

T-End Versus S2-Onset in Experimental Pulmonary Hypertension in Pigs

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Abstract

Pulmonary hypertension (PH) can lead to changes of the timing of pulmonary valve closure. The aim of this study was to investigate if deviations of the second heart sound (S2) in seismocardiograms (SCG) relative to the end of the T-wave (T-end) in the ECG can detect PH.

Methods were developed to detect T-end in the ECG and start of S2 (S2-onset) in the SCG. The data were obtained from an animal model, where pigs (n=8) were induced with PH by exposing them to hypoxemia (n=17) and hypercapnia (n=16).

The results of S2-onset to T-end show that S2-onset came 34 ms earlier for baseline and 65 ms earlier for hypercapnia (p=0.01). S2-onset came 33 ms earlier for baseline before hypoxemia and 42 ms earlier during hypoxemia (p=0.39).

Thus, a significant change of S2-onset compared with T-end was observed for pigs induced with hypercapnia.

1. Introduction

Pulmonary arterial hypertension (PH) is characterized by elevated pulmonary arterial pressure due to increased resistance in the pulmonary vasculature [1-4]. The increased pressure may lead to acute right heart failure (RHF) or, more often, to a slowly developing right ventricular (RV) hypertrophy and, ultimately, RV dilation and RHF [5]. RV dilation is associated with RV dyssynchrony and reduced contraction strength, which may result in a change of the timing of the pulmonary valve closure [6,7]. Increased myocardial stress may also by itself increase action potential duration [5] and thereby change the timing of the end of the T-wave and the closure of the pulmonary valve.

The current diagnostic procedure for PH includes the electrocardiogram (ECG), echocardiogram (ECHO), and right heart catheterization [8]. The invasive right heart catheterization provides pulmonary arterial pressure (PAP). A mean PAP > 20 mmHg indicates PH [9]. The non-invasive ECG and ECHO provide information about electrical and mechanical abnormalities [8], where ECHO is also used to follow the progression of the disease [10]. The ECG changes are non-specific for PH and will mostly occur as a late consequence of the increased pressure [11].

There continues to be a need for an objective and non-

invasive method to accurately diagnose PH, to limit hospitalization and misdiagnosis. The changing closure time of the pulmonary valve and possible changes of the QT interval as well, suggest that the interval between the end of the T-wave and the beginning of the S2 sound might be an indicator of PH. Since a study by Hegglin in 1000 subjects, it has been known that S2-onset almost coincides with T-end in normals, but that these fiducial points can be separated significantly due to various pathologies [12].

The aim of this study was to investigate how deviations of the interval between S2-onset and T-end correlate with pulmonary arterial pressure using seismocardiography (SCG) and ECG in pigs.

2. Methods

SCG and ECG data were collected from experiments conducted in pigs, with ethical approval from the Danish Animal Experiments Inspectorate, license number: 2021- 15-0201-01053. Anesthetized and ventilated pigs (n=8) were sequentially induced with hypercapnia and hypoxemia whilst recording SCG, ECG, oxygen saturation, intra-atrial blood pressure, and RV-pressure as described earlier [14].

2.1. Detection of T-end and S2-onset

To detect T-, R-, and P-peak, a combination of filtering, local maxima detection, and segmentation of the ECG was used. To detect T-end, the midpoint between T-peak and the subsequent P-peak was used. From this midpoint a line was drawn to T-peak. T-end was then defined as the point on the trailing edge of the T-wave with longest vertical distance up to the line. This method is illustrated in fig. 1.

The heart sounds were detected using an envelope of the Shannon energy of the SCG signal. To distinguish between the first and second heart sounds, the ECG attributes were used. The S2-onset point was determined by the first oscillation of S2. The detected attributes can be seen in figure 2.

2.2. Definition of time intervals

To achieve intervals where the pigs were most affected by PH, an interval of 140 seconds was defined as surrounding the maximum systolic pressure.

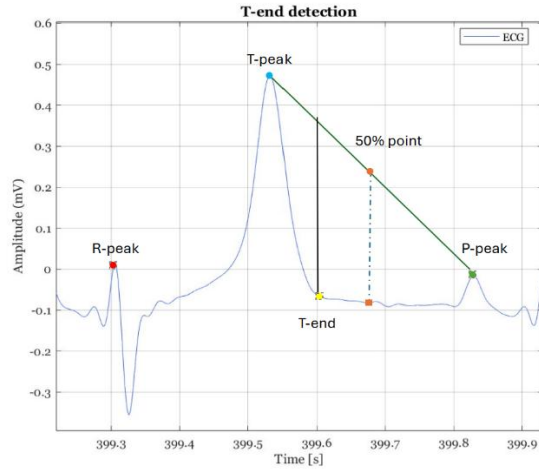


Figure 1. The method to find the T-end point. The method includes the R-, T- and P-peak, 50% point (midpoint) and T-end.

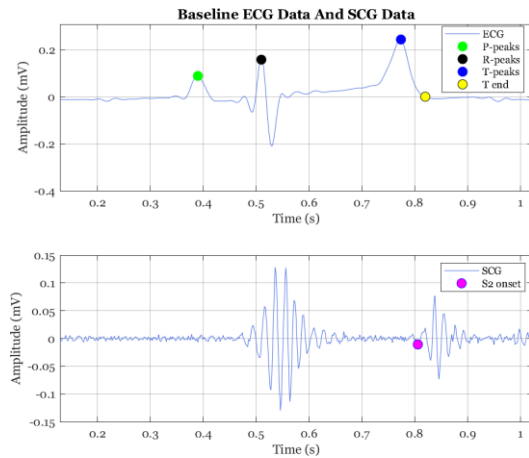


Figure 2. Detected attributes for ECG and SCG.

The attributes detected from the ECG and SCG were used to compare different intervals. The comparison from S2-onset to T-end was made to examine deviations from the baseline to the intervention. Fridericia correction formula was used to predict how the R to T-end interval changes during different heart rates (HR) to compare the baseline with the intervention [15]. To further understand the deviation in S2-onset to T-end, a comparison of the intervals from the R-peak to S2-onset and R-peak to T-end was made.

To ensure that the results gained from the comparisons were accurate, the following exclusion criteria were used: 1. Baseline detected beats $n < 50$, 2. Intervention detected beats $n < 50$, 3. Biphasic T-wave, 4. Late T-wave and high HR, 5. Missing signal, 6. P-wave hidden in T-wave.

2.3. Statistics

To determine whether the results were statistically significant, a two-tailed paired t-test was performed. A

confidence interval was presented to indicate how the timing of the intervals changed during the intervention.

3. Results

From 8 pigs, a total of 71 sessions of either hypercapnia or hypoxemia, 33 sessions were included with 16 hypercapnia episodes and 17 hypoxemia episodes. Table 1 shows the mean values of HR and RV systolic pressure during baselines and interventions.

Table 1. Mean value of HR and RV systolic pressure for baseline and intervention recordings.

Mean value	HR (bpm)	RV systolic pressure (mmHg)
Baseline for hypercapnia	69.2	30.5
Hypercapnia	96.8	53.2
Baseline for hypoxemia	68.4	31.4
Hypoxemia	89.1	41.3

Figure 3 shows the intervals from R-peak to S2-onset and R-peak to T-end. The figure and results of table 3 show that the R-peak to S2-onset intervals decrease during the interval surrounding the maximum systolic pressure. Table 2 shows a significant change from baseline due to hypercapnia, but a much smaller, not statistically significant, change for hypoxemia.

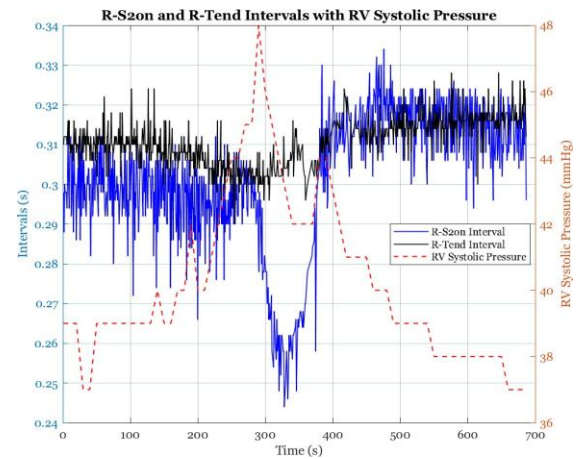


Figure 3. Systolic pressure, R-peak to T-end, and R-peak to S2-onset intervals during intervention.

Table 4 shows no significant change from baseline to the interventions in the corrected intervals of R-peak to T-end. Table 5 shows a significant change from baseline to the intervention for hypercapnia but not for hypoxemia.

4. Discussion

There are many causes leading to either a premature or delayed S2 as mentioned in section 1. The results from

R-peak to S2-onset in table 3 indicates a significant premature S2 during hypercapnia, but not hypoxemia. Since it is unknown whether the premature S2 is due to closure of the aortic valve (A2) or the pulmonary valve (P2), it is unclear which is the primary cause. If A2 is the cause for the premature S2 it could be due to a higher systemic blood pressure, which was not investigated in this study. To assume that PH causes a premature S2, further research on the systemic and pulmonary blood pressure is required. A method to investigate the timing of A2 and P2 can also give information on which valve is affected.

As mentioned in section 2.2 a higher heart rate affects the duration of the QT-interval. This is reflected in the results from table 2 where the intervals during hypercapnia are significantly different from baseline. To ensure that it is the heart rate and not an unknown cause that deviates the R-peak to T-end intervals, the corrected R to T-end interval was calculated. The results from table 4 show no significant change indicating little impact on the QT-intervals other than the heart rate.

The results from table 5 show a significant change in S2-onset to T-end intervals from baseline to hypercapnia. One reason for a premature S2 during hypercapnia is the high increase in RV systolic pressure. As mentioned in section 1, a premature S2 is caused by eccentric hypertrophy, but the pigs experienced acute ischemia. This suggests that the heart did not sufficiently compensate for

the high pulmonary arterial pressure, leading to premature S2. To be certain of the primary cause of the premature S2, further research is necessary.

Study limitations: Since there is no standardized method to detect the attributes needed for the comparison of S2-onset and T-end, a method to find T-end and S2-onset was developed. To ensure the precision of the detected points, a comparison to a gold-standard would have been ideal, to verify the methods.

Data collection from pigs: The experiments were performed on pigs, which cannot directly be transferred to humans, but in general the anatomy of a pig heart has many similarities to a human heart, such as size, valves and heart chambers. This suggests that their physiological responses can be a reliable model for how the human cardiovascular system might respond under similar conditions.

5. Conclusion

It can be concluded from this study that there is a significant change of the S2-onset to T-end interval due to PH induced by hypercapnia. Future work should investigate the correlation between the interval of S2-onset to T-end and the systemic blood pressure, furthermore it should be investigated whether A2 or P2 is the cause for the earlier onset of S2.

Table 2. R-peak to T-end statistics for differences from baseline to hypoxemia and hypercapnia. A negative difference indicates earlier occurrences of T-end during intervention, while a positive difference indicates later occurrences.

R-T-end	Mean $\pm$ sd (ms)	Diff. from mean (ms)	P-value	95% Confidence interval (ms)
Baseline before hypercapnia	344 $\pm$ 34			
Hypercapnia	297 $\pm$ 40	-47	0.04	-2 to -93
Baseline before hypoxemia	360 $\pm$ 27			
Hypoxemia	339 $\pm$ 39	-21	0.13	+7 to -50

Table 3. R-peak to S2-onset statistics for differences from baseline to hypoxemia and hypercapnia. A negative difference indicates earlier occurrences of S2-onset during intervention, while a positive difference indicates later occurrences.

R-S2-onset	Mean $\pm$ sd (ms)	Diff. from mean (ms)	P-value	95% Confidence interval (ms)
Baseline before hypercapnia	310 $\pm$ 22			
Hypercapnia	240 $\pm$ 38	-70	0.01	-22 to -118
Baseline before hypoxemia	316 $\pm$ 20			
Hypoxemia	300 $\pm$ 29	-16	0.19	+10 to -41

Table 4. RT corrected (RTc) statistics for differences between baseline to hypoxemia and hypercapnia. A negative difference indicates shorter RTc during intervention, while a positive difference indicates longer durations of RTc.

RTc	Mean $\pm$ sd (ms)	Diff. from mean (ms)	P-value	95% Confidence interval (ms)
Baseline before hypercapnia	360 $\pm$ 38			
Hypercapnia	324 $\pm$ 67	-36	0.15	+16 to -89
Baseline before hypoxemia	366 $\pm$ 41			
Hypoxemia	358 $\pm$ 38	-8	0.43	+15 to -32

Table 5. S2-onset to T-end statistics for differences between baseline to hypoxemia and hypercapnia. A negative difference indicates earlier occurrences of S2-onset during intervention.

S2-onset – T-end	Mean $\pm$ sd (ms)	Diff. from mean (ms)	P-value	95% Confidence interval (ms)
Baseline before hypercapnia	-34 $\pm$ 18			
Hypercapnia	-65 $\pm$ 27	-30	0.01	-8 to -52
Baseline before hypoxemia	-33 $\pm$ 19			
Hypoxemia	-42 $\pm$ 28	-9	0.39	+14 to -38

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