathing regularly. The difference in H during regular breathing and voluntary obstructive apnea, divided by 10 (because voluntary apneas may have induced larger changes than those experienced by patients) is Delta = (1.1627 - 0.2308) / 10 = 0.09319. Thus, the estimated sample size for study A is 46.

Studies B and C are observational investigations on subjects referred for PSG as required by their medical condition and which fulfill the inclusion/exclusion criteria described previously. The number of subjects will be calculated accordingly to the results of the pre-study (group A).

Study D is an observational prospective investigation conducted on unselected consecutive patients without recruitment restrictions, in order to validate the KCG on the real population. Since we do not know how many patients will be necessary for the validation of our screening device, we speculate a size simple of 100 subjects.

Because the KCG device is not intrusive, we do not anticipate difficulties in the recruitment. Our study will not affect in any manner the regular medical care of the patients admitted to the sleep laboratory. The present research proposal is in line with my promotor's expertise, P. van de Borne, P-F. Migeotte and G. Loas, in the study of sleep physiology (59-63), and sleep apnea (60, 61):

4. Perspectives

As explained above, SDB is a widespread disease with detrimental health effects and its prevalence is supposed to increase in the future years, as the result of the obesity pandemic in an ageing population. PSG is the gold standard for the diagnosis of sleep related disorders but it is an expensive, uncomfortable and time-consuming tool, limiting its use in the daily clinical practice, despite the high prevalence of SDB. Several home sleep tests have been proposed to screen patients suspected for SDB, but they disclose several limitations and are not recommended for patients with cardiovascular, respiratory, metabolic or neurologic co-morbidities (50). We strongly believe that the less cumbersome (57-60) KCG will screen patients for SDB accurately. One of its unique features (57-60) is also that it can directly identify the consequences of SDB and nCPAP therapy on the cardiovascular system, and in especially the presence of frequently associated cardiac arrhythmias (44). With a more efficient pre-screening, those who are most likely to be eligible for nCPAP therapy will have a better access to the currently existing sleep laboratory facilities. To summarize, we aim 1) to propose a new screening tool for patients at risk of SDB, 2) to stratify patients with SDB for adverse cardiovascular events, and 3) to highlight new physio-pathological aspect of sleep apnoea. The present research project has thus the potential of improving sleep apnoea patients care and health, at no additional societal costs.

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