Quantification of interventricular asynchrony during LBBB and ventricular pacing

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During left bundle branch block (LBBB), cardiac function is impaired most likely due to a disturbed synchrony of cardiac contraction (7). In patients with heart failure and LBBB, left ventricular (LV) or biventricular pacing therapy endeavors to improve cardiac function by restoring contractile synchrony (3, 4, 6). Indeed, in these patients, pacing therapy can produce a more synchronous pattern of contraction (9, 16) and improves cardiac function (2, 8, 9).

In general, ventricular asynchrony can be divided into intraventricular and interventricular asynchrony (IVA) (3, 9). Ventricular pacing may restore either intraventricular synchrony, interventricular synchrony, or both. Some studies (7, 9, 12) suggest the functional significance of IVA.

The duration of the QRS complex on the surface ECG is often used as a measure for total ventricular asynchrony. More detailed quantitative information about electrical asynchrony is obtained using endocardial electrical mapping techniques (17). For detailed quantification of mechanical asynchrony, MRI tagging (13) or phase imaging based on radionuclide scintography (nuclear phase imaging) (5, 7, 9, 16) has been applied. Also, echocardiography and Doppler myocardial imaging have been used to study ventricular asynchrony (7, 14). Most of these techniques provide information of intraventricular asynchrony. Only the nuclear and echocardiographic techniques have been applied to study IVA (5, 7, 9, 14, 16). More recently, assessment of IVA from LV and right ventricular (RV) pressure signals has been suggested (18, 19).

The present study was undertaken to investigate the feasibility to reliably assess IVA from simultaneously acquired LV and RV pressure signals. These pressure signals represent the combined mechanical behavior of the ventricles and expose an asynchronous time course during pacing and LBBB (11, 12). In the present study, four measures that potentially quantify mechanical IVA were derived from the pressure signals. The measures were compared and validated by computer simulations based on real pressure signals and evaluated by animal experiments during experimental LBBB and LV pacing. A reliable measure for IVA will be an important tool for future studies on elucidation of the mechanism of the influence of asynchronous activation on cardiac function.

METHODS

Animal experiments. Animal handling was performed according to the Dutch Law on Animal Experimentation and The European Directive for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (86/609/EU). The protocol was approved by the Experimental Animal Committee of the Maastricht University.

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The experiments were performed on 12 adult mongrel dogs (28 ± 4 kg wt) of either gender. The dogs were premedicated with acepromazine (0.2 mg/kg), atropine (0.1 mg/kg), and oxycodone (2 mg/kg im). Anesthesia was induced with thiopental sodium (15 mg/kg iv) and maintained by ventilation with halothane (0.8 to 1.0%) in a 1:2 mixture of O2 and N2O. A thermal mattress was used to maintain adequate body temperature. Surface ECG was derived from limb leads. LV and RV pressures were recorded simultaneously with two catheter tip manometers (Sentron) introduced through the carotid artery and jugular vein, respectively. Pressure and ECG signals were digitized at a 200-Hz sampling rate and stored on a disk for offline analysis. After the thorax was opened, temporary myocardial pacing leads (model 6500, Medtronic) were implanted at the epicardium of the LV apex and the right atrium. These leads were connected with an external pacemaker (model 5311B AV pacing System Analyzer, Medtronic). LBBB was induced by radio frequency ablation with the use of an ablation catheter (MarinR, Medtronic) and a radio frequency power generator (Atakr, Medtronic). LBBB was characterized by a broad (±100 ms) QRS complex, which, in the dogs, was positive in lead II.

Measurements were performed during sinus rhythm before induction of LBBB, after induction of LBBB, and during LBBB in combination with pacing of the LV apex. Pacing was performed in the VDD mode (atrial sensing and ventricular pacing) with AV intervals increasing from 30 ms to a maximum of 140 ms, with 10-ms steps (n = 6). Pacing at each AV delay was maintained for two to four respiratory cycles, followed by at least four respiration cycles without pacing.

Signal processing and analysis. Before offline analysis of the pressure signals, a second-order Butterworth low-pass filter with a 40-Hz cut-off frequency was used to remove high-frequency artefacts/noise. To avoid phase shifts in each of the signals, the low-pass filter was applied once in forward and once in a backward direction.

Signal processing theory states that a signal is described unambiguously when the sample frequency is at least twice the maximum signal frequency. This demand is fulfilled at the 200-Hz frequency and allows for measurement of time differences more accurately than the duration of the sampling interval (1).

QRS durations and PQ times were acquired by manual offline analysis of the ECG recorded in lead II. The effective paced AV delay (AVe delay) was determined as the time between the onset of the P wave and the pace spike. The AVe delay was used instead of the paced AV delay to correct for differences in position of the atrial sensing lead between the animals. Parameters were calculated for all heart beats within one complete ventilation cycle, of which mean values and standard deviations are reported. The first five beats after the onset of pacing or return to baseline were excluded from the analysis.

The relative timing between the onset of electrical activation of the ventricles was calculated as the difference between the PQ time during LBBB and the AVe delay. During LBBB the PQ time represents the time between the onset of atrial activation to onset of electrical activation of the RV, whereas during LV pacing the AVe delay represents the time between the onset of atrial activation and onset of LV activation. Consequently, the difference between these parameters (PQ timeLBBB − AVe delay) provides the RV-LV excitation time difference.

Quantification of IVA. In Fig. 1, typical examples of LV and RV pressure curves, acquired before induction of LBBB, during LBBB and during LBBB + LV apex pacing with a short AV delay, are presented. The curves were normalized to their full amplitude range to accentuate timing differences. By visual inspection, it is recognized that before induction of LBBB both ventricles contracted approximately synchronously (Fig. 1A), whereas during LBBB, the entire systole of the LV is delayed with respect to that of the RV (Fig. 1B). In contrast, during LV pacing with short AV delay (Fig. 1C), an earlier LV than RV contraction is observed.

For quantification mechanical IVA four measures were derived from the LV and RV pressure signals. The first measure estimates the delay between these signals (ΔTfull) by shifting them in time until the cross-correlation coefficient (xcc) between the signals reaches its maximal value

\[
\text{xicc} = \frac{\sum_{i=1}^{N} (\text{PLV}_i - \text{PLV}) \cdot (\text{PRV}_i - \text{PRV})}{\left( \sum_{i=1}^{N} (\text{PLV}_i - \text{PLV})^2 \cdot \sum_{i=1}^{N} (\text{PRV}_i - \text{PRV})^2 \right)^{1/2}}
\]

where PLV, and PRV, represent the samples of the LV and RV pressure signals, respectively, and PLV and PRV represent the mean LV and RV pressure, respectively. By restricting cross-correlation analysis to the upslope of the two pressure curves, a second measure was obtained, now providing an estimate for timing differences between the LV and RV contraction phases (ΔTup). By defining the timing difference ΔTup is positive for an earlier LV than RV upslope. Figure 2A shows the cross-correlation function for the examples of LV and RV pressure signals presented in Fig. 1. In this example, cross-correlation analysis was restricted to the upslopes. The estimated time delay between the signals upslopes, determined by the peak of the cross-correlation function, was close to zero before LBBB, negative during LBBB, and positive during pacing. In all cases, the maximal cross-correlation

![Fig. 1. Typical examples of left ventricular (LV) and right ventricular (RV) pressure curves acquired before induction of left bundle branch block (LBBB) (A), during LBBB (B), and during LBBB + LV apex pacing (C) with a short atrioventricular (AV) delay (25 ms). Pressures are normalized to their full amplitude range to emphasize timing differences.](http://ajpheart.physiology.org/)

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Fig. 2. Methods to quantify mechanical interventricular asynchrony (IVA) illustrated using the examples presented in Fig. 1. A: temporal lag resulting in the maximal cross-correlation coefficient (xcc) between the upslope of the LV and RV pressure signals determines the delay (ΔT_up, marked for LBBB). B: the area of the normalized LV-RV pressure loop (PLVn). C: the synchrony index (SI) principle (example for LBBB pressures signals only). dP/dt, first derivative of pressure development over time; LVA25, LV apex pacing at an AV delay of 25 ms; Pn, normalized pressure.

coefficient was close to 1 (>0.99), indicating a high shape similarity of the pressure wave upslopes.

The third measure for IVA is the area of the normalized LV-RV pressure diagram (Fig. 2B). This measure is based on the principle that when plotting any two arbitrary but identical shaped signals against each other, the corresponding loop area equals zero if the signals are completely synchronous, whereas the loop area increases to a maximum area of one with increasing asynchrony. The normalized loop area (A_PP) was calculated as

$$A_{PP} = \sum_{i=1}^{N-1} (PLVn_i - PLVn_{i+1}) \cdot \frac{1}{2}(PRVn_i + PRVn_{i+1}) \quad (2)$$

with PLVn_i and PRVn_i samples of the normalized LV and RV pressure signals, respectively. A_PP has been reported before in preliminary studies (18, 19) but without mentioning directional information. In the present study, A_PP is positive, by definition, for a clockwise loop direction, i.e., an earlier LV than RV pressure rise and fall, and negative for the counter clockwise direction. An intrinsic property of this measure is that it expresses asynchrony based on the pressures during the complete cardiac cycle, rather than during the contraction phase only. In Fig. 2B, the loops are shown for the three earlier mentioned situations. Before induction of LBBB, the loop has a small negative area, whereas during LBBB the loop is larger. During LV pacing with a short AV delay, the loop is also larger than before LBBB but with a reversed course.

Finally, a synchrony index (SI) was derived from the two pressure curves. The SI has been reported (15) as a measure of the synchrony of volume changes between ventricular segments with the conductance catheter technique. This index provides a measure for the time that the two signals change in the same direction, relative to the duration of the cardiac cycle. In the present study, SI was calculated by considering only that part of the cardiac cycle during which the product of the first derivative of the LV and RV pressure

Fig. 3. Simulation results for evaluation of IVA measures. Experimentally obtained LV and RV pressure signals were shifted in time with respect to each other with temporal lags ranging from -100 to 100 ms. Simulations were repeated for pressure signals acquired before induction of LBBB (pre-LBBB), during LBBB, and during LBBB + LV apex pacing at a 25-ms AV delay. Presented are the estimates for the time delay between the full LV and RV pressure signals (ΔT_full) (A), the time delay between the upslopes of the LV and RV pressure signals (ΔT_up) (B), the normalized pressure loop area A_PP (C), and SI (D). Also shown in C is the A_PP calculated without taking into account the loop direction (see *).
signal is >0. To increase the stability of the SI, both the LV and RV pressures were required to exceed the LV and RV end diastolic pressure, respectively, and only simultaneous positive pressure changes were considered, thus restricting calculation of the SI to the contraction phases (Fig. 2C).

Simulations/validation of measures of IVA. To validate the four proposed measures, computer simulations were performed with the use of pressure signals obtained from the experiments. To study how each measure responds to a timing difference, the LV and RV pressure curves were shifted in time with respect to each other approximating gradual changes in timing, similar to those presented in Fig. 1. To enable shifting the pressure curves with respect to each other with 1-ms steps during simulations, the signals were reinterpolated at 1 KHz. For each temporal lag $\Delta T_{\text{full}}$, $\Delta T_{\text{up}}$, $A_{\text{PP}}$, and SI were determined. For the loop area method, the $A_{\text{PP}}$ as a function of the temporal lag was also calculated without taking into account the directional information. Simulations were performed using pressure curves acquired during sinus rhythm before induction of LBBB, after induction of LBBB, and during LBBB + LV apex pacing at short AV delay, to demonstrate the effect of different initial pressure curve shapes.

To study the influence of shape changes of the pressure signals in more detail, gradual changes in rate of pressure rise and width of the pressure signals were simulated. LV maximal first derivative of pressure development over time ($dP/dt_{\text{max}}$) was changed by application of a low-pass filter, whereas the RV pressure curve was not changed. The cutoff frequency of the filter was decreased until a desired change in $dP/dt_{\text{max}}$ was attained. The width of the LV pressure signal was changed by reinterpolating the LV pressure signals followed by setting the time resolution to 1 ms.

The frequency at which reinterpolation was performed was varied until a desired change in curve width is attained, characterized by its full width at half maximum (FWHM). Again, the RV pressure curve was not changed. For each of the initial LV pressure waves, the width was changed in a range from −20 to 20 ms. To ensure that the curve upslope ($dP/dt_{\text{max}}$) was not affected, only the part of the curve after instance of the peak pressure was reinterpolated.

RESULTS

Simulation results. Figure 3 depicts how the simulated temporal lag between in vivo recorded LV and RV pressure signals influences the four proposed measures of IVA. A linear relation was found between the applied temporal lag and estimated $\Delta T_{\text{full}}$ and $\Delta T_{\text{up}}$ (Fig. 3A and B). The offset in $\Delta T$ between the pre-LBBB, LBBB, and LBBB + pacing results can, among others, be attributed to timing differences in LV and RV pressure signals between the different experimental conditions. The relation between $A_{\text{PP}}$ and the imposed temporal lag was nonlinear and shows a different behavior for each of the three experimental conditions (Fig. 3C). Neglecting the loop direction results in a measure for IVA without an indication of which ventricle is activated first (always positive values).

By definition also the SI was always positive and therefore did not include directional information. Comparison of the three experimental conditions showed different maximum values for each experimental situation (Fig. 3D). The plateau around the maximum originated from differences in duration of the LV and RV contraction phases, the shorter phase coinciding with the longer phase for a range of subsequent temporal lags.
Figure 4 depicts the effect of changes in LV $dP/dt_{\text{max}}$ on the behavior of the four measures. The absolute errors were only 1 ms for $\Delta T_{\text{up}}$ (Fig. 4B) whereas errors introduced in $A_{\text{PP}}$ and SI were significantly larger (Fig. 4, C and D). Figure 5 shows that changing FWHM introduced significant errors in $\Delta T_{\text{full}}$ (Fig. 5A), $A_{\text{PP}}$, and SI (Fig. 5, C and D), whereas $\Delta T_{\text{up}}$ is not affected by the FWHM (Fig. 5B).

Experimental results. Table 1 presents the values of $\Delta T_{\text{full}}$, $\Delta T_{\text{up}}$, $A_{\text{PP}}$, SI, and hemodynamic values measured before and directly after induction of LBBB. After the induction of LBBB, $\Delta T_{\text{full}}$, $\Delta T_{\text{up}}$, and $A_{\text{PP}}$ decreased significantly compared with pre-LBBB values. Induction of LBBB significantly increased QRS duration and decreased LV $dP/dt_{\text{max}}$ but did not change heart rate and RV and LV systolic and end-diastolic pressures.

In Fig. 6, the relation between $\Delta T_{\text{up}}$ and the paced AV delay is presented, showing a large variation between the animals. This variation completely disappeared when the AV delay was standardized with the use of the RV-LV excitation time difference (Fig. 7B).

Figure 7 depicts the relation between the four IVA measures during LV apex pacing with different AV delays as a function of the RV-LV excitation time difference (PQ time$_{\text{LBBB}}$ – AVe delay, see METHODS). For $\Delta T_{\text{full}}$, $\Delta T_{\text{up}}$, and $A_{\text{PP}}$, a sigmoid relation was found with the lowest values during pacing with the longest AV delays and the highest values during pacing with the shortest AV interval (25–30 ms). For $\Delta T_{\text{up}}$, an excellent match of the results from the various dogs was found. $\Delta T_{\text{up}}$ increased in an almost linear fashion from approximately −35 to 35 ms when the RV-LV excitation time difference increased from 0 to 80 ms. Linear regression provided an $r^2 = 0.95$, a slope = 0.7, and an intercept with the horizontal axis of 29 ms.

Table 1. Changes in interventricular asynchrony, QRS duration, and hemodynamics due to induction of LBBB

<table>
<thead>
<tr>
<th></th>
<th>Pre-LBBB</th>
<th>Post-LBBB</th>
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<tbody>
<tr>
<td>$\Delta T_{\text{full}}$, ms</td>
<td>$-21.1 \pm 14.0$</td>
<td>$-51.7 \pm 12.0^*$</td>
</tr>
<tr>
<td>$\Delta T_{\text{up}}$, ms</td>
<td>$-6.9 \pm 7.0$</td>
<td>$-33.9 \pm 7.6^*$</td>
</tr>
<tr>
<td>$A_{\text{PP}}$, ms</td>
<td>$-0.38 \pm 0.11$</td>
<td>$-0.68 \pm 0.09^*$</td>
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<tr>
<td>SI, %</td>
<td>$20.6 \pm 4.5$</td>
<td>$18.4 \pm 4.6$</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>$64.5 \pm 10.5$</td>
<td>$123.7 \pm 20.2^*$</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>$113 \pm 18$</td>
<td>$126 \pm 21$</td>
</tr>
<tr>
<td>LV $dP/dt_{\text{max}}$, mmHg/s</td>
<td>$1,627 \pm 644$</td>
<td>$1,345 \pm 413^*$</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>$98.8 \pm 12.0$</td>
<td>$92.2 \pm 16.3$</td>
</tr>
<tr>
<td>RVSP, mmHg</td>
<td>$20.8 \pm 5.2$</td>
<td>$24.5 \pm 4.5$</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>$10.3 \pm 5.9$</td>
<td>$5.6 \pm 3.6$</td>
</tr>
<tr>
<td>RVEDP, mmHg</td>
<td>$3.0 \pm 2.6$</td>
<td>$4.4 \pm 3.7$</td>
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Values are means ± SD. $\Delta T_{\text{full}}$, time delay between pressure signals; LBBB, left bundle branch block; $\Delta T_{\text{up}}$, time delay between upstroke of LV & RV pressure waves; $A_{\text{PP}}$, normalized loop area; SI, synchrony index; LV, left ventricular; $dP/dt_{\text{max}}$, maximum first derivative over time; LVSP, LV systolic pressure; RVSP, right ventricular systolic pressure; LVEDP, LV end-diastolic pressure; RVEDP, RV end-diastolic pressure. $\Delta T_{\text{full}}$, $\Delta T_{\text{up}}$, and $A_{\text{PP}}$ and the QRS duration exposed significant differences between pre-LBBB and post-LBBB, whereas SI did not. LV $dP/dt_{\text{max}}$ decreased significantly after LBBB was induced, whereas other hemodynamic parameters and heart rate did not change significantly. *P < 0.05, significant changes compared with pre-LBBB values (paired t-test).
similar sigmoid shape for \( \Delta T_{\text{full}} \) and \( \Delta T_{\text{up}} \) was found, but with more variation between animals. The data for SI were very noisy, caused by both beat-to-beat and inter-animal differences (Fig. 5D).

In Fig. 8 the relation between QRS duration and \( \Delta T_{\text{up}} \) is presented for measurements before and after induction of LBBB and during LBBB + LV apex pacing for all AV delays. A good correlation was found for the combined before and after LBBB measurements (\( r = 0.81 \)) but a poor and completely different correlation was present during LBBB + LV apex pacing (\( r = 0.63 \)).

Figure 9 shows the changes in LV and RV curve width difference (\( \Delta \text{FWHM}_{\text{LR}} = \text{FWHM}_{\text{LV}} - \text{FWHM}_{\text{RV}} \)) as a function of the RV-LV excitation time difference. In most cases, the LV curve was clearly wider than the RV curve but pacing significantly affected \( \Delta \text{FWHM}_{\text{LR}} \). Moreover, RV-LV curve width differences and its changes during pacing varied considerably between experiments.

Finally, Table 2 shows the changes in heart rate and QRS duration and hemodynamic parameters measured during LBBB + LV apex pacing at the AV delays at which \( \Delta T_{\text{up}} = 0 \). LV dP/dt_{max} increased significantly by 15.1 \( \pm \) 5.9%. There was a good correlation between \( \Delta T_{\text{up}} \) and improvement in LV dP/dt_{max} (\( r = 0.86 \) \( \pm \) 0.10). QRS duration, heart rate, and other hemodynamic parameters showed no significant changes, except for a slight decrease of RV systolic pressure.

**DISCUSSION**

The present study shows that IVA can be reliably assessed from simultaneously acquired LV and RV pressure signals. The time difference between the up-
slope of the pressure signals estimated by cross correlation proves to be the most reliable measure because it is virtually insensitive to changes in the shape of the curves, the experimental results show an excellent reproducibility of $\Delta T_{up}$ changes between the animals, there is a linear relation between $\Delta T_{up}$ and the applied RV-LV excitation time difference, and it provides a beat-to-beat measure for asynchrony in milliseconds, RV-LV excitation time difference, and it provides a beat-to-beat measure for asynchrony in milliseconds, RV-LV excitation time difference, and it provides a beat-to-beat measure for asynchrony in milliseconds, RV-LV excitation time difference, and it provides a beat-to-beat measure for asynchrony in milliseconds, RV-LV excitation time difference, and it provides a beat-to-beat measure for asynchrony in milliseconds, RV-LV excitation time difference, and it provides a beat-to-beat measure for asynchrony in milliseconds, RV-LV excitation time 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In patients with dilated cardiomyopathy and QRS durations >150 ms, IVA values determined with echocardiography ranged between -77 ± 15 and -88 ± 26 ms (14). Similar values (~85 ± 31 ms) were found with nuclear phase imaging for patients with isolated LBBB (7). The smaller IVA values for dogs found in the present study (~33.9 ± 7.6 ms) are not surprising because the QRS duration is also smaller in dogs (123.7 ± 20.2 ms) than in patients.

Although the decrease in LV dP/dt\textsubscript{max} after induction of LBBB is associated with an increase in IVA (more negative ΔT\textsubscript{up} and QRS duration (Table 1), the increase in LV dP/dt\textsubscript{max} due to interventricular resynchronization (Table 2) leaves the QRS duration unaltered. This finding, together with the good correlation between IVA and improvement in LV dP/dt\textsubscript{max}, supports the idea that IVA contains important information. Further studies, including indexes of intraventricular asynchrony and IVA and the use of other pacing sites, are required to fully elucidate the importance of the various aspects of asynchronous activation for ventricular function.

A disadvantage of the currently presented method is its invasive nature requiring biventricular catheterization. Noninvasive alternatives may be provided by echocardiography or tissue Doppler imaging. MRI tagging can only provide IVA if the RV tags can also be analyzed. This has not been reported yet. In the echocardiography and tissue Doppler imaging study (14) mentioned earlier, IVA was assessed as the timing difference between the opening of the pulmonary and aortic valves and the timing difference between onset of the positive waves recorded at the lateral corners of the tricuspid and mitral annulus. In nuclear phase imaging studies, timing differences are derived from a user-defined region of interest in a cross section of the ventricles excluding the septum (7, 9).

An important advantage of the cross-correlation method, however, is that it incorporates the full contraction phase of the ventricles and that the pressure curves represent the true average of the contraction of the entire ventricles. Consequently, this method is more sensitive to timing differences and less sensitive to noise than a single point measurement in time, such as the opening of valves. Other advantages of the currently presented technique to assess IVA from LV and RV pressure curves are the accuracy and the relatively plain techniques. Moreover, this IVA measure provides beat-to-beat values and does not require the injection of radioisotopes.

In conclusion, mechanical IVA can be quantified reliably as the ΔT\textsubscript{up} of the LV and RV pressure waves with the use of cross correlation. Induction of LBBB increases both QRS duration and ΔT\textsubscript{up} significantly, but LV pacing during LBBB increases ΔT\textsubscript{up} at unchanged QRS duration. ΔT\textsubscript{up} relates linearly with the applied electrical delay between the ventricles during LV apex pacing at different AV delays. Interventricular resynchronization is associated with an improvement of LV dP/dt\textsubscript{max}. Therefore, ΔT\textsubscript{up} provides important information about the asynchronous contraction between the LV and RV during LBBB with our without ventricular pacing.

REFERENCES


