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Seismocardiography as a Tool for Assessment of Bi-Ventricular Pacing

Kasper Sørensen, Peter Søgaard, Kasper Emerek, Ask Schou Jensen, Johannes Jan Struijk, Samuel Emil Schmidt

Abstract. *Objective* Conduction-induced heart failure in patients with left bundle branch block (LBBB) can benefit from cardiac resynchronization therapy (CRT). However, some patients are non-responders to the therapy with one contributing factor being poor optimization of the atrioventricular (AV) pacing delay. In this study, we have investigated the pacing-induced changes in the seismocardiogram (SCG). *Approach* 14 patients with heart failure, LBBB, and CRT were included. SCG was recorded with pacing turned on and off. Based on a mean SCG heartbeat from each patient, fiducial points were annotated, and cardiac timing intervals (CTI) and amplitudes were derived. These were compared between the CRT group and a group of healthy normal subjects (n = 14). Echocardiography was also used to derive CTI. Intervals derived from the SCG and echocardiogram were correlated. *Main Results* The isovolumetric contraction time (IVCT) derived from SCG was significantly shorter in the CRT group when the pacemaker was turned on (63.2 to 52.6 ms, p = 0.027). The first peak-to-peak amplitude in the systolic complex was significantly larger with the pacemaker turned on (p = 0.002), as well as the |max-min| amplitude in the systolic complex (p = 0.003). Isovolumetric relaxation time and left ventricular ejection time (LVET) were not significantly different between pacemaker settings. Compared to normal subjects, IVCT was significantly prolonged with the pacemaker turned off. All amplitudes were significantly larger in the healthy subject group. IVCT and LVET derived from SCG were significantly correlated to the echocardiogram. *Significance* IVCT shortened and SCG amplitudes increased in response to CRT, indicating a more efficient ventricular contraction. This demonstrates the possibility to detect cardio-mechanic changes in response to treatment with the SCG. However, for the patients the systolic part of the SCG was abnormal and difficult to characterize, raising concerns about the correct interpretation of the SCG.

Keywords: Biventricular Pacing, Cardiac Timing Intervals, Cardiac Vibrations, Seismocardiography (SCG), Left Bundle Branch Block (LBBB), Isovolumic Contraction Time (IVCT), Left Ventricular Ejection Time (LVET)

1. Introduction

Cardiac resynchronization therapy (CRT) was introduced in the mid-1990s as a way to stimulate the left and right ventricles in patients with heart failure and cardiac dyssynchrony [1, 2]. Left bundle branch block (LBBB) is one of the causes of cardiac

dyssynchrony and in approximately 25% of all heart failure patients, a widening of the QRS complex to more than 120 ms in the ECG is observed [3]. This condition is associated with a 1.7-fold increased risk of sudden cardiac death [1, 3]. In patients with LBBB, CRT can improve the mechanical contraction of the heart and thus improve exercise tolerance, health-related quality of life, reduce hospitalization rate and improve oxygen uptake and reduced mortality [4, 5, 6, 3, 7, 2]. There is, however, a subgroup (about 30%) of patients that are non-responders to the treatment [8]. One of several factors contributing to being a non-responder is a suboptimal setting of the atrioventricular (AV) pacing interval [9]. Optimization of pacing settings can be achieved in several ways. These include the use of parameters from the ECG such as QRS duration or area, stroke volume and mitral flow from echocardiography, and maximum rate of left ventricular pressure rise (dP/dt max) from invasive pressure guidewire [10]. However, there is no consensus on which method to use [10]. Echocardiography is time-consuming and requires highly specialized clinicians [11, 12] whereas the use of invasive methods during follow-up is not ideal. Even though echocardiography is used widely for optimizing the pacing delay, its use has in some cases been as effective as the nominal device setting [13]. Thus, finding an alternative method for deriving some of the same measures as currently used methods could prove to be beneficial in pacemaker optimization. This could be used in cases where echocardiography is not available, beneficial, or required.

In 1959 Patrick Mounsey published the first paper on a new method for recording cardiac vibrations on the chest using an accelerometer, which he coined præcordial ballistocardiography [14]. Mounsey was able to relate the morphology of the signal to events in the cardiac cycle. Bozhenko named the method "Seismocardiography" (SCG) in 1961 [15] and, since then, researchers have used the latter terminology for the recording of the acceleration of micro-vibrations on the chest caused by the beating of the heart. Following a period of relative silence from 1965, the method was revisited around 1990, primarily by John Zanetti and David M. Salerno [16, 17, 18]. With the development of small, lightweight micro-electromechanical systems (MEMS) accelerometers the signal has become more widely known, but besides being used for research purposes, the method is not widely used in the clinic [19].

In 2007 Frank Marcus and co-workers investigated how cardiac timing intervals derived from the SCG changed due to bi-ventricular pacing in patients treated with CRT [20]. They compared, among others, timing intervals and isovolumetric contraction time (IVCT) derived from the SCG of CRT patients and healthy subjects. IVCT changed from being significantly prolonged in patients when the pacemaker was turned off, to being non-significantly prolonged when turning the pacemaker on [20]. Marcus suggests that the accelerometer could be used as an alternative to echocardiography to optimize pacemaker settings. Jensen and co-workers investigated changes to the first heart sound, in CRT treatment and found that the energy of the sound was significantly higher, with the pacemaker turned on, compared to off [21]. Accelerometers implemented in the tip of pacemaker leads (the SonR system) have recently been shown to be as safe and

effective as echocardiography-guided CRT optimization [22, 23, 12].

In the current study, we investigate the effect of bi-ventricular pacing on both cardiac timing intervals and amplitudes derived from the SCG. Cardiac timing intervals from the SCG, as described in the literature, were correlated with those derived from the echocardiogram to investigate the agreement between the modalities. The study further investigates the usability of the measures derived from the SCG to assess CRT treatment.

2. Methods

The study was approved by the local ethical committee of North Jutland (Identification number: 2012-0068) and performed at the Department of Cardiology at Aalborg University Hospital. All methods were performed following relevant guidelines and regulations. 19 patients with bi-ventricular pacemakers were enrolled in the study. All patients signed written informed consent before participating in the study. This study further investigates the data from previous preliminary work [24].

Inclusion criteria were CRT implanted more than 3 months ago, stable CRT with a pacing percentage higher than 95%, freedom from atrial fibrillation and frequent ectopic beats, and the ability to cooperate.

2.1. Seismocardiographic Signal Recording

The patients participated in the study as part of their regular routine follow-up after CRT implantation. Patient demographic data were obtained.

Patients were placed in the supine position for the recording session. The iWorx IX/228 signal recorder was used to record the physiologic signals. Electrodes for a three-lead ECG were attached in a standard configuration, with electrodes on the left and right shoulders and the left and right iliac crests. For the SCG recording, a Colibrys accelerometer model SF1600S.A was used. The MEMS accelerometer was situated in a 3D printed ABS plastic housing (19 mm wide, 21 mm long, and 11 mm high, weighing 5 grams) and was connected to the signal recorder with a thin flexible wire, allowing the accelerometer to move freely. The accelerometer was attached to the lower part of the sternum (xiphoid process) using a double adhesive patch. A G.R.A.S 40AD microphone situated in a 3D printed ABS coupler was attached to the patient's skin with a double adhesive patch in intercostal space 4 (IC4) at the left sternal border for the recording of the phonocardiogram (PCG).

All signals were recorded with a 5000 Hz sampling frequency. The patient was instructed to breathe normally and not talk while the recording was obtained for a minimum of at least 2 minutes, while the pacemaker was turned on in its most optimal setting (defined below in the following section). The pacemaker was then turned off and the signals were recorded for a minimum of two minutes. A blanking period of a minimum of 2 minutes was allowed between pacemaker settings. As the recording of the

signals was performed as part of a routine checkup for some of the patients, the initial pacing-delay settings were subsequently optimized, based on cardiac output measured with echocardiography. A minimum of two minutes of recording of the SCG and ECG was obtained with the optimized pacemaker setting and used as the "pacing on" setting.

2.2. Echocardiographic image recording

Echocardiographic images were obtained following the period of SCG and ECG recording in the two states of pacing on and off. Using M-mode Tissue Doppler Image of the mitral leaflet IVCT, isovolumic relaxation time (IVRT) and left ventricular ejection time (LVET) were calculated [25]. The timing intervals were calculated by the same operator who performed the echocardiographic scanning of the patients. The echocardiogram was used by the clinician to assess the CRT setting making sure that the "pacing on" setting provided the most optimal pacing setting for the patient concerning cardiac output. Thus, the setting "pacing on" resulted in the best cardiac contractile function, assessed by the clinician.

2.3. Signal processing

The recorded signals were exported to MATLAB format where the rest of the data analysis was performed (2019b. The MathWorks, Inc.). Guided by the R-peaks in the ECG, individual heartbeats were segmented and aligned as described by Jensen et al. and Sørensen et al., to construct two mean beats for each patient, one with biventricular pacing turned on and one without pacing [21, 26]. The natural variation in time from the first to the second heart sound (S1 and S2) causes the characteristics of S2 to be slurred when computing a mean beat using R-peak-triggered averaging [26]. Thus, the heart sound recorded with the microphone from IC4 was used to align the individual beats to S2. This was achieved by forward-backward filtering the individual heart sounds recorded from IC4 with a 1^{st} order bandpass Butterworth filter with cutoff frequencies at 25 and 150 Hz. The envelopes of the individual beats were computed using the Hilbert transform. The Hilbert transforms of the mean beats were also computed. The peak of the 2^{nd} heart sound was identified in both the envelope of the mean beat and in the individual beats. Lags between the peak of the individual beats and the peak of the mean beat were calculated and used to align the individual beats to the mean beat. A new mean beat was then computed, and the procedure was repeated one more time to realign the individual beats to the new mean beat. This procedure maximizes the characteristics of the diastolic complex in the SCG as well as in the PCG [26].

The individual beats were forward-backward filtered, first with a 1st order low-pass Butterworth filter with a cutoff frequency of 90 Hz and then a 3^{rd} order high-pass Butterworth filter at 0.05 Hz before a mean SCG beat was calculated. A selection of fiducial points in the mean beats was manually annotated according to previous work by [26]. The fiducial points annotated in this study were E_s, F_s, G_s, J_s and K_s in the systolic complex of the SCG and B_d, C_d, D_d and F_d in the diastolic complex.

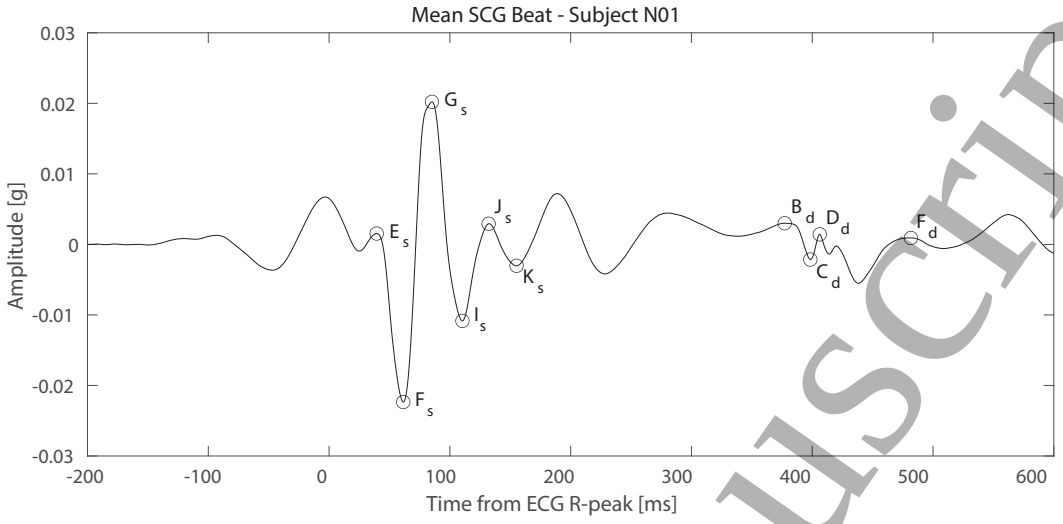

Figure 1. Example of an SCG recorded from a healthy subject. Fiducial points are labeled accordingly to previous work [26]. The first part of the signal is aligned to the R-peak of the ECG and the second part of the signal (from 300 ms after the ECG R-peak) is aligned to the peak of the S2 envelope.

See Figure 1 for reference to the location of the fiducial points. Fiducial points E_s and G_s are correlated to the mitral valve closure and aortic valve opening, respectively. The location of E_s was guided by the high pass filtered signal recorded from IC4 (as described above). B_d and F_d is correlated to the aortic valve closure and mitral valve opening, respectively [26].

The time intervals derived from the SCG were correlated with the intervals derived from the echocardiogram to test if the two methods agree. From an initial subset of the results, a difference of approximately 25-30 ms between IVCT based on the echocardiogram and the SCG was observed. Thus, IVCT was derived as the interval between E_s and G_s and between E_s and J_s in the SCG. Likewise, LVET was derived from both G_s to B_d and J_s to B_d. With this explorative approach, it was possible to calculate both Pearson's correlation and the temporal difference between the modalities. Further, the amplitude between the minimum and the maximum in the systolic complex (defined from E_s to K_s) was derived from the SCG. The remaining fiducial points were used in amplitude calculations, as described in the following.

2.4. Timing intervals, amplitudes, and statistical analysis

Using the fiducial points, the following time intervals were calculated:

- Isovolumetric contraction time (IVCT) from E_s to G_s
- Isovolumetric relaxation time (IVRT) from B_d to F_d
- Left ventricular ejection time (LVET) from G_s to B_d
- Alternative IVCT from E_s to J_s

- Alternative LVET from J_s to B_d

The following peak-to-peak amplitudes were calculated:

- From F_s to G_s (Systolic Amplitude 1)
- From G_s to I_s (Systolic Amplitude 2)
- From B_d to C_d (Diastolic Amplitude 1)
- From C_d to D_d (Diastolic Amplitude 2)
- |max - min| amplitude between E_s and K_s both locations inclusive

Mean values of the time intervals and amplitudes were calculated together with their standard deviations. The intervals and amplitudes were tested for normality using the Shapiro-Wilk test. The analysis showed that the amplitudes were non-normally distributed and that the time intervals were normally distributed. Hence, Wilcoxon Signed Ranked and Mann-Whitney U-test was used to test for a significant difference in the amplitudes within the patient group (biventricular pacing on and off) and compare to the group of healthy subjects respectively (described below). For the time intervals, the one and two-sample students t-test were used. P-values below 0.05 were considered significant.

Using previously obtained fiducial points from healthy subjects, the cardiac intervals and amplitudes from the CRT patients were compared with those of the healthy subjects [26, 27]. This healthy subject group consists of 42 subjects with a mean age of 46.8 ($\pm$ 17.4) years. To match the CRT patient group a subset of 14 healthy subjects with a mean age of 65 ($\pm$ 4) years was extracted.

For visualization of the results, delta values for both intervals and amplitudes were calculated, by subtracting the values derived from the SCG when the pacemaker was turned off from the values when it was turned on.

3. Results

A total of 19 patients were recruited for the study. One patient withdrew from the study. For four of the patients, it was assessed, by the clinician, that turning off the pacemaker would be harmful to the patient. Thus, these patients were excluded from the study. Two of the recordings were performed with an incorrect sampling frequency. To account for this, the signals were resampled to match the other recordings from the other patients. All patients were responders to the CRT treatment with a positive absolute change in left ventricular ejection fraction within one year after implantation. For three subjects the absolute change was between 5 and 7%. For the remaining subjects, the change was at least 10%.

For the final data analyses, we included 14 patients, four of those were females. Patient demographics are included in Table 1. For one subject, weight and height were not obtained, thus, the values presented in Table 1 do not include these data. For two of the CRT patients and two of the healthy subjects the fiducial point, J_s was not

Table 1. Demographic data for the patients and subjects included in the study. Note that for one CRT patient weight and height were not obtained. The p-value for the two-sample t-test between patients and healthy subjects is listed

Variable	CRT patients (n = 14)	Healthy subjects (n = 14)	p-value
Age [Years]	61.1 ± 11.9	65.0 ± 4.0	0.26
Weight [kg]	82.1 ± 12.5	72.6 ± 13.2	0.07
Height [cm]	175.2 ± 8.4	171.3 ± 6.4	0.18
Males / Females [n]	10 / 4	6 / 8	0.14

detectable. In these cases, IVCT (E_s to J_s) and LVET (E_s to B_d) was treated as missing data when performing the statistical tests. Demographic data from the healthy subject group is presented in Table 1 as well.

3.1. Changes in timing and amplitudes in the CRT group

Results from the time interval analysis and the amplitude analysis are presented in Tables 2 and 4 respectively. IVCT derived from the SCG (with both G_s and J_s as the fiducial point for aortic valve opening) was significantly shorter when the pacemaker was turned on compared to off. Shorter IVCT derived from the SCG was observed in 11 and 12 of the 14 patients (79% and 86%) when using G_s and J_s as indicators for aortic valve opening respectively. IVRT was not changed when turning on the pacemaker. For LVET (derived from both G_s and J_s) a tendency toward a shorter temporal interval was observed when turning on the pacemaker but the change was not statistically significant. Changes in time intervals are represented in Table 2 and Figure 2.

For the systolic amplitude 1, a significantly larger amplitude was observed when turning the pacemaker on. The systolic complex amplitude 2 had a tendency towards a larger amplitude when turning on the pacemaker, but the change was not significant. For the diastolic amplitudes, we did not observe significant changes, but the diastolic amplitude 2 showed a tendency to be larger when turning the pacemaker on compared to off. The systolic amplitude |max-min| was significantly larger when turning on the pacemaker compared to off. The results of the amplitude analysis are presented in Table 2 and Figure 3. A typical example of an SCG signal from a CRT patient with the pacemaker turned on and off is visualized in Figure 4.

When dividing two groups, one with males and one with females, a significantly longer LVET was observer for females compared to males, when the pacemaker was turned on. This was observed with both G_s (median difference of 45.8 ± 3.2 ms, $p = 0.026$) and J_s (median difference of 37.7 ± 5.0 ms, $p = 0.019$) as the fiducial point for aortic valve opening. No changes was observed in amplitude or heart rate regardless of the pacemaker setting.

Table 2. Timing intervals and peak-to-peak amplitudes derived from fiducial points in the SCG. Mean values are presented together with standard deviation. P-value for t-test (for the time intervals) or Wilcoxon Signed Rank test (for the amplitudes) between pacing off and pacing on presented.

Variable	p-values	Pacing off Mean (± SD)	n	Pacing on Mean (± SD)	n	Median difference (± SD)
IVCT [ms]	0.027	63.2 (± 20.9)	14	52.6 (± 14.4)	14	-7.0 (± -6.5)
IVRT [ms]	0.920	77.0 (± 20.8)	14	77.7 (± 18.1)	14	1.4 (± -2.7)
LVET [ms]	0.362	312.1 (± 49.7)	14	303.5 (± 26.8)	14	-7.9 (± -23.0)
IVCT (E_s to J_s) [ms]	0.009	111.9 (± 18.9)	13	92.9 (± 12.5)	13	-18.7 (± -6.4)
LVET (J_s to B_d) [ms]	0.610	268.7 (± 46.3)	13	264.8 (± 25.5)	13	5.5 (± -20.8)
Systolic Amplitude 1 [mg]	0.002	4.7 (± 3.5)	14	8.8 (± 9.0)	14	2.4 (± 5.4)
Systolic Amplitude 2 [mg]	0.135	4.3 (± 4.2)	14	6.8 (± 6.8)	14	1.7 (± 2.5)
Diastolic Amplitude 1 [mg]	0.173	2.5 (± 1.6)	14	2.0 (± 2.0)	14	-0.9 (± 0.5)
Diastolic Amplitude 2 [mg]	0.903	2.2 (± 1.9)	14	2.6 (± 2.9)	14	-0.5 (± 1.0)
|max-min| [mg]	0.003	6.1 (± 4.4)	14	9.8 (± 9.1)	14	1.7 (± 4.7)
Heart Rate (BPM)	0.119	66 (± 10)	14	68 (± 8)	14	-2 (± 5)

Table 3. Timing intervals and peak-to-peak amplitudes derived from fiducial points in the SCG. Mean values are presented together with standard deviation. Comparison between CRT patients with the pacemaker turned on and off and normal healthy subjects.

Variable	p-value - pacing off vs healthy (n = 14)	p-value - pacing on vs healthy (n = 14)	Mean (± SD) healthy subjects (n = 14)
IVCT [ms]	0.042	0.493	48.9 (± 14.0)
IVRT [ms]	0.041	0.036	93.6 (± 19.9)
LVET [ms]	0.313	0.496	296.0 (± 30.6)
IVCT (E_s to J_s) [ms]	0.002	0.212	84.4 (± 20.2)
LVET (J_s to B_d) [ms]	0.615	0.711	260.4 (± 33.3)
Systolic Amplitude 1 [mg]	<0.001	<0.001	30.0 (± 14.1)
Systolic Amplitude 2 [mg]	0.001	0.012	15.1 (± 9.8)
Diastolic Amplitude 1 [mg]	<0.001	<0.001	6.7 (± 3.4)
Diastolic Amplitude 2 [mg]	<0.001	<0.001	9.1 (± 4.6)
Systolic Amplitude |max-min| [mg]	<0.001	<0.001	33.5 (± 14.2)

3.2. Comparison with normal healthy subjects

IVCT (derived from both G_s and J_s) was significantly prolonged for the CRT patients with the pacemaker turned off, compared to the healthy subjects, see Table 4. IVRT

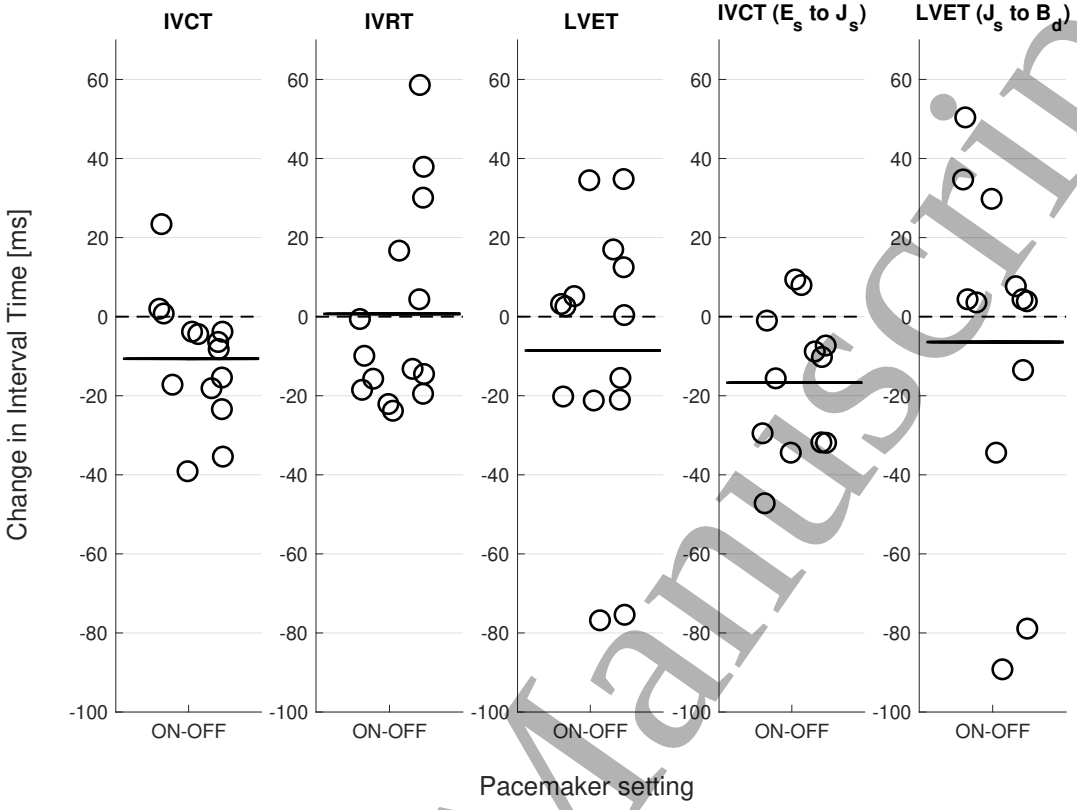

Figure 2. Delta values for the timing intervals derived from SCG. The circles present values for each subject and the horizontal line presents the mean change in time. Jitter is added to the x-axis location for the visual presentation.

was significantly shorter in the CRT patients with both the pacemaker turned on and off compared to the healthy subjects. In general, the amplitudes derived from the SCG signals in the CRT patients were lower, compared to the normal healthy subjects, see Table 4. Turning on the pacemaker did not alter the amplitudes enough, to become of the same magnitude as the healthy subjects.

When dividing the healthy subjects into two groups based on sex, a significantly longer IVCT was observed for males compared to females, using G_s as the fiducial point for aortic valve opening (median difference 20.2 $\pm$ 4.9 ms, p = 0.01).

3.3. Correlation between the SCG and echocardiogram

Pearson's correlation was computed between the timing intervals derived from the seismocardiogram and those derived from the echocardiogram, see Table 4. For the CRT patients, the correlations were calculated dependent on the biventricular pacing setting. The temporal differences between IVCT and LVET calculated using G_s and J_s were significantly different in all cases.

Table 4. Pearson's correlation (r), p-values and mean temporal difference between echocardiogram and SCG.

	Biventricular pacing on				Biventricular pacing off				Healthy Subjects		
Interval	r	p-value	Difference	n	r	p-value	Difference	n	r	p-value	Difference	n
IVCT	0.63	0.015	27.2 (± 14.8)	14	0.46	0.098	45.4 (± 24.6)	14	0.90	<0.001	-2.2 (± 6.5)	14
LVET	0.72	0.004	-23.0 (± 25.4)	14	0.66	0.010	-65.0 (± 38.4)	14	0.92	<0.001	-1.3 (± 14.1)	14
IVRT	-0.26	0.360	60.5 (± 52.6)	14	-0.37	0.199	100.2 (± 53.4)	14	-0.15	0.603	12.2 (± 24.1)	14
IVCT (E_s to J_s)	0.46	0.117	-13.2 (± 17.8)	13	0.79	0.001	-2.2 (± 16.5)	13	0.71	0.009	-38.1 (± 14.2)	14
LVET (J_s to B_d)	0.58	0.036	15.7 (± 31.2)	13	0.55	0.054	-18.0 (± 42.3)	13	0.97	<0.001	34.7 (± 9.2)	14

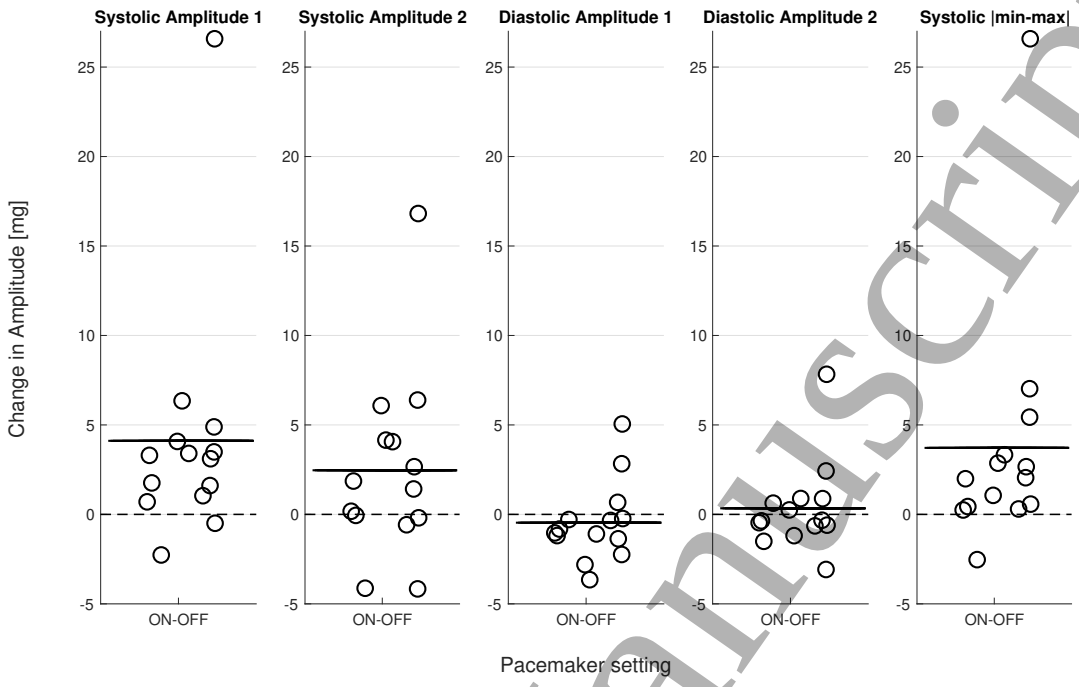

Figure 3. Delta values for the peak-to-peak amplitudes derived from SCG. The circles present values for each subject and the horizontal line presents the mean change in amplitude. Jitter is added to the x-axis location for the visual presentation.

4. Discussion

We found that for all but three subjects, IVCT derived from SCG improved when the pacemaker was turned on compared to off. In the echocardiogram, we saw an improvement in IVCT in all of the subjects. This demonstrates how CRT can improve the cardiac contractile function as shortening in IVCT is associated with a positive response to the resynchronization therapy and improved cardiac contractile function [20]. The observed significant longer IVCT in the CRT patients compared to the healthy subjects, normalized to the healthy subject group when turning the biventricular pacemaker on, as also demonstrated by Marcus and coworkers [20]. The shortening of IVCT can in turn indicate an increase in the rate of left ventricular pressure rise (dP/dt).

In the systolic complex, we observed a significantly larger peak-to-peak amplitude between the fiducial points F_s and G_s as well as a significantly larger |max-min| amplitude. The time period between the F_s and G_s fiducial points in SCG signal is commonly related to the isovolumetric contraction [14, 26]. With the shorter time of IVCT, it seems natural that this amplitude should also increase, as the pressure in the left ventricle builds up faster, before exceeding the pressure in the aorta. As the heart contracts and becomes more spherical, the acceleration measured on the xiphoid process will be outwards and away from the body. The faster contraction will thus cause a faster acceleration leading up to the fiducial point G_s. The increase in amplitude and shortening in IVCT is a result of a more synchronous contraction of the ventricles when

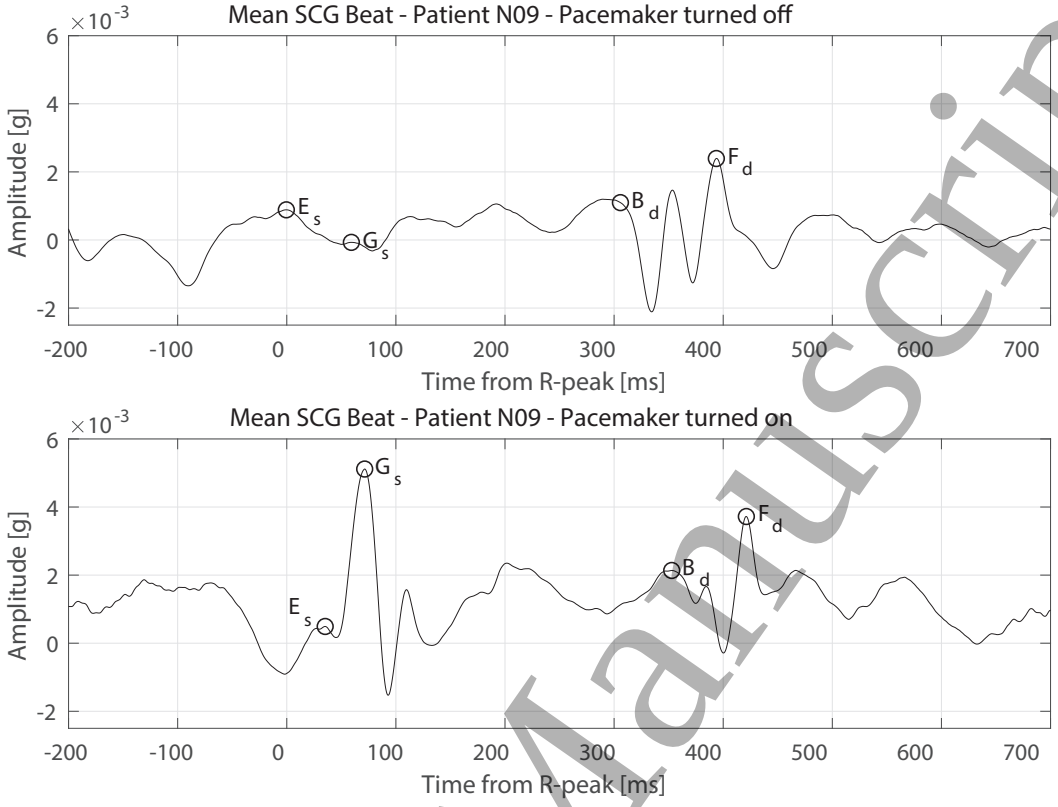

Figure 4. Example of a typical SCG signal. In panel (A) the pacemaker is turned off, in panel (B) the pacemaker is turned on. The signals presented in the figures are composed of two mean beats each. The first part of the signal is aligned to the R-peak of the ECG and the second part of the signal (from 300 ms after the ECG R-peak) is aligned to the peak of the S2 envelope.

the pacemaker is turned on.

We did not observe a significant change in the IVRT between the pacing settings in the CRT group. This is concurrent with the study by Marcus [20]. We did observe a significantly shorter IVRT for the CRT patients with the biventricular pacer turned on and off, compared to the healthy subjects. We have previously demonstrated that the location of the fiducial point F_d, associated with mitral valve opening, can be difficult to locate, even in an SCG signal recorded from a normal healthy subject [26]. Therefore, the time interval of IVRT might be inaccurately derived, due to incorrect placement of the fiducial points F_d associated with mitral valve opening. This is further supported by the low and non-significant correlation between IVRT derived from the SCG and echocardiogram and a temporal difference of approximately 80 ms. When comparing the cardiac timing intervals found in our study to those derived by Marcus, we find that our mean interval for IVCT is shorter. Mean IVCT reported by Marcus with bi-ventricular pacing turned on is 71.5 ms compared to 52.6 in our study. For the IVCT interval derived from the fiducial point E_s to J_s, our interval of 92.9 with bi-ventricular pacing turned on is longer compared to Marcus' findings. For IVRT Marcus reports

117.0 ms with pacing on, compared to 77.7 ms in our study. LVET was reported by Marcus to be 284.3 ms compared to 303.5 ms found in our study. LVET derived from J_s to B_s yields 264.8 ms in our study. For the normal healthy subjects, we observed a difference in the IVCT interval from Marcus' study to ours, 58.2 compared to 48.9 ms, but only a neglectable difference in IVRT and LVET of 93.5 compared to 93.5 ms and 302.1 compared to 296.0 ms respectively.

In the diastolic complex, we observed a tendency towards a larger magnitude of the diastolic amplitude 2 and a tendency towards a lower amplitude in the diastolic amplitude 1. It was previously established that improved left ventricle relaxation is associated with a larger amplitude in the diastolic complex following the E_d point [24, 28]. We did not observe this when the pacemaker was turned on. The larger amplitude related to the aortic valve closure would be caused by a faster ventricular relaxation. Our finding is concurrent with previous findings [29]. Comparing the CRT group to the healthy subject group shows that the amplitudes for the CRT group are smaller than for the normal subject. As the SCG signal measures the acceleration of the vibrations from the beating heart, it seems reasonable that patients with impaired cardiac contraction do not produce an SCG signal with as much contraction force as normal healthy subjects. This could indicate a generally weaker and less synchronous contraction of the heart for CRT patients compared to normal healthy subjects. It has previously been shown that for normal healthy subjects there is a significant correlation between age and the systolic amplitude 1 [27]. For the subset of elderly healthy subjects, this is not the case. There is however a significant linear relationship between age and the systolic amplitude 2.

The temporal difference between the timing intervals derived from SCG compared to echocardiography is of concern. With the biventricular pacer turned on, we observed a significant correlation between IVCT derived from SCG and echocardiography using the G_s fiducial point as an indicator for aortic valve opening. However, there is a large temporal difference of 27 ms between the two modalities. Using J_s as an indicator for aortic valve opening reduces this difference to -13 ms but the correlation is non-significant between the modalities. With the pacemaker turned off, we observed a short temporal difference in IVCT between the modalities when using the J_s fiducial point and a strong significant correlation. Using G_s as an indication for aortic valve opening with biventricular pacer turned off resulted in a temporal difference of 45 ms and a non-significant correlation.

Previous work by Dehkordi et al., Markus et al., and Sørensen et al. has shown that there is a strong correlation between the physiologic events in the cardiac cycle and certain fiducial points in the SCG, the current study suggests that this might not always be the case [26, 20, 30]. Thus, further investigations of the SCG, especially from patients with heart disease, should be conducted.

Besides the improvement in some of the SCG-derived parameters, we observed that the morphology of the signal changes when turning the pacemaker on (see Figure 4). For the majority of the signals, the morphology had a better resemblance to the normal

seismocardiogram [26] when the pacemaker was turned on compared to turned off. This is a subjective measure. Besides the improvement in Systolic Amplitude 1, Systolic Amplitude |max-min|, and IVCT this could also be of clinical value. Optimizing the pacemaker settings based on the morphology of the SCG signal would of course require a larger study, to obtain knowledge about different types of "CRT influenced SCG signals".

This approach for CRT is not automatic like the SonR with the accelerometer implanted in the pacing-leads [12]. However, with the external accelerometer, we see the possibility for an operator-independent approach for CRT optimization for patients with existing pacemakers as an alternative, in certain situations, to using echocardiography [11]. Using the accelerometer to assess the CRT setting may be less operator dependent than using echocardiography and require less specialized clinicians to perform the optimization of the CRT treatment. As stated by Brugada and co-workers in 2017: even though studies have shown improvements in the non-responders to CRT due to Echo optimization, clinicians do not perform this regularly due to "lack of precision, availability of skilled staff, resources, and logistical challenges" [12, 11].

5. Limitations

The annotation of the fiducial points in the SCG was done manually by one author (KS) and validated by one other author (SES). The authors were not blinded to the pacemaker setting when annotating the signals. Likewise, the cardiologist evaluating the echocardiograms was not blinded when annotating the echocardiograms for deriving the cardiac time intervals. To further investigate if the SCG is a viable tool for the assessment of CRT optimization studies with more patients are needed. This study only includes a total of 14 patients submitted to CRT, which is a limitation to the study and the results.

6. Conclusion

Cardiac resynchronization therapy changes the morphology of the seismocardiographic signal in heart failure patients. Turning the pacemaker on significantly increases the magnitude of two amplitudes in the SCG signal and significantly shortens IVCT derived from the SCG. A significant correlation between the cardiac timing intervals derived from SCG and echocardiogram was found. However, the correlation and temporal difference varied between the modalities, depending on the pacemaker settings, indicating that the SCG is not yet fully understood.

7. Future Perspectives

With a larger longitudinal study, it would be possible to investigate the effects of optimization based on SCG to validate if this method can be used for pacemaker

optimization. Further, it would be of interest to investigate if SCG can be used to find patients with mechanical dyssynchrony but QRS ¡ 120 ms [31, 1]. Even though these patients should most likely not be treated with a CRT, they should be followed and the reason for their mechanical dyssynchrony investigated. Most importantly, however, further investigation of the correlation between the physiologic events in the cardiac cycle and the fiducial points in the SCG is needed, before this method can be applied in the clinic.

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