Porcine Model for Validation of Noninvasive Estimation of Pulmonary Hypertension

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Abstract

The diagnosis of pulmonary hypertension (PH) is often delayed in the course of the disease, contributing to its high mortality rate. Seismocardiography (SCG) is non-invasive and less time-consuming and could potentially replace echocardiography for early detection of PH. The aim of this study was to assess the potential of SCG in detecting PH by comparing cardiac events in pigs with PH and pigs with normal pulmonary circulation. ECG and SCG data were collected from 10 pigs undergoing right heart catheterization. PH was induced with hypoxemia or hypercapnia. The SCG signals showed, in hypoxemia, a significant prolongation (in % relative to the RR-interval) in isovolumetric contraction time (IVCT) from 4.48% (± 1.36) to 5.58% (± 1.88) (p = 0.01), and isovolumic relaxation time (IVRT) from 7.33% (± 1.72) to 9.64% (± 3.84) (p =0.00). In hypercapnia, left ventricular ejection time (LVET) significantly increased from 34.6% (± 6.0) to 41.0% (± 10.8) (p =0.03), IVRT increased from 7.33% (± 1.73) to 11.9% (± 5.1) (p =0.00) and IVCT increased from 4.18% (± 1.07) to 6.61% (± 2.11) (p = 0.00). This study found an increase in the SCG time intervals for IVCT and IVRT in pigs with induced PH. Thereby, indicating a potential value of capturing PH in humans utilizing SCG.

1. Introduction

Approximately 1% of adults is affected by pulmonary hypertension (PH). PH is often a comorbidity and can produce unspecific symptoms, thus often delaying the diagnosis. [1] Early detection of the disease is essential for the prognosis, but delayed diagnosis of PH is common and can lead to lower expected lifespan and higher morbidity [2]. PH is currently identified and confirmed with the non-invasive transthoracic-echocardiogram (TTE) and right heart catheterization (RHC), an invasive tool [1]. However, a complete TTE examination is highly operator-dependent and does not offer continuous monitoring [3]. Seismocardiography (SCG) is a non-invasive measurement that measures the local vibrations of the chest wall produced by the heart in relation to the contraction of the atria and ventricles, together with the opening and closure of the valves [4]. These vibrations are measured using an accelerometer, a method first introduced by Patrick Mounsey in 1957 [5]. Advantages of SCG are that it is less time-consuming, low-cost, does not require specialized staff for measuring and does provide continuous monitoring. Early detection of PH could be increased by monitoring cardiovascular measurements routinely, this could even be conducted at home.

Studies have shown, by comparing SCG, electrocardiography (ECG), and TTE, that the low-frequency amplitude wave displayed by the SCG corresponds to known physiological cardiac events [6]. The study by *Agam et al.* [7] showed a high correlation between the amplitudes from the diastolic SCG and the early diastolic variable e' from echocardiography. Another study by *Inan et al.* [8] demonstrated the ability of SCG to monitor left ventricle function via estimation of health parameters. Furthermore, the study by *Sørensen et al.* [6] found an association between fiducial points in the SCG and cardiac events from echocardiographic imaging. The correlation between the SCG waves and cardiac performance has yet to be fully understood and could potentially make the usage of SCG a diagnostic tool when evaluating the cardiovascular system.

The aim of this study was to investigate if there was a significant difference in SCG measurements of pigs with PH induced by hypoxemia or hypercapnia, compared with normal pulmonary circulation.

2. Methods

SCG data were collected from pigs undergoing RHC. PH was provoked with pulmonary vasoconstriction by hypoxemia or hypercapnia. Multiple revertible sessions were performed for both hypoxemia and hypercapnia on each animal. The experiment received approval from the Danish Animal Experiments Inspectorate, license number: 2021-15-0201-01053.

2.1. Experimental design

The pigs were anaesthetized and mechanically ventilated, undergoing arterial catheterization and right ventricle catheterization (Swan-Ganz catheter). For all the pigs, SCG, three-lead ECG, oxygen saturation, arterial blood

pressure and right ventricle pressure were recorded simultaneously during the entire session. The peak systolic pressure in the right ventricle (RVSBP) was used as a surrogate measure of the Pulmonary Artery Pressure (PAP). SCG from two triaxial accelerometers and ECG were simultaneously recorded utilizing an iWorx data acquisition system.

The accelerometers were Silicon Designs 1521 in 3D-printed plastic housings (19 mm wide, 21 mm long, 11 mm high, and weighing 5 g). These were placed over the lower border of the sternum and over the fourth intercostal space near the left sternal border. The SCG utilized in the current study was derived from the accelerometer on the sternum. Hypoxic pulmonary vasoconstriction was caused by replacing inhalation oxygen with nitrogen and hypercapnic pulmonary vasoconstriction was caused by adding carbon dioxide to the inhalation air. Nitrogen and carbon dioxide administration were each repeated 2-3 times in each pig. Consecutive experiments were conducted after the animal returned to a baseline state.

2.2. Signal processing

Due to the data being recorded continuously throughout the entire session, windows for the analysis were selected at baseline periods and PH periods. A baseline analysis was conducted before either hypercapnia or hypoxemia. Since the baseline window was initialized after the pig reached a steady state after the previous intervention, the window interval ranged from 61 to 1335 seconds. The PH window was 180 seconds centered at the peak PAP pressure obtained under each intervention.

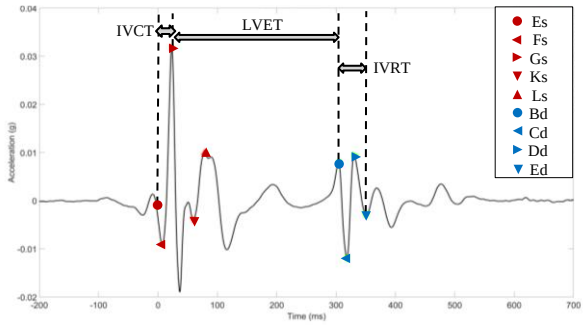

Figure 1: Demonstration of SCG with fiducial points used in the study. The red marks are the systolic and the blue marks are the diastolic variables. IVCT = Isovolumetric cardiac ejection time, LVET = Left ventricular ejection time, IVRT = Isovolumetric relaxation time, g = gravitational constant.

The SCG signals were segmented into separate heartbeats using an ECG-based segmentation model described by Jensen et al. [9] This approach utilizes either ECG lead I or II to partition the signal into individual heartbeats, relying on the identification of the R-peak. Both a mean SCG beat, and a mean ECG beat were calculated based on the ECG alignment. An automated fiducial point detection algorithm was used to identify the SCG fiducial points as defined by Sørensen et al. [6]. All fiducial points were manually reviewed and adjusted in cases, where the algorithm did not comply with the study by Sørensen et al. Three time intervals related to isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT), and left ventricular ejection time (LVET), were analyzed. In addition, three SCG amplitudes were included in the current analysis, see Figure 1 and Table 1. The signal data was processed in the iWorx system and Matlab (Mathworks, USA).

2.3. Statistical analysis

The statistical normality of all data derived from the SCG was verified through histogram visualization and Shapiro-Wilk test. A pairwise comparison of means was calculated to compare the SCG data collected: baseline compared to hypercapnia and baseline compared to hypoxemia, respectively. SCG time intervals were adjusted for RR-intervals from ECG to standardize the interpretation of the SCG across different heart rates. A paired sample t-test between baseline, hypoxemia and hypercapnia was performed for normal distributed data and Wilcoxon Sign Rank test for non-normal distributed data. Significance thresholds were set at p-values <0.05, indicating the rejection of the null hypothesis of no significant difference in SCG measurements of pigs with PH induced by hypoxemia or hypercapnia, compared with normal pulmonary circulation. All statistical analyses were executed utilizing STATA for Mac, version 18.0 (StataCorp., College Station, TX, USA).

3. Results

Ten pigs were studied, with 73 measurements taken: 20 for hypercapnia, 21 for hypoxemia, and 19 baseline measurements. Thirteen SCG measurements were excluded due to poor signal quality.

RVSBP increased under both conditions, with arterial systolic blood pressure (ASBP) rising during hypercapnia and falling during hypoxemia (see Table 1). HR increased in both conditions. Both conditions also led to an increase in the relative isovolumetric contraction time (IVCT) and the relative isovolumetric relaxation time (IVRT) (see Table 1 and Figure 2). However, relative LVET was only significantly increased under hypercapnia. Consistently, both conditions increased systolic acceleration measured at peak Gs (see Figure 1), while only hypoxemia increased the diastolic peaks Bd and Cd.

4. Discussion

In the current study, we utilized a method for reversible PAP modification using hypercapnia and hypoxemia.

We found a significant increase in SCG-derived relative IVCT, when the pigs were exposed to the induced PH both in the hypoxemia and the hypercapnia groups. This is consistent with the study by Akgül et al. [10], where a prolonged IVCT was found in patients with PH compared to patients without PH. On the other hand, studies [11], [12] show that the correlation between IVCT and elevated PAP is not linear and that a prolonged IVCT can be found in both elevated and normal PAP. A study by Shandhi et al. [13] also explored the correlation between PAP and IVCT with the help of SCG. In both cases a strong correlation between changes in PAP and distance between the Es to Gs signals from the SCG, which refers to the IVCT [14], was found.

Furthermore, we found a significant increase in the relative IVRT in both the hypoxemia and hypercapnia groups, which is contradictory to, the study by Akgül et al. that found a similar IVRT in patients with and without PH, but in line with the study by Stojnic et al. [15] that showed a significant prolonged IVRT in patients with PH.

The increased systolic SCG amplitude indicates that the heart responds to the decreased filling, caused by pulmonary artery vasoconstriction, with increased contractility.

In summary these findings indicate that the SCG has the potential to investigate or monitor PH non-invasively in the future.

Although both hypoxia and hypercapnia resulted in the expected increase in PAP, these methods are also known to trigger a wide range of physiological responses, suggesting that the observed SCG alterations may have multiple sources. However, the strength of the current model is that arterial systolic blood pressure responded bidirectionally to hypoxia and hypercapnia, indicating that any unidirectional response is not caused by changes in arterial systolic blood pressure.

5. Conclusion

This study found that hypoxia and hypercapnia, which increase PAP, altered the SCG signal in pigs, indicating a potential application of SCG for detecting and monitoring PH.

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	Baseline	Hypoxemia		Hypercapnia	
	Mean (SD)	**Mean of peak (SD)**	**P-value**	**Mean of peak (SD)**	**P-value**
RVSBP	28.8 mmHg (± 9.8)	40.8 mmHg (± 10.4)	.001	53.1 mmHg (± 19.6)	.001
ASBP	116.2 mmHg (± 21.2)	104.7 mmHg (± 16.3)	.005	207.9 mmHg (± 66.8)	.001
HR	70.5 mmHg (± 12.9)	94.3 mmHg (± 28.5)	.001	111.6 mmHg (± 40.6)	.001
	Mean (SD)	**Mean difference (SD)**	**P-value**	**Mean difference (SD)**	**P-value**
Time intervals (% of the RR interval)					
Gs-Cd (LVET)*	34.7% (± 6.8)	4.178% (± 10.67)	.088	6.330% (± 11.61)	.025
Es-Gs (IVCT)*	4.2% (± 1.2)	1.104% (± 14.56)	.014	2.424% (± 2.066)	.001
Bd-Ed (IVRT)*	7.1% (± 1.9)	2.316% (± 11.03)	.001	4.589% (± 4.802)	.000
Amplitudes (mg)					
Gs amp	24.9 (± 16.1)	18.1 (± 21.6)	.001	18.7 (± 22.3)	.001
Bd amp	6.5 (± 3.3)	4.9 (± 4.9)	.006	-3.6 (± 22.0)	.852
Cd amp	-13.2 (± 6.9)	-4.0 (± 7.0)	.017	3.0 (± 7.0)	.391

Table 1: Heart rate (HR), Arterial systolic blood pressure (ASBP), Right ventricular systolic blood pressure (RVSBP) for the pigs and the results from the SCG data. * = Corrected for RR

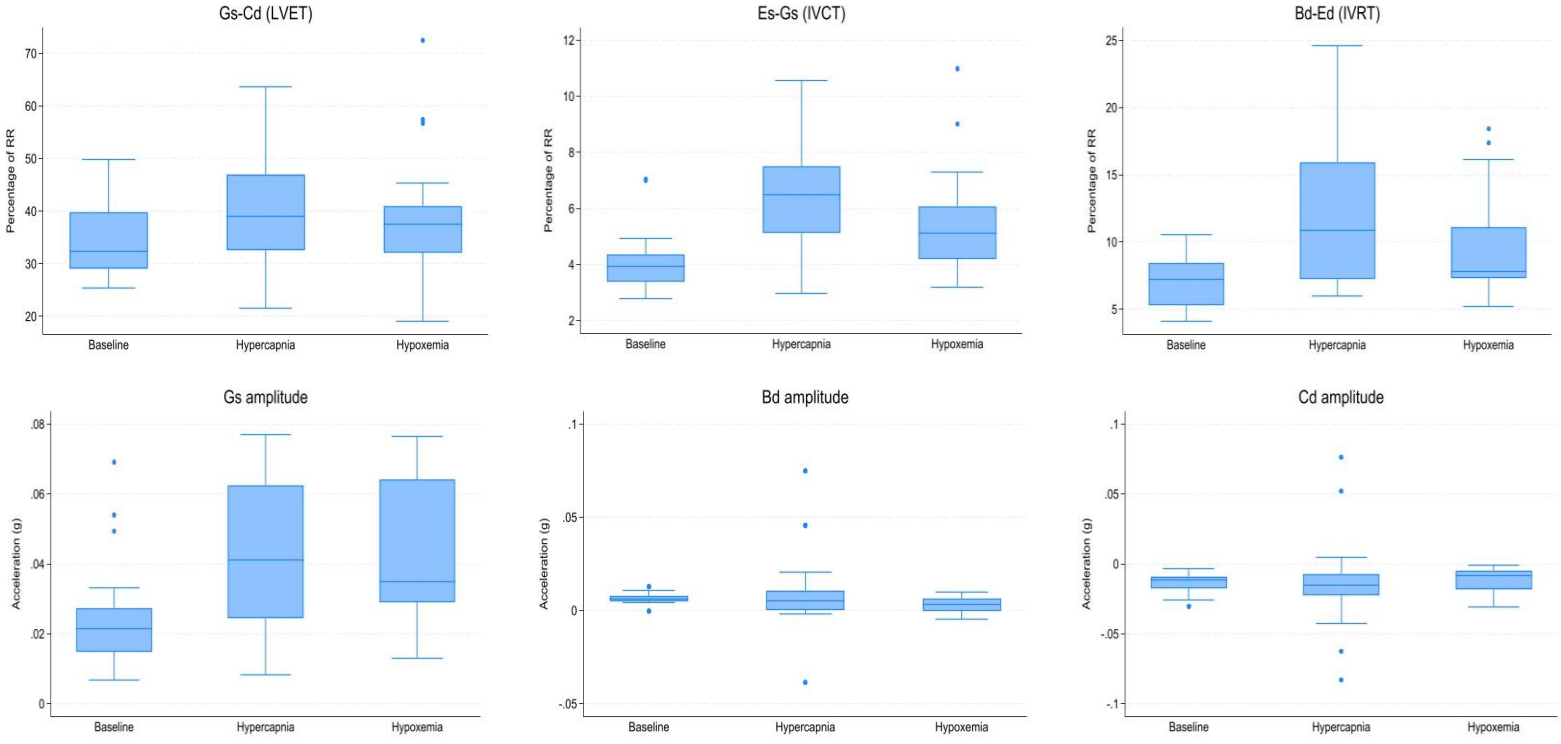

Figure 2: Boxplots of the time intervals (above) and boxplots of the amplitudes (below), where baseline can be compared with hypercapnia and hypoxemia, respectively.