Validation of a Marker of Atrial Contraction in the SonR Signal

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Abstract

Introduction: The main component of the endocardial acceleration signal (SonR) is today used for cardiac resynchronization therapy (CRT) optimization. This prospective, single center pilot study focuses on another signal component, SonR4 that may provide further information on the atrial activity. Methods and Results: SonR signal and ECG tracings were recorded simultaneously during a CRT-D optimization procedure in 15 patients (12 men, 68 ± 9.5 years, ischemic heart disease 53%) indicated for CRT. Correlation between SonR4 signal, recorded using SonR and atrial contraction, identified by Echo Doppler was evaluated by Pearson and Student’s t tests under different Atrio-Ventricular (AV) delay programming. From 15 consecutive screened patients, 9 had concomitant analyzable SonR4 and ECG recordings and were included in the study population. The presence of the SonR4 component was systematically correlated to the presence of the A wave. A significant correlation was observed between SonR4 and atrial contraction timings (r = 0.75, p = 0.02) according to different AV delays, with a high reproducibility in SonR4 assessment. Conclusion: A strong correlation between SonR4 and atrial contraction timings was observed, further suggesting that SonR4 is a marker of the atrial contraction. Additional assessments in larger populations are required to confirm these results and build further applications.

Keywords
Endocardial Acceleration (EA), Hemodynamic Sensor, SonR, Cardiac Resynchronization Therapy, Heart Sound, Atrial Contraction

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1. Introduction

Cardiac Resynchronization Therapy (CRT) is indicated for the treatment of severe Heart Failure (HF), in patients with Left Bundle Branch Block (LBBB) \[1\] \[2\]. However, despite generally encouraging results, a third of the patients do not respond to CRT therapy \[3\]. Several studies have shown the interest of optimizing settings of inter-ventricular (VV) and atrio-ventricular (AV) delays for improving the response to this therapy \[4\]. However, these parameters change constantly particularly during exercise \[5\] and their regular setting is time consuming.

In this context, device-based methods are currently developed allowing automatic optimization of AV and VV delays. The hemodynamic SonR sensor, a micro-accelerometer placed in a sealed capsule located at the tip of an atrial pacing lead, detects mechanical vibrations propagating throughout the entire heart during the cardiac cycle. The major component of the SonR signal, SonR1, is concomitant with the first heart sound \[6\] and has been shown to correlate with LVdP/dt_max \[7\]-\[10\]. The use of this signal for automatic optimization of AV and VV delays in CRT has been already validated \[11\]-\[14\]. According to the CLEAR pilot study \[13\], the SonR system significantly improves the clinical response rate to CRT as compared to standard medical practice (76% vs. 62%, \(p = 0.0285\)).

However, continuously adapting CRT system should include atrial electrical and mechanical monitoring \[15\]. A new component of the SonR signal, initially highlighted in pigs \[7\] and called SonR4 \[16\] \[17\] is assumed to correspond to the vibrations generated by the atrial contraction, which produces the A wave flow at echocardiography. It has not been established whether the SonR4 signal originates from the left atrium, the right atrium or the sum of two components. It likely corresponds to the fourth heart sound, usually present in ischemic patients or patients with impaired diastolic function \[18\]-\[20\].

The main objective of this pilot study was to further analyze the SonR4 component in HF patients indicated for CRT-D. The primary endpoint of the study was to assess the relationship between the SonR4 signal and the A wave determined by echocardiography and corresponding to the left atrial systole.

2. Methods

2.1. Study Design and Objectives

This study is a single center, prospective study, conducted in accordance with the declaration of Helsinki and all applicable local laws and approved by the local ethic committees. All patients gave their informed consent to participate.

All enrolled patients were implanted with a Paradym RFTM SonR CRT-D device (Sorin CRM, Clamart, France) according to applicable guidelines connected to the atrial SonRTipTM lead encapsulating the SonR sensor.

The primary objective was the evaluation of the simultaneous occurrence of the SonR4 component and the A wave (corresponding to the left atrial systole) and the analysis of the SonR4 morphology. For this purpose, the SonR signal was recorded during AVD scan acquisitions simultaneously to the Doppler ECG. SonR4 component and A wave were then retrieved and the reproducibility of the SonR4 component among 15 consecutive beats was evaluated.

The secondary objective was to correlate the timings of the SonR4 component and the A wave. For this purpose, 1) the timing of the SonR4 component was assessed according to different AVD and; 2) the correlation between the timings of the SonR4 component and the A wave was assessed.

Data collection, including SonR signal assessment and cardiac echocardiography Doppler measurements, was carried out during a standard CRT-D settings optimization procedure.

2.2. CRT-D Settings Optimization Procedure

The procedure consisted in AV delay optimization in a fixed biventricular pacing configuration and was performed in two steps. Firstly, a manual AV delay optimization was performed with the SonR system, allowing retrieving the PR interval of the patient as well as an indication of the optimal AV delay. Secondly, an AV delay scan was performed in order to assess the presence and the timing of the SonR4 component and the A wave at different AV delays. The AV delay scan ranged from 65 ms to a value equal to PR-40 ms (4 to 6 AV delays tested) based on previous PR interval estimation.
2.3. Cardiac Echocardiography Doppler Measurements

The cardiac echo Doppler was performed with a Philips IE33 device and a S5-1 probe (Philips Healthcare, Andover, MA, USA). The transducer was positioned at the apex of the heart with 4-cavities view for the measurement of the mitral flow and then 5-cavities view for the measurement of the aortic ejection flow. The same operator performed all echocardiography measurements.

The following timings were assessed from the beginning of the QRS:

1) On the mitral filling flow: the timings of the E wave start, the E wave end, the beginning of A wave, the peak of A wave, the end of A wave, the mitral closure (marked by a slight click closure associated with a negative pulsed Doppler flow), the amplitude of E and A waves peak. Finally, the truncation of the A-wave was defined by an asymmetrical slope or premature interruption of the A wave.

2) On the aortic ejection flow of continuous Doppler: the time of aortic opening, the time of the aortic ejection peak and the time of aortic closure, marked by a closure click.

All these timings were synchronized with the sensed P wave by adding the programmed AVD and averaged over 3 consecutive beats.

2.4. SonR Signal Assessment

The SonR signal was recorded by the SonR™ micro accelerometer (Sorin CRM SAS, Clamart, France) placed at the tip of a right atrial lead as previously described [2]. SonR4 templates were retrieved and computed during series of 15 consecutive beats. For each beat, a window was defined between the sensed P wave and the SonR1 onset. The content of this window was then realigned and averaged with the content of the previous beats, to produce the SonR4 template. Timings, synchronized with the sensed P event were then manually extracted from the template presenting the highest correlation between beats.

2.5. Statistical Analysis

The reproducibility of the SonR4 component was evaluated by averaging the correlation of each beat to the template, and then, for a given patient, averaging the correlation over the different AV delays tested for the patient. To describe the global stability over the population, average and standard deviation of these correlations were computed.

The timings of the SonR4 component and of the A wave peak were described using mean and standard deviation averaged over the different AV delays for each patients, and finally expressing a global stability by averaging the standard deviation over the patients.

Finally, the correlation between SonR4 and A wave timings was assessed using the Pearson’s and Student’s t-distribution. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Population and Follow up

The study population consisted of 15 consecutive patients (12 men, 68 ± 9.5 years, ischemic heart disease in 8 patients (53%), LVEF = 27.4% ± 5.2%, NYHA I/II/III/NA: 1/9/3/2). No patient has been hospitalized or underwent cardiac failure before enrollment. The cardiac condition was considered stable when measurements were carried out, between May and November 2012. The atrial lead was positioned in the right atrial appendage in 13 patients, in the lateral wall in 1 patient and in the Septum in 1 patient.

Five patients were excluded from the analysis: three patients with atrial pacing presented with artifacts in the SonR signal related to the atrial spikes (Figure 1); in one patient the SonR signal was not assessable due to a low quality; finally one patient showed a highly unstable sinus rhythm that required atrial pacing, therefore precluding the analysis.

Consequently, 10 patients were included in the final analysis: 9 patients in stable sinus rhythm and 1 patient in atrial flutter during echographic recordings.

3.2. SonR4 Occurrence and Morphology

In the 9 patients in sinus rhythm, the spontaneous atrial depolarization (As) was systematically followed by the
SonR4 component (Figure 2(a)). The SonR4 wave occurred a few milliseconds after the atrial sensing from the atrial lead. In the patient with atrial flutter, the SonR4 component presented an irregular morphology and very low amplitude (Figure 2(b)). The SonR4 component, averaged among 15 consecutive cardiac cycles based on a beat-to-beat analysis of morphology and temporal position with respect to the atrial event, led to the identification of two opposite waves with an average correlation coefficient of $r = 0.76 \pm 0.11$ (Figure 3).

### 3.3. SonR4 and A Wave Timings

The timing of the SonR4 component ($t_{\text{SonR4}}$) was defined in the middle of the positive and negative waves (Figure 3). The timing of the A wave was defined as the timing of the peak of the A wave ($t_{\text{A wave}}$) based on Echo Doppler tracing.

$t_{\text{SonR4}}$ and $t_{\text{A wave}}$ were averaged over different AV delays in each patient. The average standard deviation of $t_{\text{SonR4}}$ over the patients was low (3.2 ms), thus showing a low variability of $t_{\text{SonR4}}$ following the atrial contraction (Figure 4). Moreover, a strong correlation between $t_{\text{SonR4}}$ and patient heart rate was observed ($r = 0.78, p = 0.015$). On the opposite, the average intra patient variability of $t_{\text{A wave}}$ was significantly higher (18.8 ms, $p = 0.001$).

A strong correlation between $t_{\text{SonR4}}$ and $t_{\text{A wave}}$ was observed ($r = 0.76; p = 0.019$) (Figure 5).

### 4. Discussion

This is the first evaluation of a newly identified mechanical component of the cardiac cycle, SonR4, as a marker of the atrial contraction, in a population of HF patients implanted with a CRT-D device. Bordachar et al. previously highlighted in a porcine model the presence of this marker, which coincided with the atrial contraction [7]. This study confirms the existence of this marker in HF patients and shows its correlation with the active filling phase associated with the atrial myocardial contraction, as represented by the A wave on echocardiography.

As shown in our recordings, the SonR4 component is mainly biphasic and requires further research to better define the relevance of its two components. Moreover, these results cannot state if the SonR4 signal comes from the right, the left atrium or both chambers. Different studies on the SonR signal suggest that this type of component is an expression of vibrations of the whole cardiac tissue, regardless of the lead position [2], and that it is rather the expression of events taking place in the left chambers, especially because pressures level are less important in the right atrium.

The fact that the SonR4 component has a constant duration even for very short AV delays suggests that it is primarily an expression of the early phase of the atrial contraction, or even its peak, but not the final part. It in-
Figure 2. (a) SonR signal in patients in sinus rhythm. As: marker of atrial depolarization; Vp: marker of ventricular pacing; SonR1: first component of the SonR signal; SonR4: fourth component of the SonR signal. (b) SonR signal in the patient in atrial flutter. As: marker of atrial depolarization; Vs: marker of ventricular depolarization; SonR1: first component of the SonR signal; Circles indicate absence of SonR4 component after As.

Figure 3. SonR4 component morphology. Presence of two opposite peaks.
Figure 4. The average timing of the SonR4 component (t_SonR4) in each patient.

Figure 5. Correlation between t_SonR4 and t_A wave.

Indicates the presence of an effective atrial contraction, possibly in its most efficient phase, although it does not seem to predict any A wave truncation. As shown in Figure 2, the SonR4 component presented irregular morphology and low amplitude in one patient with atrial flutter although SonR recording was acceptable. Another argument for the relation between SonR4 and atrial contraction is the presence of the marker during an episode of ventricular fibrillation (VF) in one patient implanted with the same device in whom the SonR monitoring permitted to record the SonR4 marker and the persisting P wave during VF (Figure 6). All these facts are strong arguments for the potential role of SonR4 in monitoring atrial contraction. Further analysis would require the monitoring of SonR4 in different interventions changing the A wave such as exercise, Dobutamine or volume-overload.

The use of SonR4 signal may offer indeed several advantages. By directly reflecting atrial timing, it allows a sharper definition of atrial contraction, particularly at the end of passive ventricular filling. This might allow, in future applications, the inclusion of this component in various algorithms aiming to optimize the AV delay, since the sensor offers a means of measuring the delay between atrial and ventricular contraction either at rest or during exercise. It could also be included in algorithms designed to improve the detection of atrial arrhythmias by implanted devices. Finally, it could address challenges or limitations of sensing of atrial electrical activity by adding a marker of mechanical contraction. A recording of this signal over the long term might offer an additional indicator of the evolution of cardiac function in device recipients.
5. Limitations

This evaluation must be weighted by the occurrence of expected measurement errors. On one side this study required two different interfaces that are echocardiography and CRT-D device programmers. Although echocardiography measurements were all made from the beginning of the QRS, we have extrapolated data from the beginning of the P wave for a better correlation with SonR4 measurements and to avoid cycle-by-cycle errors due to heart rate variation. There is an intrinsic measurement error with the use of echocardiography [21] even though it is currently recognized as the reference method. We tried to limit this bias by performing measurements by a single operator and averaging the results of different AV delays. This bias didn’t prevent us from establishing a strong correlation between the two components.

Finally, this pilot work was carried out on a limited number of patients, all affected by heart disease. This should be taken into account in the results interpretation.

6. Conclusion

This pilot study validates the SonR4 signal as a marker of atrial contraction. Additional assessments in larger populations are warranted to further establish this tool in multiple clinical applications, such as better tachycardia detection, additional AVD optimization and HF monitoring.

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Conflicts of Interest

Dr. F. Broussous has no conflict of interest to declare. A. Kobeissi, J. Dumont and F. Renesto have received a salary from Sorin as employees. Pr. J. Mansourati has received lecture honorary/travel support from Sorin; he performs/has performed clinical studies supported by Sorin.

Authors’ Contribution

F. Broussous contributed to data analysis/interpretation and drafting of the manuscript. A. Kobeissi contributed to study concept/design, data analysis/interpretation, and critical revision of the manuscript. J. Dumont contributed to data analysis/interpretation and drafting of the article. F. Renesto contributed to study concept/design,
data analysis/interpretation and final revision of the manuscript. J. Mansourati contributed to study concept/design, data analysis/interpretation, drafting of the manuscript.

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**List of Abbreviations**

**AV**: Atrio-Ventricular;  
**AVD**: Atrio-Ventricular Delay;  
**CRT-D**: Cardiac Resynchronization Therapy-Defibrillator;  
**ECG**: Electrocardiogram;  
**HF**: Heart Failure;  
**LVEF**: Left Ventricular Ejection Fraction;  
**EA**: Endocardial Acceleration;  
**VV**: Inter-Ventricular.