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Impedance cardiography: a useful and reliable tool in optimization of cardiac resynchronization devices

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Aims Optimizing cardiac resynchronization therapy (CRT) devices has become more complex since modification of both atrioventricular (AV) and interventricular (VV) stimulation intervals has become possible. The current paper presents data from the routine use of impedance cardiography (IC)-based cardiac output (CO) measurements to guide the optimization of AV- and VV-interval timing of CRT devices.

Methods and results Forty-six patients with heart failure (left ventricular ejection fraction $<35\%$, New York Heart Asociation (NYHA) III–IV) and left bundle branch block (>130 ms) in sinus rhythm were evaluated 3–5 days after implantation of a CRT device by means of IC. CO was measured without pacing and with biventricular pacing using a standard protocol of VV- and AV-interval modification from -60 to $+60$ ms and 80 to 140 ms, respectively, in 20 ms steps. Mean CO without pacing was 3.66 ± 0.85 L/min and significantly increased to 4.40 ± 1.1 L/min ($P < 0.05$) with simultaneous biventricular pacing and an AV interval of 120 ms. 'Optimizing' both VV and AV intervals further increased CO to 4.86 ± 1.1 L/min ($P < 0.05$). Maximum CO was measured in most patients with left ventricular pre-excitation. The proportion of 'non-responders' to CRT was reduced by 56% following AV- and VV-interval modification using IC guidance.

Conclusion Modification of both AV and VV intervals in patients with a CRT device significantly improves CO compared with standard simultaneous biventricular pacing and no pacing. IC is a useful non-invasive technique for guiding this modification. Marked variability of optimal AV and VV intervals between patients requires optimization of these intervals for each patient individually.

Introduction

Cardiac resynchronization therapy (CRT) has developed from an experimental method[1] to an established adjunctive treatment for patients with advanced heart failure. CRT aims to improve cardiac output (CO) by lessening the inter- and intra-ventricular conduction delay caused in part by left bundle branch block (LBBB).[2,3] CRT reduces clinical symptoms of heart failure and hospitalization,[4–6] improves haemodynamic parameters (including ventricular performance),[7] and has been shown to reduce mortality.[8–10] Acceptance of this therapy is reflected by its incorporation into current guidelines for the management of heart failure.[11,12]

Successful CRT in any given patient depends upon many variables, such as the appropriate positioning of the LV lead,[13–15] and also on achieving optimal biventricular stimulation timing.[16,17] This latter variable has attracted particular interest recently in an attempt to reduce the substantial proportion (20–30%) of patients who derive no apparent benefit from CRT, despite meeting appropriate implantation criteria and having had technically straightforward device implantation ('non-responders').[18]

CRT devices have become significantly more complex recently. Many now have the facility to programme different atrioventricular (AV) and interventricular (VV) stimulation timing intervals.[19,20] Data exist to show that tailoring these intervals to suit the patient in hand further improves the haemodynamic benefits brought by CRT. However, questions remain as to which method of haemodynamic assessment is best for guiding the adjustment of the device settings to suit any given post-implant patient.

In the measurement of cardiac function, invasive methods (e.g. dp/dt estimation of contractility or the thermodilution method for CO) are the gold standards but are not suitable for routine use during routine follow-up of patients with implanted CRT devices. Non-invasive methods used in optimizing device settings include echocardiographic techniques,[21–24] radionucleotide ventriculography,[25] finger photoplethysmography,[26] and more recently, impedance cardiography (IC).[6,27]

IC is an established technique for haemodynamic assessment and is capable of calculating CO on a beat-to-beat basis.[28] It relies upon changes in impedance (resistance) to current flow through the chest between strategically placed electrodes. Given that most current takes the path

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of least resistance (principally the blood-filled aorta) and that the impedance changes with blood flow, these variables can be used to calculate CO. IC has been used in patients receiving dual chamber pacemakers[29–31] and in the assessment of patients with heart failure.[6,32–34] IC as a technique may supplement or even replace invasive measurements and Doppler echocardiography[6,27,35] in the optimization of implanted CRT devices.

This paper presents data from the routine use of IC in optimizing CRT by adjusting AV and VV intervals to obtain maximum CO in post-implant patients. To our knowledge, this is the first report on the combined manipulation of AV- and VV-interval timing in biventricular pacing devices using IC.

Methods

Patient characteristics

Forty-six consecutive patients (37 males, 9 females, mean age 63 ± 9 years) with heart failure [left ventricular ejection fraction (LVEF) <35%; NYHA III–IV], LBBB (>130 ms), and sinus rhythm were evaluated 3–5 days after implantation of a CRT device. Baseline characteristics of study patients are detailed in *Table 1*. All patients had been receiving optimal (guideline compliant[11,12]) medical treatment for heart failure for at least 1 month before device implantation. Evaluation of patients before CRT included 12-lead surface ECG. Echocardiography was undertaken pre-implant, and post-CRT device optimization according to a standard template was performed with a System FiVe (GE VingMed) machine coupled to a 2.5 MHz transducer. In all patients, measurement of left ventricular (LV) dimensions, LVEF and evaluation for valve disease, particularly mitral regurgitation was undertaken. Transmitral flow was assessed using pulsed wave Doppler imaging in the apical 4-chamber view. Coronary angiography was performed in patients who had not previously had this done or where patients had symptoms of active coronary disease requiring further imaging. The echocardiography and coronary angiography form part of our standard patient 'work-up' for device implantation, but these results were not part of the prospectively chosen datasets gathered for the purpose of the study.

Device implantation

All patients received a CRT device in combination with a cardioverter–defibrillator (Contak Renewal, Guidant, St. Paul, MN, USA) except one patient who received only a CRT device (Contak Renewal). Forty-five of the 46 CRT devices were implanted in our catheterization laboratory by a cardiologist and a cardiac surgeon. The other patient received a device with epicardial leads implanted during surgical mitral valve reconstruction. Device implantation was similar in all cases. Initially the right ventricular (RV) lead was placed in the RV apex, then the coronary sinus lead was positioned using the over-the-wire technique, and finally the right atrial lead was implanted. The device was programmed in DDD-Mode with a lower rate limit at 40–50 bpm, producing atrial synchronous biventricular tracking of the intrinsic sinus rhythm (VAT-Mode).[36] The AV interval was set at 120 ms as a standard value[6] without LV or RV pre-excitation (VV interval = 0). This 'standard' pacing set-up was kept from implantation until optimization.

Table 1 Patient characteristics

Patients	46
Age (years)	63 ± 9
Gender (female/male)	9/37
% CAD/% DCM	20/80
QRS	187 ± 26 ms
PQ	197 ± 40 ms
LVEF	27 ± 8%

Impedance cardiography

Optimization of biventricular pacing was performed using a commercially available system for IC (Task Force Monitor Systems, CNSystems, Graz, Austria) as described by Braun *et al.*[6] Two electrodes were placed bilaterally to the inferior chest wall in combination with one electrode at the neck. Low-amplitude high-frequency current was delivered via these surface electrodes, and transthoracic impedance (resistance) to this current flow was measured. Changes in transthoracic impedance (mainly influenced by changes of systolic aortic blood flow) were measured by means of four additional surface electrodes: one pair placed bilaterally to the sternum and the second pair bilaterally to the abdomen. Cardiac output was calculated on a beat-to-beat basis from the transthoracic impedance signal.[37] *Figure 1* shows an example of the IC measurement acquired by the Task Force Monitor System.

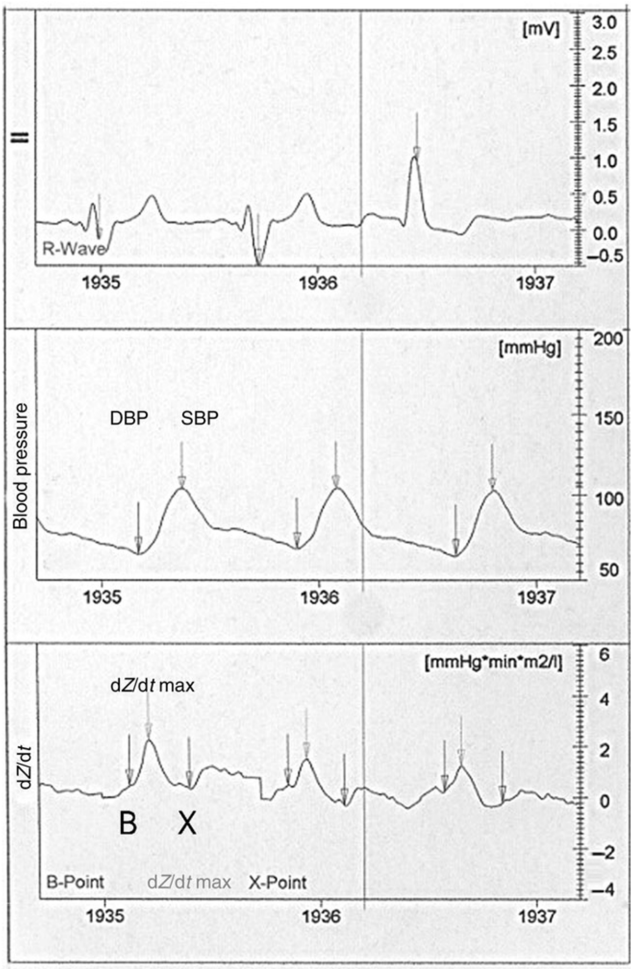

Figure 1 Example of the impedance cardiography measurement acquired by the Task Force Monitor System. There are two paced beats and one beat without pacing. From top to bottom: lead II from the surface ECG, blood pressure, and the first derivative d*Z*/d*t* of the impedance. DBP, diastolic blood pressure; SBP, systolic blood pressure; B, aortic valve opening; d*Z*/d*t* max, maximum of the first derivative of the impedance signal; X, aortic valve closure.

Pacing study protocol

To optimize the CRT set-up, all patients were examined in the supine position in a silent environment to reduce the impact of sympathetic activation by external stimuli.

A standard protocol involving a period of stabilization and equilibration followed by VV-interval optimization and then AV-interval optimization was employed in all patients. Pacemakers were programmed in a DDD-Mode with a lower rate limit of 40 bpm to avoid effects of atrial pacing on the AV interval.[36] During data acquisition, telemetry between the implanted device and the programmer was disconnected to prevent interference with the measurement of impedance. AV-interval values relate to the atrio-RV stimulation interval, and VV intervals relate to interventricular interval with negative figures implying LV pre-excitation.

The first stage of the pacing protocol was a period of stabilization and equilibration. The baseline CO without pacing was recorded, and this was alternated three times with 'standard' simultaneous biventricular pacing with an AV interval of 120 ms for 50 s at each setting. Once consistent values for CO in both modes were confirmed, we proceeded to the 'optimization' stage of the pacing protocol.

With the AV interval fixed at 120 ms, VV intervals were adjusted through a set of seven steps ranging from LV pre-excitation of −60 ms to an LV delay of +60 ms in steps of 20 ms (as reported previously[38]). The CO was recorded for 50 s at each setting. Then, the VV interval was set at zero while the AV interval was adjusted from 80 to 140 ms stepwise in 20 ms increments. Again, CO at each setting was recorded. We found that 10 s were sufficient for stabilization in values after any change in the stimulation set-up. Finally, the device was set at whichever combination of AV and VV intervals produced highest CO in that patient.

We defined an increase in CO of greater than 10% above baseline (i.e. without pacing) as a 'positive response' to biventricular pacing, in keeping with data previously published.[39] Where maximum CO was identified by IC to occur at very short AV intervals (i.e. A to RV or A to LV of <80 ms), an echocardiogram was performed to exclude a truncated A wave caused by atrial contraction against closed AV valves.

Statistics

All data are presented as means ± standard error. Statistical analysis was performed using multiple analysis of variance, Kruskall–Wallis test, and Fisher's exact test to compare more than two sets of data. For a comparison of two sets of data, a student's *t*-test was performed. A *P*-value of < 0.05 was considered to be significant. Data was processed using commercially available software (Statgraphics Plus for Windows).

Results

Cardiac resynchronization therapy

Forty-six CRT devices were successfully implanted, 45 by the transvenous approach and 1 by the transthoracic approach during surgical mitral valve repair. The LV lead was placed in a posterolateral ($n = 35$) or an anterolateral ($n = 10$) side branch. There were no complications.

There were no significant differences between the heart rates without pacing (75.1 ± 10.7 bpm), with initial simultaneous biventricular pacing (74.7 ± 10.9 bpm), or optimized biventricular pacing (74.8 ± 10.2 bpm, $P > 0.05$). Thus, results for CO obtained at each CRT set-up were unaffected by the heart rate.

Cardiac output without pacing vs. simultaneous biventricular pacing vs. optimized biventricular pacing

The alternation between three cycles of no pacing with simultaneous biventricular pacing during stabilization and equilibration revealed (across all patients) a mean increase in CO of 21.6 ± 22.1% ($P < 0.05$) with pacing. The mean range (i.e. variation) between the three recordings (in each patient) without pacing was 10.1% and between the three recordings with pacing was 11.8%.

Figure 2 shows data obtained for a typical patient at different VV intervals with a fixed AV interval of 120 ms. In this patient, the maximum CO was measured during LV pre-excitation of 20 and 40 ms relative to RV stimulation. Still, earlier LV pre-excitation, simultaneous biventricular pacing, and RV pre-excitation resulted in a lower CO.

Data collected from all patients at each stimulation set-up with VV optimization at a fixed AV interval of 120 ms and with AV optimization at a VV interval set to zero are shown in *Figure 3*.

In detail, the maximum CO was achieved with the following VV intervals (when combined with an AV interval of 120 ms): −60 ms in 15 pts, −40 ms in 6 pts, −20 ms in 9 pts, ±0 ms in 5 pts, +20 ms in 2 pts, +40 ms in 2 pts, and +60 ms in 3 pts, so the majority of patients (30 of 46 patients) achieved peak CO with LV pre-excitation. The remaining four patients achieved maximum CO with simultaneous biventricular pacing, two with an AV interval of 80 ms, and two with an AV interval of 140 ms.

The combination of an AV interval of 120 ms and LV pre-excitation of 40 ms yielded the highest mean CO of

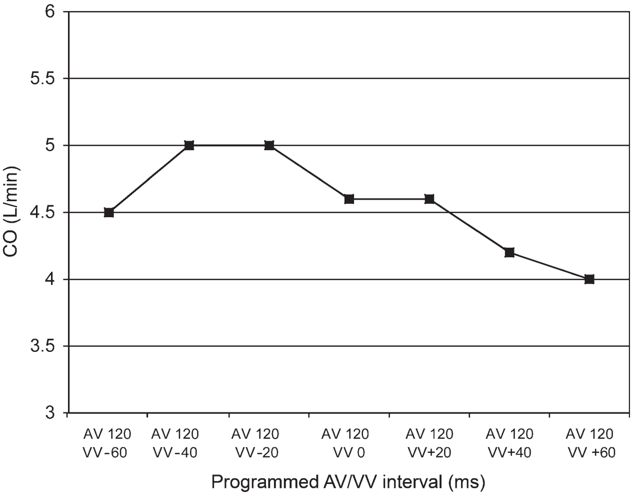

Figure 2 Cardiac output measured by impedance cardiography at different ventriculo-ventricular intervals at an atrioventricular interval of 120 ms in a representative patient. Optimum cardiac output was yielded at a left ventricular pre-excitation of −40 and −20 ms.

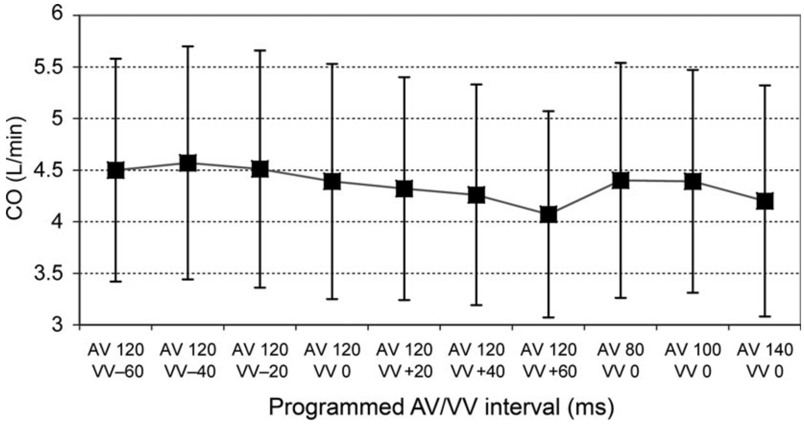

Figure 3 Cardiac output measured by impedance cardiography at different ventriculo-ventricular and atrioventricular intervals for all patients. Data are presented as mean ± standard deviation. Maximum cardiac output was yielded at a left ventricular pre-excitation of −40 ms and an atrioventricular interval of 120 ms.

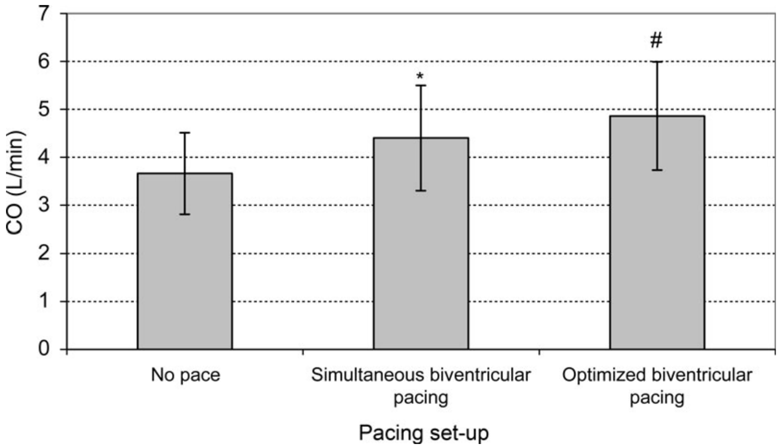

Figure 4 Cardiac output measured by impedance cardiography without pacing, with simultaneous biventricular pacing (and an atrioventricular interval of 120 ms), and with 'optimized' biventricular pacing. Asterisk represents $P < 0.05$, simultaneous biventricular pacing vs. no pace; ash represents $P < 0.05$, optimized biventricular pacing vs. simultaneous biventricular pacing and vs. no pace.

4.57 ± 1.1 L/min. Similar values were obtained by LV pre-excitation of 20 and 60 ms (4.51 ± 1.3 and 4.50 ± 1.2 L/min, respectively). The optimal pacing set-up varied widely from patient to patient. As a result of this variability, there was no significant difference in CO when the results from different AV and VV intervals were compared. No single combination of AV and VV intervals could be recommended for application to the whole study population, because no single combination of intervals showed statistically significant superiority over other combinations.

For the population as a whole, when the CO obtained with 'optimized' biventricular pacing (i.e. the CO measured at whichever AV and VV intervals produced the highest value in that patient) is compared with the CO obtained with 'standard' simultaneous biventricular pacing and compared with the CO obtained with no pacing, a statistically significant difference is seen (*Figure 4*). CO without pacing was 3.66 ± 0.85 L/min. CO increased to 4.40 ± 1.1 L/min ($P < 0.05$) with simultaneous biventricular pacing using a standard AV interval of 120 ms.

The mean increase in CO changing from no pacing to simultaneous biventricular pacing was 21.6 ± 22.1%, $P < 0.05$). 'Optimizing' VV and AV intervals further increased the mean CO to 4.86 ± 1.1 L/min. This corresponds to an increase in mean CO of 32.8% without pacing and an increase of 11.2% compared with simultaneous biventricular pacing, all three set-ups resulting in significantly different CO ($P < 0.05$, *Figure 4*).

Taking an increase in CO ≥10% as a definition of a positive haemodynamic response to CRT,[39] 16 of the 46 patients (35%) were 'non-responders' with standard simultaneous biventricular CRT. In five of these patients, CO with standard biventricular pacing was lower than without any pacing. The mean CO in this group of 16 'non-responders' (with standard simultaneous biventricular CRT) was 100.8 ± 4.9% (where CO without pacing was 100%). After optimization, 9 of these 16 patients (who were 'non-responders' to standard simultaneous biventricular CRT) experienced an increase of ≥10% in CO to become 'responders'. In this group of nine patients, the mean CO increased significantly from 101.3 ± 3.6% to 121 ± 5.1% ($P \leq 0.05$). In the seven patients who failed to respond despite 'optimization,' the mean CO was 106.6 ± 2.6% with optimized pacing. Nevertheless, after modification of AV and VV intervals to produce the

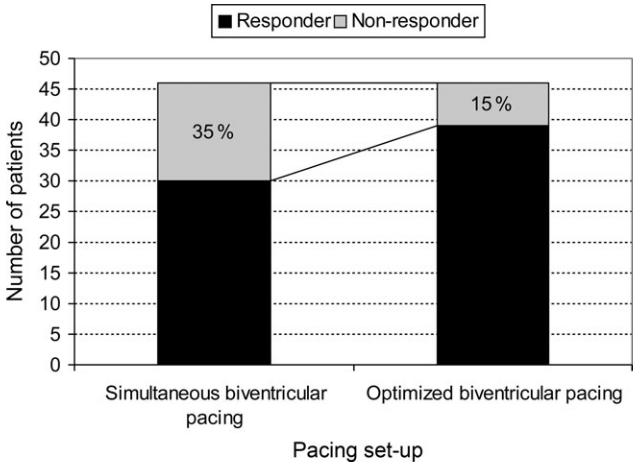

Figure 5 Comparison of the percentage of 'non-responders' to cardiac resynchronization therapy (definition see text) with simultaneous biventricular pacing (with an atrioventricular interval of 120 ms) vs. atrioventricular- and ventriculo-ventricular-interval optimized biventricular pacing according to the cardiac output measured by impedance cardiography for the whole study population.

maximum CO, the number of haemodynamic 'non-responders' was reduced to 7 of the 46 patients, i.e. the number of non-responders was reduced by 56% (*Figure 5*).

Discussion

In the present study, we described the use of IC to guide optimization of the AV and VV timing following CRT. To our knowledge, this is the first report of both AV and VV manipulation using IC as a guide in CRT optimization. We found IC to be simple to apply and capable of yielding rapid results in a reliable and reproducible fashion. We found that the optimal CRT-timing settings varied substantially between patients underlining the need to optimize each patient's device individually in order to gain most benefit from device. Using this technique, we were able to significantly improve CO by manipulating both AV and VV intervals. By optimizing both settings, we were able to further improve the CRT-related increase in CO in 'responders' and, furthermore, could produce a significant increase in CO in patients who, with 'standard' or simultaneous biventricular pacing, had demonstrated no increase in CO ('non-responders'). In part, this reflects the importance of 'electrical repositioning' of the LV lead by VV-interval manipulation. Thus, using this technique, we were able to reduce the rate of non-responders to CRT by 56% (from 35 to 15%) by IC haemodynamic criteria.

Assessment of optimal biventricular stimulation: current methods

Although invasive measurements of CO and other parameters remain the 'gold standard' for the evaluation of heamodynamics, they are not suitable for routine follow-up and optimization of CRT device settings because such invasive procedures are unpleasant for the patient and have potentially serious complications.[8,40]

Most units favour non-invasive methods for the optimization of CRT devices. The use of echocardiographic techniques for this purpose has received more attention in the literature, although there is no consensus as to which of the many echo-based parameters is the best surrogate for CO in the context of CRT optimization.

Mitral[41] and aortic[42] valve Doppler velocity time integrals (VTI) as well as several other[24] echocardiographic parameters have been assessed as an alternative to invasive measures and as a surrogate for CO in the optimization of pacing devices. Recently, there has been promising data using advanced tissue Doppler imaging techniques and real-time 3-D echo (particularly in selecting the optimal lead positioning for biventricular pacing), but despite these advances, the echocardiographic lead optimization of CRT remains complex and time consuming. It requires an experienced operator and has significant problems relating to reproducibility and objectivity.

Impedance cardiography: a reliable alternative technique?

Several studies have demonstrated that IC is capable of providing a reliable and accurate measurement of CO when compared with invasive methods.[28,32,43] The utility of IC has been shown in patients with decompensated cardiac failure[33] and in optimizing dual chamber pacemakers.[44] A direct comparison of IC and echo techniques in optimizing AV intervals for pacemakers has been made in several studies[30,31] with a recurring theme being that optimal AV intervals calculated by IC tend to be shorter than those obtained by echocardiography.[45] Recently, Braun *et al.*[6] provided data using IC to guide the manipulation (primarily) of AV intervals and showed that IC-based optimization is comparable with transaortic VTI, but IC was felt to be more sensitive to small changes in CO and easier to apply.

Limitations of impedance cardiography

The limitations of IC was usefully reviewed by Kinderman.[46] In a study of 14 patients with dual chamber pacemakers, data from IC overestimated CO if very short AV intervals were programmed. This phenomenon seems to be attributable to a decrease in the thoracic impedance caused by a retrograde flow into the great thoracic veins induced by atrial contraction against closed AV valves. In these cases, optimization of AV interval solely according to the impedance signal would result in a truncated A wave of the transmitral flow, causing potentially deleterious effects. In our study, if IC indicated that optimum CO was seen at more than one AV or VV interval, the longer AV interval and the shorter VV interval were programmed. If IC indicated optimum CO at short AV intervals (below 80 ms), transmitral flow was checked by Doppler echocardiography to exclude a truncated A wave. Of the 46 patients in the present study, this echocardiographic 'check' was required in two, neither of whom required a lengthening of AV interval.

Importance of optimizing both VV and AV intervals

The early generations of CRT devices enabled programming of the AV interval only.

Prospective randomized trial data have shown that AV-interval optimization not only improves the haemodynamic response to CRT, but also improves NYHA functional class and quality of life scores.[47]

The current generation of devices allows the manipulation of both AV and VV intervals.

Since activation of the interventricular septum is mainly influenced by the RV lead, modification of the VV interval affects not only inter-ventricular dyssynchrony, but also intra-ventricular dyssynchrony of the LV. The capacity to manipulate VV intervals may thus further improve the haemodynamic response to CRT.

There is increasing evidence that sequential biventricular pacing is superior to simultaneous biventricular pacing in many patients with a CRT device.

Perego *et al*. examined the impact of sequential biventricular pacing while invasively monitoring dp/dt in both ventricles simultaneously. Simultaneous ventricular pacing produced an increase in dp/dt of 29% over baseline, but sequential pacing produced a significantly greater increase of 35% ($P < 0.01$). The mean optimal VV interval was LV pre-excitation of 25 ms, and there was no detriment to RV function.[38] Similar findings were reported by van Gelder *et al.*[20]

This pattern of haemodynamic improvement with both AV and VV optimization has been verified using Doppler echocardiography,[48] 3-D echocardiography[49] and radionuclide ventriculography.[25] The largest benefit is obtained in most cases by LV pre-excitation. Our study is the first to validate the previous data, showing the additional benefit of optimizing both AV and VV intervals using IC as the method of assessment.

Where no facility for optimizing CRT devices in individual patients exists, we would recommend an AV interval of 120 ms and LV pre-excitation of 20–40 ms as empirical intervals in CRT programming. However, due to significant heterogeneity between patients, we were unable to identify any single set of AV and VV intervals as being superior and thus suitable for application to the whole CRT population on an empirical basis. This variation between patients is to be expected, since there is a substantial heterogeneity between patients of conduction pattern, ventricular size, scar tissue formation, ventricular function (especially with respect to regional wall motion abnormalities) CRT lead placement positions, and other variables. The facility to manipulate VV intervals in effect allows the operator to 'electrically reposition' the LV lead to help overcome some of these variations to maximize the haemodynamic response to the device.

This work has been an early, descriptive study of the feasibility of using IC to manipulate both AV and VV intervals in optimizing CRT devices. Further work is required before this technique can enter mainstream use. For instance, in any given patient, since AV and VV intervals are likely to be interdependent, the ideal IC protocol would test every AV-interval setting against every VV-interval setting and vice versa. With current equipment, this would be impractical. Another simpler method of combining these interdependent values of AV and VV intervals would be to identify the optimal VV interval (i.e. A to LV interval) and keeping this fixed (rather than re-setting this to zero as our protocol did), and then adjusting the AV (i.e. A to V interval) to identify the optimal CO. We suspect that this method of combined optimization of AV and VV intervals by IC may yield still higher CO values, and hence hopefully reduce the number of non-responders. Further studies are required.

Conclusions

The present paper is the first to report the utility of IC in the optimization of both AV and VV intervals in biventricular pacemaker set-up in routine clinical practice. Using IC, we demonstrated that manipulating both AV and VV intervals is feasible and may result in a significant improvement in the haemodynamic response to CRT compared with 'standard' simultaneous biventricular pacing and no pacing. The results show the importance of optimizing CRT set-up in each patient individually, since the variability between patients' means that no single set of intervals can be identified as being suitable for all or even most patients.

In our opinion, IC is a promizing method of CRT optimization and may compare well with other techniques in routine use. It carries less risk of complications than invasive techniques and is more comfortable for the patient. The validity and reliability of IC has now been reported by several authors.[28,31–33,43] Notwithstanding its limitations, which include a tendency to relative CO overestimation and the potential for selecting inappropriately short AV intervals, IC has an emerging role in the optimization of CRT parameters in routine clinical practice. Further work is required to make best use of IC derived data in combining AV and VV intervals to ideally suit any given patient.

Conflict of interest: none declared.

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