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Left ventricular mechanical activity detected by impedance recording

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Aims Recording and analysing impedance fluctuation along the cardiac cycle in the right (RV) and left ventricles (LV).

Methods and results During a biventricular (BiV) implantation procedure, impedance was sequentially derived between the atrial ring electrode and either electrode (tip or ring) of the RV lead [transvalvular impedance (TVI)], and between the atrial ring and either the tip or ring electrode of a coronary sinus lead, positioned in a cardiac vein [left ventricle impedance (LVI)]. The LVI signal was also recorded by the implanted pacemaker at the 1 day and 3 months follow-ups. With intrinsic conduction, TVI showed an average increase of $53 \pm 29\ \Omega$ during ventricular systole, whereas at the same time, LVI decreased by $45 \pm 21\ \Omega$ (25 and 23 patients, respectively, out of 28 tested cases). Transvalvular impedance and LVI displayed a similar time course, which appeared to be related to the systolic timing in the RV and LV. Both LVI amplitude and duration decreased as a function of the cardiac rate. The LVI deflection started immediately after LV stimulation, and often anticipated the R-wave sensing after contralateral pacing. At the 3-month follow-up, LVI amplitude was decreased in 70% of cases and increased in the remainder, with a non-significant average change of $-5 \pm 85\%$ with respect to the acute recordings.

Conclusion Transvalvular impedance properties are consistent with the assumption of an inverse relationship with RV volume. Though LVI requires a different physical interpretation, the waveform duration might reflect the timing of LV myocardial contraction. In this hypothesis, the relationship between TVI and LVI could provide insight into the effects of BiV pacing on mechanical synchronization.

Keywords Cardiac resynchronization therapy • Mechanical synchronization • Transvalvular impedance • Left ventricular impedance

Introduction

Biventricular (BiV) pacing is widely acknowledged as a valuable approach to the treatment of heart failure complicated by left ventricular conduction delay.[1] The essential aim of this pacing therapy is the correction of ventricular dyssynchrony, thus improving systolic and diastolic function.[2,3] This can in turn induce a process of reverse myocardial remodelling, leading eventually to chronic structural benefits.[4,5] In order to increase the chance of a positive response to the treatment, stimulation sites and timing should be chosen with the aim of optimizing the mechanical aspects of inter- and intra-ventricular synchronization,[6] which are usually assessed by complex and time-consuming echocardiographic techniques before and after the implantation.[7] However, it would be preferable to obtain information on the intrinsic and paced mechanical activity of the heart when the implantation procedure is in progress, so that the location of the leads could be modified if the acute effects of BiV stimulation were not satisfactory.

Cardiac impedance recording represents an interesting option to detect changes in ventricular mechanics without the use of echocardiography. Cardiac impedance can be measured with standard pacing electrodes as soon as they are positioned and is

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modulated by structural and geometric modifications occurring along the cardiac cycle.[8] Several methods have been developed to record impedance fluctuation in the right ventricle (RV), including unipolar, bipolar and transvalvular impedance (TVI).[9–11] Although RV impedance has been extensively studied, little is known at present on impedance changes produced by the activity of the left ventricle (LV). The present study was designed to address this issue, characterizing the impedance signal detected by a coronary sinus lead inserted in a cardiac vein for transvenous LV stimulation.

Methods

The study was carried out in 28 patients with standard indications for BiV pacing, undergoing the implantation of a three-chamber pacemaker equipped for high-resolution impedance recording (Helios 300, Medico, Italy). The J-shaped atrial lead was positioned in the right appendage; the RV lead was positioned in the mid-low septum by active fixation (screw-in); the LV lead was positioned in a posterolateral vein in 21 cases and in the inferolateral vein in 7 cases. Pre-shaped or linear, bipolar or unipolar LV leads of different manufacturers were used, according to the anatomy of each patient. In all cases but one, lead insertion was performed through the left subclavian vein.

Acute impedance recording was obtained on implantation, using a dedicated external device with 1 kHz sampling rate. The impedance fluctuation was first derived in RV with transvalvular configuration (TVI), i.e. between the ring electrode of the atrial lead and either the ring or the tip electrode of the RV lead. In the second step, impedance was recorded between the atrial ring electrode and either the tip or the ring of the LV lead [left ventricle impedance (LVI)], and between the same LV electrode and a steel retractor put in contact with the patient's skin in the left-pectoral region. Then, the atrial contribution to the TVI and LVI signals was assessed by recording the impedance between the atrial ring electrode and the patient's skin [right atrium impedance (RAI)]. Transvalvular impedance, LVI, and RAI waveforms were all recorded with intrinsic atrioventricular conduction (AVC). In addition, TVI and RAI were recorded during RV pacing, and LVI with pacing in the LV. After the series of acute measurements, the LV lead was permanently connected to the impedance detector of the implanted pacemaker. LVI was assessed on the first day after implantation and the next monitoring session at 3-month follow-up. The impedance signal was sampled at 60 Hz and transmitted to the pacemaker programmer by real-time telemetry. LVI was recorded during intrinsic AVC and unilateral stimulation in RV and LV, as well as with synchronous BiV pacing.

The study complies with the Helsinki declaration and was approved by the local Ethics Committee. All patients provided informed consent. Both acute and chronic impedance measurements were performed with DC coupling. All recordings were stored in digital form and analysed off-line by means of standard software (AcqKnowledge, BIOPAC Systems and Microsoft Excel 2000). Data are reported as mean ± standard deviation. The statistical significance of differences has been evaluated with one-way ANOVA and Student *t*-test, adjusted for multiple comparisons.

Results

Transvalvular impedance waveform

Transvalvular impedance was recorded with RV ring or RV tip electrodes in 14 and 11 cases, respectively, choosing the electrode configuration in order to maximize the signal-to-noise ratio in each patient. In both instances, TVI recorded with intrinsic AV conduction increased during the ventricular systole and decreased back to the baseline in diastole, starting from the decay phase of the T-wave (*Figure 1A*). The cyclical TVI excursion ranged from 17 to 98 Ω in different patients. *Table 1* reports the average amplitude of the TVI waveform in the patient group, and the average time

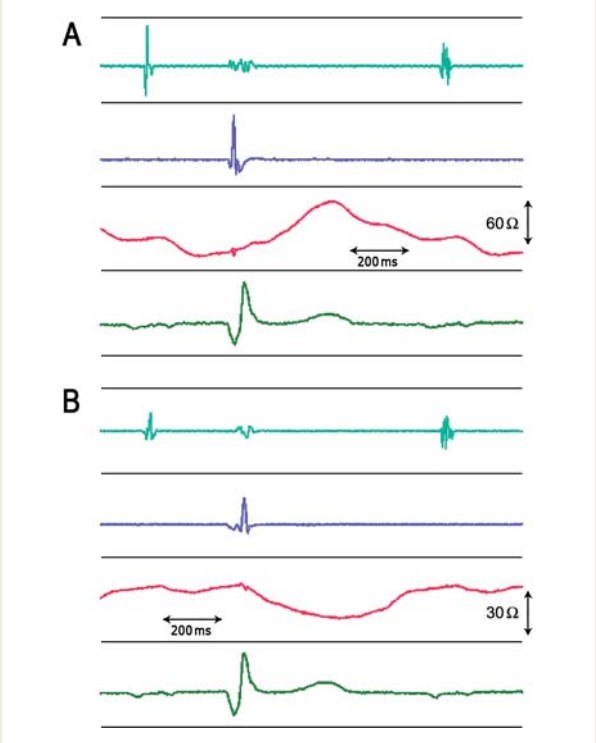

Figure 1 From top to bottom tracings: atrial electrogram, ventricular electrogram, impedance waveform, surface ECG (III). The ventricular input was derived from the right ventricular tip electrode in (*A*), and the left ventricular ring electrode in (*B*). Each panel shows the average signals over 10 consecutive cardiac cycles. The two sets of tracings were recorded in sequence and have been synchronized by taking the QRS complex as the common time reference. The transvalvular impedance (TVI) waveform shown in (*A*) is characterized by a marked systolic increase, which was completed at the start of T-wave decay. In the same phase of the cardiac cycle, LVI was decreased (*B*). Note that the gain was doubled for LVI with respect to TVI.

Table 1 Impedance signals with intrinsic atrioventricular conduction

	TVI	LVI	RAI
Systolic excursion (Ω)	53 ± 29	−45 ± 21	1 ± 2
Reversal time (ms)	432 ± 93	431 ± 68	n.d.

The signal reversal time corresponds to the time interval from R-wave sensing in RV and LV to the start of impedance decay (TVI) or recovery (LVI). The parameter was not detectable (n.d.) for RAI.

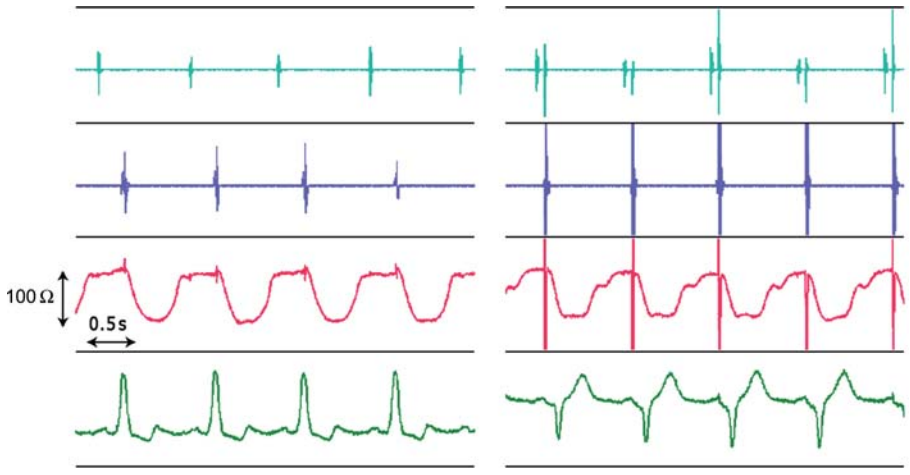

Figure 2 From top to bottom tracings: atrial electrogram, left ventricular electrogram, LVI waveform, surface ECG (I). The ventricular input was derived from the left ventricular tip electrode with intrinsic atrioventricular conduction (left-hand panel) and VDD pacing with 80 ms atrioventricular delay (right). Left ventricular stimulation applied in the posterolateral region induced a mild decrease in the amplitude of LVI waveform and a slower impedance recovery.

interval between R-wave detection in RV and the onset of TVI decline, referred to as the signal reversal time. Three cases (12%) were not included in the general evaluation, as noisy TVI signals with an unusual pattern were recorded with both RV ring and tip electrodes.

VDD pacing with fully evoked QRS complexes entailed a reduction of TVI amplitude with respect to the value measured in each patient with intrinsic AVC ($-16 \pm 26\%$; $P < 0.05$), and a non-significant prolongation of the signal reversal time (32 ± 74 ms). In some cases, the paced waveform also showed morphological modifications and more than one peak could be noticed in the Q-T interval. Nevertheless, the maximum TVI peak always occurred in telesystole, followed by a phase with negative slope in diastole.

Table 2 Post-implant modification in LVI waveform

Time	15 min	90 min	180 min	1 Day
Systolic excursion (Ω)	-112 ± 12	-116 ± 13	-108 ± 9	-90 ± 7*
Reversal time (ms)	590 ± 17	566 ± 14*	521 ± 18*	497 ± 17*

LVI signals with intrinsic atrioventricular conduction. Data from a single patient showing the progressive shortening of the reversal time, and a significant decrease in LVI amplitude at 1-day follow-up.
*$P < 0.01$ vs. the previous step; one-way ANOVA and Student *t*-test adjusted for multiple comparisons.

LVI waveform

LVI was recorded with LV ring or LV tip electrodes in 10 and 13 cases, respectively. With any electrode configuration and ventricular activation modality (intrinsic AVC or LV stimulation), all implantations performed in a posterolateral vein showed a marked impedance decrease during the ventricular systole, followed by a progressive rise in diastole (*Figure 1B*). Five cases (18%) implanted outside the posterolateral region for anatomical constraints, featured unstable impedance signals heavily affected by respiratory components, and were therefore excluded from the general evaluation. LVI mean amplitude and reversal time (i.e. the time interval between R-wave detection in LV and the onset of LVI increase) measured on implantation with intrinsic AVC, are reported in *Table 1*. The peak-to-peak amplitude of the LVI waveform ranged from -23 to $-110\ \Omega$ in the patient group.

LVI signals recorded with intrinsic AVC and sequential LV stimulation are compared in *Figure 2*. The systolic decrease in LVI started immediately after the pacing spike or the R-wave detection in the LV, which generally occurred in the late phase of the QRS complex. In all cases, switching the activation pattern from intrinsic AVC to LV stimulation produced some changes in the LVI waveform. In particular, the paced signal showed a reduced amplitude ($-19 \pm 13\%$; $P < 0.05$) and a slower time course, due to delayed impedance return to baseline (72 ± 65 ms; $P < 0.05$).

The LVI waveform derived by the implanted pacemaker right after implantation fully corresponded to the signal recorded in the same patient by the external device and remained essentially stable for some hours (*Table 2*). In the chronic follow-up, the signal amplitude was found to be decreased in 70% of cases and increased in the remaining 30%. On average, LVI amplitude recorded with intrinsic AVC showed a non-significant reduction to $82 \pm 56\%$ and $95 \pm 85\%$ of the corresponding acute value, 1 day and 3 months after implantation, respectively.

RAI waveform

The impedance recorded between the atrial ring electrode and the patient's skin in the left thorax showed only small changes during the cardiac cycle, mostly restricted to the time of atrial systole.

Table 3 Effects of cardiac rate on LVI parameters

	VVI pacing in LV		
	45 b.p.m.	80 b.p.m.	100 b.p.m.
Systolic excursion (Ω)	−23.1 ± 1.6	−15.6 ± 2.7*	−12.1 ± 2.3*
Reversal time (ms)	428 ± 9	396 ± 20*	361 ± 17*

Data refer to a representative single patient. Both parameters decreased significantly as a function of the rate.
*$P < 0.01$ vs. the previous step; one-way ANOVA and Student t-test adjusted for multiple comparisons.

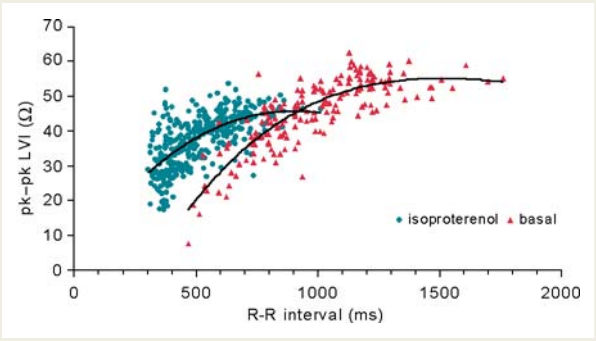

Figure 3 Amplitude of LVI fluctuation (absolute values) in single cardiac beats as a function of the RR interval in the previous cycle, at basal (green triangles) and during isoproterenol infusion (red circles), with respective best-fit curves. The basal RR interval was spread over a wide range, due to intermittent conduction of atrial fibrillation. Adrenergic stimulation shifted upward the relationship between LVI amplitude and cycle length.

While the DC offset of RAI represented a substantial component of TVI and LVI offset, the atrial contribution to the impedance fluctuation taking place during ventricular ejection and passive filling was negligible (*Table 1*).

Factors affecting LVI

LVI signal amplitude and duration were both dependent on the cardiac rate, decreasing when the rate increased. *Table 3* reports a typical example of the effects of stepwise pacing rate changes in a patient with VVI stimulation applied in the LV. In addition, the amplitude of LVI fluctuation was modulated by the adrenergic input. *Figure 3* shows the LVI excursion in individual cardiac beats as a function of the RR interval in the previous cycle, in a patient with intermittent AVC of paroxysmal atrial fibrillation. LVI amplitude (reported as absolute value in the graph) lessened with the decreasing RR interval, at rest as well as in the case of isoproterenol administration. In spite of the marked increase in ventricular rate induced by the adrenergic agonist, data were homogeneously distributed in the range of RR intervals from 450 to 700 ms (the mean cycle length within this range was 590 ± 66 and 569 ± 68 ms, respectively, before and during isoproterenol infusion), allowing the comparison of LVI signals recorded in both conditions. If only beats with a cycle length ranging from 450 to 700 ms were selected, the amplitude of LVI fluctuation proved significantly higher during adrenergic challenge than at rest (−40.5 ± 4.9 and −26.8 ± 8.5 Ω, respectively).

The LVI waveform was also influenced by the pattern of ventricular activation. In comparison with the signal recorded with intrinsic AVC in each patient, the time interval from QRS onset to the start of the LVI ascending phase was prolonged with RV unilateral pacing (22 ± 14 ms) and shortened with LV and BiV pacing (−57 ± 47 and −68 ± 60 ms, respectively). All changes were statistically significant with $P < 0.05$. With contralateral pacing, the start of LVI negative deflection often anticipated the R-wave detection in the LV.

In contrast, the LVI waveform was not affected by the orientation of the electric field through which the impedance was measured. The signal recorded by an electrode placed in a postero-lateral cardiac vein did not change at all if the reference pole was moved from the atrial ring to the patient's skin in the implantation area, i.e. from the right to the left side of the thorax.

Discussion

During the ventricular systole, a prominent rise in RV impedance is consistently detected with different recording techniques, all based upon the use of endocavitary electrodes of transvenous pacing leads in unipolar, bipolar, or transvalvular configuration.[8–11] In most previous reports, RV impedance was measured with ventricular leads positioned in the apical region. However, the present study shows that similar results can also be obtained by TVI recording in the mid-low septum. The observation that the main properties of the TVI signal were not dependent on the location of the RV electrode involved in impedance sampling and were maintained if the ring electrode was used instead of the tip, supports the concept that the systolic rise in TVI could reflect the RV volume decrease occurring in the ejection phase.[8,12] Indeed, an increase in the total impedance sensed by an electrode placed inside the ventricle can be predicted whenever the ventricular cross-section is reduced, as the conductivity of the myocardium is lower than that of the blood.[11] In accordance with this interpretation, TVI started to decline in the last part of the T-wave, a time compatible with RV myocardial relaxation and passive filling, which could well anticipate the LV repolarization in patients presenting with delayed LV conduction. Moreover, previous experience demonstrated that the assessment of ventricular volume inferred from TVI data provided reliable information on acute changes in the adrenergic tone, allowing a physiological regulation of the pacing rate.[13–15]

In the present study, an opposite impedance waveform characterized by a marked reduction in systole was recorded with transvenous pacing leads in the LV postero-lateral region. LVI fluctuation is probably unrelated to LV volume changes, as it started immediately after LV stimulation, without a pre-ejection interval. Nevertheless, the close relationship between the onset of TVI decay in the RV and LVI rise in the LV suggests that the LVI trend reversal could represent a marker of the end of LV systole. Consistently, the time course of LVI decrease was shortened by cardiac rate acceleration, which is known to reduce the systole duration. The amplitude of the LVI waveform was also

sensitive to changes in cardiac activity, decreasing as a function of pacing rate and related filling-time reduction, and increasing during adrenergic stimulation. Indeed, when the basal LVI excursion was compared with the fluctuation recorded during isoproterenol administration within the same range of cardiac rate, a clear-cut increase in the LVI downstroke was demonstrated.

A model to explain LVI generation

At present, the real nature of the LVI signal is just a matter of speculation. It must be pointed out that, in a three-dimensional conducting volume where the electric field decreases as a function of the distance from the current source, the largest part of the total impedance detected by a voltage-sampling electrode is actually concentrated around the electrode itself. As a result, the impedance changes recorded from a cardiac vein should mainly reflect local modifications in the conducting medium, rather than events occurring in remote areas. This principle seems to hold true, as the LVI signal remained constant when the counter-electrode of the recording dipole was moved from the atrial ring to the patient's skin in the implantation area, that is, the left pectoral region. Only the LVI offset was affected by the geometric configuration of the electric field, while the impedance fluctuation was unchanged, suggesting that the waveform was fully modulated by phenomena taking place in proximity to the LV electrode. Accordingly, no relevant change in RAI was detected during the ventricular systole.

Given the above, the systolic decrease in LVI cannot be explained by a shortening of the interelectrode distance in the impedance recording dipole, which can only occur when the reference electrode is put on the right, not on the left side, of the thorax. In addition, the amplitude of LVI excursion, which was close to 100 Ω in some cases, would hardly be justified by any electrode movement. An alternative mechanism that could be considered is related to the blood flow in the cardiac veins. During LV contraction, the myocardial vein branches are squeezed and blood is pushed toward the epicardial veins and the coronary sinus, transiently increasing their congestion. If draining is hampered by the presence of the pacing lead, the blood content of the implanted vein will be increased as long as myocardial contraction is in progress, thus creating the physical basis for a local reduction in electric impedance. Even in partially occluded veins, a small leak of blood could be sufficient to produce big impedance changes on both the tip and ring electrodes. Furthermore, the impedance could be affected by blood reflow from the coronary sinus. The increase in LVI amplitude during isoproterenol administration could well reflect an enhanced coronary perfusion, due to the vasodilating effects of β-adrenergic stimulation coupled with increased cardiac metabolism. Accordingly, the influence of cycle length on LVI amplitude could be explained by the relationship between diastolic perfusion time and the amount of blood stored in the myocardial vein branches at the systole onset. In chronic LV implants, thrombosis might possibly develop in the occluded vein and stop the local blood flow, which would result in a drastic depression of LVI fluctuation. However, in our experience, all cases featuring the LVI signal on implantation still showed the same kind of waveform 3 months later. Though a marked amplitude reduction was noticed in some patients, the signal was actually strengthened in others, so that no significant difference with the acute recordings was demonstrated in the group.

Potential clinical implications

The application of impedance measurements as a potential tool to gain information on haemodynamic function is stimulating increasing interest. A reduction in intrathoracic impedance, derived between the can of an implanted defibrillator and the lead coil, is considered an early marker of fluid accumulation in the lungs, allowing timely medical care in acute heart failure.[16,17] Transthoracic impedance cardiography (IC), performed by a set of surface electrodes applied on the skin, is used to assess the cardiac output (CO) as a surrogate of invasive haemodynamic techniques, and has been proposed as a practical tool to tailor the timing of BiV pacing in each single patient.[18,19] However, a poor correlation between the optimal interventricular delay based on IC-CO and LV maximum d*P*/d*t* was demonstrated in a recent study.[20] A positive correlation between LV impedance fluctuation and stroke volume and a negative correlation between diastolic impedance and pressure have been reported in animal experiments using LV electrodes placed on the epicardial surface, outside the cardiac veins.[21–23] In other studies, quadripolar systems involving transvenous LV leads have been applied for impedance recording between RV and LV.[24,25] In these cases, however, it is impossible to tell if the transventricular impedance signal reflects the activity of the LV, RV, or both. The present study demonstrates that impedance changes of opposite sign can be detected at the same time in the RV and LV, respectively, with endocardial and transvenous electrodes. The relative contribution of each electrode to the overall transventricular impedance depends on the distribution of the electric field in the conducting volume. With a bipolar system, where the same electrode dipole was used for both current injection and voltage sampling, the transventricular impedance waveform fully corresponded to the algebric sum of the separate waveforms recorded in the RV and LV, the resulting signal resembling the largest of the two components, but with reduced amplitude.[26]

Even if the mechanism underlying the LVI signal is not fully established, the waveform time course seems to provide consistent indications on the timing of LV systole and diastole in a portion of the LV myocardium larger than the area directly involved in electrical sensing and stimulation. In this respect, it is noteworthy that the LVI decrease induced by unilateral RV pacing could start before the R-wave detection in the LV. The LVI duration could be proposed as a measure of mechanical activity dispersion in the LV area involved in the signal generation, which might possibly correspond to the myocardial region tributary of the implanted cardiac vein. However, some caution is advisable, because the LVI reversal time can be shortened within a few hours after implantation, as if some elastic phenomena present in acute conditions were removed or reduced with the progress of time. The comparative evaluation of the TVI and LVI time course might provide information on the lag between RV and LV contraction and relaxation, potentially useful for appropriate setting of AV and VV delay. In our opinion, TVI should be more suitable than LVI for permanent haemodynamic monitoring, as cardiac volume changes are better detected by impedance recording with endocardial electrodes.

Limitations

The present study provides preliminary information on the impedance fluctuation detected by a coronary sinus lead electrode. The signal time course suggests a possible relationship with the timing of LV contraction, which has not yet been directly confirmed and will be the subject of further research. A method to set the stimulation timing aimed at the synchronization of TVI and LVI waveforms can be envisaged, but the analysis of its clinical value was beyond the limit of the present study.

As the LVI signal as described in the present paper is typically recorded with transvenous electrodes positioned in a posterolateral cardiac vein, which is the first choice in coronary lead placement but cannot be obtained in all the implantations, LVI recording and evaluation might not be useful in all cardiac resynchronization therapy patients.

Conclusions

The present study suggests that LVI could be a valuable tool to assess the timing of LV mechanical activation. Further work is required to confirm the correspondence of LVI indications with haemodynamic and echocardiographic markers of LV systole and diastole, and to better understand the physiological mechanisms underlying the LVI fluctuation along the cardiac cycle.

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