Review Article

The Contribution of Echocardiography to Cardiac Resynchronisation Therapy

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About a third of patients with systolic heart failure show widening of the QRS complex on the surface ECG, usually in combination with left bundle branch block (LBBB).[1,2] LBBB adversely affects prognosis in patients with heart failure and is also associated with increased overall mortality and higher risk of sudden death.[3,4] Furthermore, LBBB causes a delay in the activation and hence in the depolarisation and systole of the left ventricle, particularly its inferior and posterolateral segments. This delay results in a loss of synchronisation between the two ventricles (interventricular dyssynchrony), or among the various segments of the left ventricle (intraventricular dyssynchrony) during systole. It is also well-established that patients with heart failure exhibit a third type of dyssynchrony, attributed to the asynchronous contraction of atria and ventricles (atrioventricular dyssynchrony).

The various types of ventricular dyssynchrony have adverse effects on myocardial function, since they cause "paradoxical" motion of the interventricular septum, reducing its contribution to left ventricular systolic performance; they prolong isovolumic contraction and relaxation, reduce left ventricular diastolic filling time and aggravate mitral regurgitation. The final result of these changes is a reduction in stroke volume, ejection fraction and cardiac output.[5-8]

Cardiac resynchronisation may be achieved through biventricular pacing, synchronised with the atrial systole, or through left ventricular pacing alone. Left ventricular pacing is carried out using a special electrode lead implanted via the coronary sinus, preferably in the lateral or posterolateral coronary vein. Alternatively, an epicardial pacing lead may be placed via a small thoracotomy or via robotic-enhanced thoracoscopy.[9-13] Biventricular pacing accomplishes the following: a reduction in the paradoxical motion of the interventricular septum; a decrease in isovolumic contraction and relaxation times; an increase in diastolic filling time; a reduction in mitral regurgitation; an improvement in left ventricular function and a reversal of ventricular remodelling.[14] Randomised, controlled clinical studies have shown that resynchronisation therapy improves heart failure symptoms, the patients' functional capacity and their quality of life.[15-18] The COMPANION trial, which was ended prematurely in November 2002, showed that the implantation of a biventricular pacemaker resulted in a statistically significant reduction in the combined primary endpoint of the study (total mortality and total hospital admissions), while a statistically significant reduction in total mortality alone was only achieved by implantation of a biventricular pacemaker-defibrillator.[19] Furthermore, two meta-analyses of four (CONTAK-

CD, InSync ICD, MIRACLE and MUSTIC)[20] and nine (MUSTIC-SR, MUSTIC-AF, Garrigue et al, PATH-CHF, CONTAK-CD, RD-CHF, MIRACLE, MIRACLE-ICD, and COMPANION)[21] large clinical studies, as well as a recent randomised study (CARE-HF)[22] showed that biventricular pacing significantly reduces overall mortality.

The contribution of echocardiography to the selection of candidate patients for cardiac resynchronisation

The selection criteria for patients who will undergo resynchronisation therapy, as reported in the latest guidelines from the American College of Cardiology, American Heart Association and North American Society of Pacing and Electrophysiology,[23] were defined on the basis of the inclusion/exclusion criteria of the MIRACLE,[16] MIRACLE-ICD[17] and CONTAK-CD[18] trials. Based on these guidelines, biventricular pacing is indicated in New York Heart Association (NYHA) functional class III or IV patients with drug-refractory dilated or ischaemic cardiomyopathy, with a prolonged QRS complex (≥130 ms), left ventricular end-diastolic diameter ≥55 mm and ejection fraction ≤35% (indication: class IIa, level of evidence A).

In spite of the large amount of evidence providing ample proof of the benefits that result from biventricular pacing, around 30% of patients with heart failure, prolonged QRS and LBBB show no favourable response to resynchronisation therapy.[24-26] Recent data cast doubt on the value of QRS duration as a predictive index for the response to resynchronisation therapy.[24,27-31] According to data from the InSync Italian Registry,[25] width of QRS, previous hospitalisations for heart failure, ejection fraction and NYHA functional class were unable to predict a favourable clinical response to biventricular pacing.

In addition, results from other studies have shown that QRS duration is not an appropriate index for the estimation of mechanical dyssynchrony.[32] Yu et al[33] demonstrated in a recent study that a significant percentage of patients (>40%) with systolic heart failure and normal QRS duration showed dyssynchrony in left ventricular systolic and diastolic function, while in the same study the degree of left ventricular dyssynchrony was not related to the QRS duration. Ghio et al reported that 12.5% of patients with left ventricular systolic dysfunction (ejection fraction ≤35%) and QRS duration <120 ms showed significant interventricular dyssynchrony, while 29.5% had significant intraventricular dyssynchrony.[34] Also, according to Bader et al, 56% of patients with QRS width <120 ms showed significant intraventricular dyssynchrony, while there was no significant correlation between the width of the QRS complex and inter- or intraventricular dyssynchrony.[35] In a recent study, Bleeker et al found that 27% of patients with severe heart failure (NYHA class III-IV, ejection fraction ≤35%) and QRS <120 ms showed significant intraventricular dyssynchrony, while 30-40% of patients with QRS >120 ms had no intraventricular dyssynchrony, which probably explained their lack of response to resynchronisation therapy.[36] The same group of investigators, verifying the above results, found that one third of patients with heart failure (ejection fraction ≤35%) and a narrow QRS (≤120 ms) showed significant intraventricular dyssynchrony, while they observed no correlation between QRS duration and the degree of intraventricular dyssynchrony.[37]

The differences between the percentages reported above for the prevalence of dyssynchrony in patients with heart failure and normal QRS duration could be partly attributed to the different parameters used to assess dyssynchrony in the individual studies. It should be noted that recent studies have shown that biventricular pacing[38] and left ventricular pacing[39] in patients with heart failure, echocardiographic evidence of intra- and interventricular dyssynchrony, but a normal QRS duration, are associated with a significant improvement in functional, haemodynamic and clinical parameters, including ejection fraction, NYHA functional class, and left ventricular end-diastolic and end-systolic diameters.

Thus, given the limited value of QRS duration in the assessment of mechanical dyssynchrony and in the prediction of the response to resynchronisation therapy, it has been proposed that the quantitative evaluation of mechanical dyssynchrony should be performed directly using imaging techniques, especially echocardiography.

Interventricular dyssynchrony

Patients with left ventricular dysfunction may exhibit dyssynchrony between the right and left ventricular systole. The most widely used index of interventricular dyssynchrony is the interventricular mechanical delay, which is defined as the difference between the pre-ejection period of the left ventricle, i.e. the time from the beginning of the QRS to the onset of aortic flow (beginning of the aortic flow envelope on the pulsed Doppler tracing), and the pre-ejection period of the right ventricle, i.e. the time from the beginning of the QRS to the onset of pulmonary artery flow (start of the pulmonary

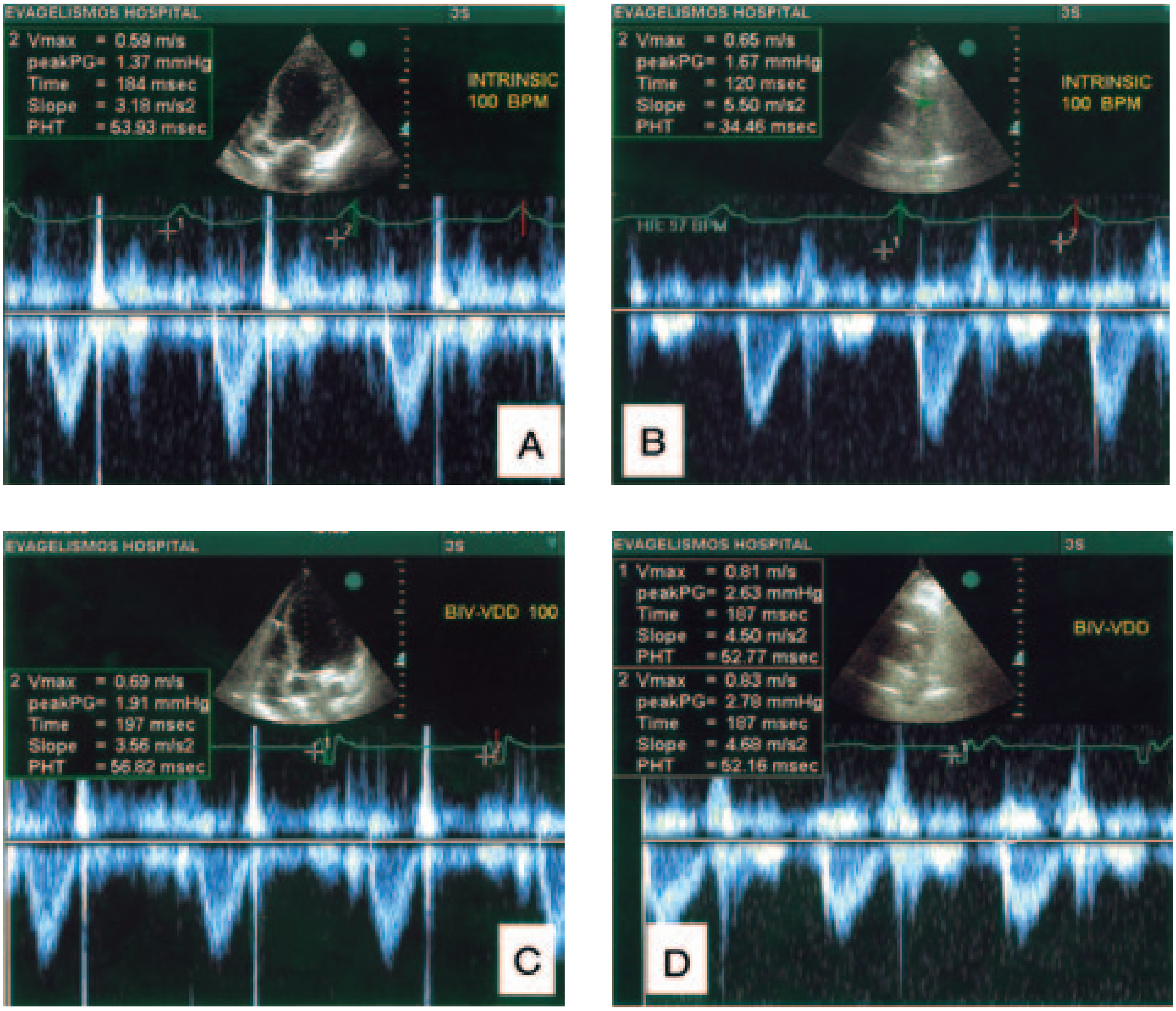

Figure 1. Improvement in interventricular mechanical delay following implantation of a biventricular pacemaker. The interventricular mechanical delay was reduced from 64 ms before implantation (intrinsic rhythm: A, B) to 10 ms after resynchronisation therapy (biventricular pacing: C, D).

artery flow envelope on the pulsed Doppler tracing) (Figure 1). The normal value of interventricular mechanical delay is around 8 ms,[5] while a cut-off value of 40 ms has been proposed as a marker of significant interventricular dyssynchrony.[40] Additionally, values for left ventricular pre-ejection period longer than 140 ms are indicative of significant interventricular dyssynchrony (normal values 93 ± 14 ms)[40] (Figure 2).

The assessment of interventricular dyssynchrony may also be performed using tissue Doppler imaging (TDI), which enables the measurement of the peak systolic velocities of the right ventricular wall and of the lateral wall of the left ventricle in the apical four-chamber view, as well as the time of their occurrence in relation to electrical activity (onset of the QRS on the ECG), expressed by T_S (S=systolic, Figure 3). Yu et al showed that the difference between the T_S of the lateral left ventricular wall and the T_S of the right ventricle was an index of interventricular mechanical delay, which was reduced during biventricular pacing.[8] However, recent studies have cast doubt on the usefulness of interventricular mechanical delay in the identification of patients who will show a beneficial response to biventricular pacing and have suggested that the estimation of intraventricular dyssynchrony is more suitable for that purpose.[41,42]

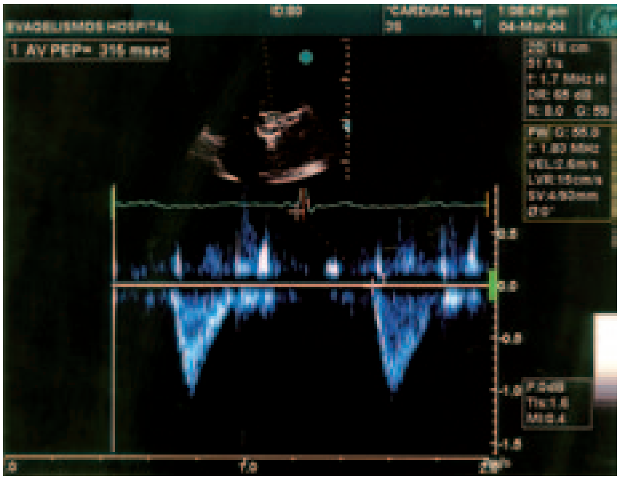

Figure 2. Patient with a particularly prolonged left ventricular pre-ejection period (315 ms), which is an index of significant interventricular dyssynchrony. The pre-ejection period was measured as the interval from the onset of the QRS to the onset of aortic flow (start of the aortic flow envelope on pulsed Doppler). AVPEP – aortic valve pre-ejection period.

Intraventricular dyssynchrony

The delay in the electromechanical activation of the various segments of the left ventricle may be assessed by a number of different echocardiographic parameters, of which the most widely used is the intraventricular delay. Pitzalis et al[41] used M-mode echocardiography to evaluate intraventricular dyssynchrony, calculating the delay of the inward movement of the left ventricular posterior wall in relation to the motion of the interventricular septum (septal-posterior wall motion delay). However, intraventricular dyssynchrony is mainly assessed using TDI, which allows the evaluation of the functioning of both longitudinal and radial myocardial fibres. A difference >60 ms between the time of occurrence of the peak systolic velocity of the basal lateral left ventricular wall and that of the basal interventricular septum is indicative of significant intraventricular dyssynchrony[43,44] (Figure 4).

Intraventricular dyssynchrony of the left ventricle may also be evaluated from measurement of the T_S (as defined above) of the septal, lateral, anteroseptal, posterior, anterior and inferior left ventricular wall at both basal and mid levels, followed by calculation of the maximum difference between any two of the estimated T_S values and the standard deviation of T_S ($T_{S\text{-}SD}$) of the twelve myocardial segments. The higher the value of $T_{S\text{-}SD}$, the greater the intraventricular dyssynchrony.[8] Yu et al, using a cut-off value for $T_{S\text{-}SD}$ of 32.6 ms (mean value + 2 standard deviations from the distribution of a large control population) as an index of severe intraventricular dyssynchrony, found that 43% of pa-

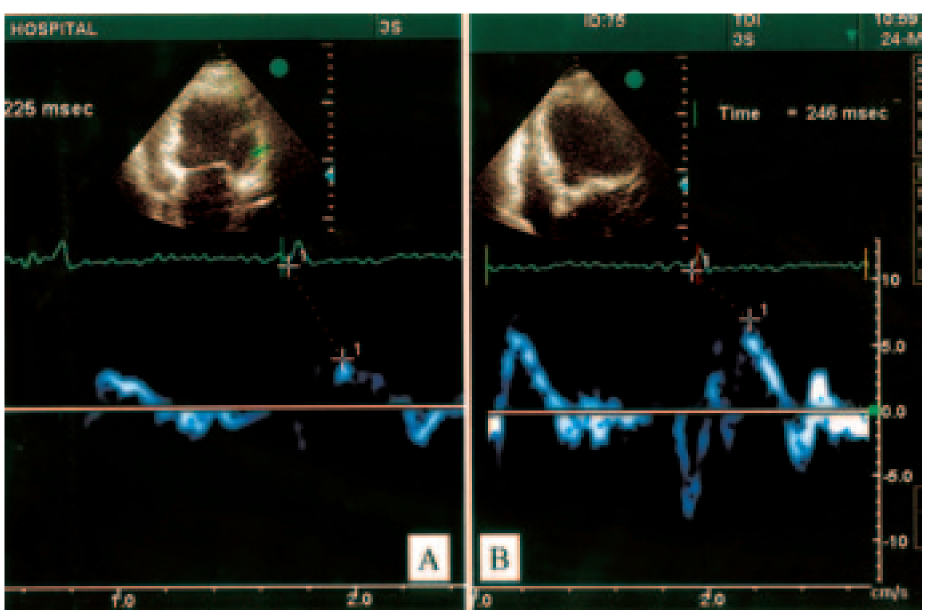

Figure 3. Assessment of interventricular dyssynchrony with the aid of tissue Doppler imaging. A: Measurement of the time interval from the start of the QRS to the occurrence of the peak systolic velocity of the left ventricular lateral wall in the apical four-chamber view (lateral wall T_S). B: Measurement of the time interval from the beginning of the QRS to the occurrence of the peak systolic velocity of the right ventricular wall in the apical four-chamber view (right T_S). The difference [lateral wall T_S - right T_S] is an index of interventricular dyssynchrony.

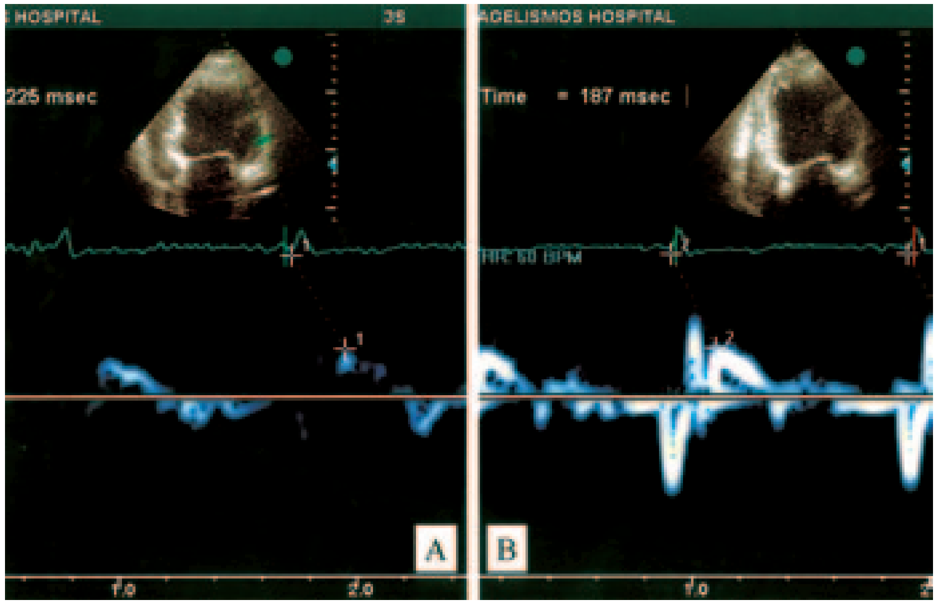

Figure 4. Evaluation of intraventricular dyssynchrony with the aid of tissue Doppler imaging. A: Measurement of the time interval from the onset of the QRS to the occurrence of the peak systolic velocity of the left ventricular lateral wall in the apical four-chamber view (lateral wall T_S). B: Measurement of the time interval from the onset of the QRS to the occurrence of the peak systolic velocity of the interventricular septum (septal T_S). Intraventricular delay is defined as the difference between these two values [lateral wall T_S – septal T_S] and is an index of intraventricular dyssynchrony.

tients with heart failure and a narrow QRS and 64% of those with a wide QRS had dyssynchrony.[8]

It should be noted that during the assessment of both inter- and intraventricular dyssynchrony using TDI, velocity measurements in real time can normally be made only once in a given cardiac cycle, which results in a considerable degree of variation due to the heart rate, ventricular loading and respiration. This technical difficulty can be overcome by performing offline multiple measurements in a given cardiac cycle by using digitally stored TDI recordings, or by using commercially available software that allows the making of simultaneous multiple-site measurements in real time.

Notabartolo et al[45] proposed a new TDI index for the assessment of intraventricular dyssynchrony, the peak velocity difference, which is defined as the maximum difference in time to peak velocity between any of the basal segments of the septal, lateral, inferior, anterior, anteroseptal and posterior walls immediately below the mitral annulus.

Two new echocardiographic techniques, tissue tracking and strain rate analysis, have also been used for the evaluation of intraventricular dyssynchrony. Tissue tracking is a parametric imaging method that requires correct synchronisation with the phases of the cardiac cycle and allows colour imaging of the displacement of the myocardial walls in the direction of the long axis of the left ventricle. Strain rate analysis, which is a development of TDI, expresses the rate of myocardial distortion and is superior as regards the better discrimination between active systole and passive displacement of the wall, especially in segments with scar tissue. Limitations in its use are a poor signal to noise ratio and low reproducibility because of inter-observer variability.[46,47]

A wealth of evidence supports the value of intraventricular dyssynchrony as a predictive index for the response to cardiac resynchronisation therapy. Bax et al[44] found that the sole predictive factor of improvement in ejection fraction following resynchronisation therapy was the presence of significant intraventricular dyssynchrony in the left ventricle. In a recent study, the same group of researchers reported that patients with an intraventricular delay ≥65 ms showed a favourable response and had an excellent prognosis after implantation of a biventricular pacemaker. The presence of baseline intraventricular dyssynchrony, using a cut-off value of 65 ms, had a sensitivity and specificity of 80% in predicting clinical improvement and 92% in predicting reverse left ventricular remodelling.[48] Similarly, Pitzalis et al reported that patients with an intraventricular delay ≥130 ms – time difference between the peak systolic motion of the interventricular septum and the posterior wall, as measured by M-mode in the short parasternal axis at the level of the papillary muscles – responded favourably to resynchronisation therapy, demonstrating left ventricular reverse remodelling[41] as well as long term clinical improvement, assessed on the basis of delayed heart failure progression.[49]

In a recent study, Penicka et al confirmed the value of intraventricular dyssynchrony in the prediction of a beneficial therapeutic effect of biventricular pacing, while also showing that the index with the highest predictive accuracy (highest sensitivity and specificity) was the sum of inter- and intraventricular dyssynchrony, using a cut-off value of 102 ms.[31] Finally, Notabartolo et al found that among patients with heart failure and QRS duration >120 ms who underwent cardiac resynchronisation therapy, those with peak velocity difference >110 ms showed a favourable response, with improvement in clinical and echocardiographic parameters.[45]

Taking into consideration the existence of multiple echocardiographic indices that have been proposed as useful in predicting a favourable response to cardiac resynchronisation therapy, Yu et al[50] compared the relative prognostic value of various echocardiographic parameters based on TDI and strain rate in predicting left ventricular reverse remodelling three months after resynchronisation therapy. The investigators concluded that the $T_{S\text{-}SD}$ index (standard deviation of the time to peak systolic velocity of the twelve left ventricular segments, as assessed by TDI) was the most powerful predictor of left ventricular reverse remodelling in patients with heart failure of either ischaemic or non-ischaemic aetiology. In addition, the same study concluded that interventricular dyssynchrony and parameters of strain rate imaging could not predict left ventricular reverse remodelling following resynchronisation therapy.[50]

In view of the contribution of echocardiography to the assessment of mechanical dyssynchrony and the prediction of the likely response to resynchronisation therapy, recent clinical studies have included among their enrolment criteria echocardiographic indices of left ventricular dyssynchrony. The CARE-HF trial,[22] which was designed to evaluate the long term effect of atrio-biventricular cardiac resynchronisation on the mortality of patients with heart failure, enrolled patients with long QRS duration (>150 ms) as well as patients with QRS duration between 120 and 150 ms and left ventricular dyssynchrony, based on the presence of two of the following three echocardiographic criteria:

- Left ventricular pre-ejection period >140 ms;
- Interventricular mechanical delay >40 ms;
- Delayed activation of the left ventricular posterolateral wall, defined as the maximal posterolateral wall inward movement, using M-mode or tissue Doppler echo, occurring later than the start of left ventricular filling, using the transmitral Doppler flow signal.

According to the findings of this study, resynchronisation therapy in the above patient population was associated with a statistically significant reduction in total mortality (p=0.0019), as well as in the combined endpoint of total mortality or an unplanned hospitalisation for a major cardiovascular event (p<0.001), over a mean follow up period of 30 months.[22] It is noteworthy that for every nine biventricular pacemakers implanted, one death and three hospitalisations for major cardiovascular events were prevented.[22] This favourable effect was in addition to the benefit derived from the pharmacologic therapy and was similar to the corresponding reduction in the risk of death achieved by the administration of beta-blockers compared to placebo in similar patient populations.[22,51] The hazard ratio for death among patients who received a biventricular pacemaker in the CARE-HF trial was similar to that achieved in the biventricular-defibrillator arm of the COMPANION trial, where as stated above the implantation of a biventricular pacemaker alone was not associated with a significant reduction in total mortality. The greater efficacy of resynchronisation therapy in the CARE-HF trial, as shown by the reduction of the "hard" endpoint of total mortality, which had not been observed in any previous study, probably reflected the better selection of candidate patients for biventricular pacing, given that the selection process took account of the presence of dyssynchrony as assessed by the three criteria given above. In consequence, assessment of mechanical dyssynchrony is of primary importance for the correct choice of suitable candidate patients who may be expected to reap the greatest possible benefit and to prolong their expected survival following this invasive therapy.

The contribution of echocardiography to pacing lead implantation and left ventricular pacing

Although it is well known that imaging of the coronary sinus can be performed in the haemodynamic laboratory with injection of contrast medium, or indirectly following coronary angiography, an initial echocardiographic evaluation of its anatomical position may also be useful. Echocardiography is unable to visualise the coronary veins in which the left ventricular pacing lead will be placed, but imaging of the ostium and the body of the coronary sinus is feasible (Figure 5). There is

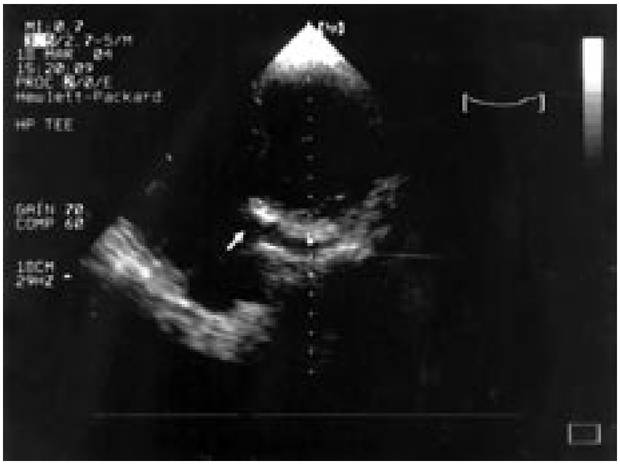

Figure 5. Transoesophageal view from the mid oesophagus for the imaging of the coronary sinus ostium (white arrow).

thus the possibility of excluding pre-procedurally the presence of a suitable coronary sinus anatomy for transvenous implantation of the left ventricular lead and taking the decision to place the left pacing lead epicardially. Bashir et al recently showed that using transoesophageal echocardiography to image the coronary sinus ostium throughout the procedure reduces the time required for catheterisation of the coronary sinus and implantation of the left ventricular lead.[52] Additionally, continuous echocardiographic monitoring allows the evaluation of left ventricular function and the immediate recognition of possible complications, such as cardiac tamponade.

Using tissue Doppler imaging, it is also possible to identify the segment of the left ventricle with the greatest electromechanical delay, which is the ideal site for implantation of the left ventricular lead. Ansalone et al[53] found that the greatest improvement in left ventricular performance after biventricular pacing in patients with non-ischaemic heart failure was demonstrated in those who were paced at the most delayed segment of the left ventricle. However, it must be emphasised that the echocardiographic identification of the optimum implantation site for the left electrode is often of limited practical value, since the anatomy of the coronary veins at the most delayed left ventricular site may not be suitable for pacing lead implantation. Furthermore, it is not clear whether pacing of regions with scar tissue, even when these show the greatest electromechanical delay, is associated with a clinical benefit following resynchronisation therapy, a point that reflects the importance of the underlying aetiology of the heart failure.

The contribution of echocardiography to programming the optimum atrioventricular and interventricular delay

Determining the ideal functional parameters of a biventricular pacemaker and programming it accordingly are of primary importance to ensure the greatest possible benefit from cardiac resynchronisation therapy. In spite of data indicating that the greatest haemodynamic and clinical improvement in patients with heart failure, of either ischaemic or idiopathic origin, may be achieved through biventricular pacing with small or medium atrioventricular (AV) delays (80-120 ms),[54] the optimum AV delay should be determined for each patient individually with the aid of echocardiography. A sequence of AV delay settings are programmed in every patient, in order to determine the value which maximizes mitral flow (maximum velocity-time integral of transmitral flow) and optimises the left atrial contribution to left ventricular filling (separation between the E and A waves).

It is important to note that the programmed AV delay during atrial pacing must be greater than the AV delay during atrial sensing, because of the endogenous delay between right atrial pacing and left atrial systole. Programming the paced AV delay on the basis of the optimal sensed AV delay, without taking into account the endogenous interatrial conduction delay, will result in almost simultaneous left atrial and left ventricular contraction during pacing, thus failing to optimise left ventricular filling and cardiac output. It is noteworthy, however, that it has not yet been fully elucidated whether the primary aim of resynchronisation therapy should be the optimization of AV delay or ventricular resynchronisation (interventricular or intraventricular).

Another parameter of biventricular pacing that must be programmed with the aid of echocardiography is the interventricular (VV) delay. Sogaard et al[55] and Mortensen et al[56] confirmed the value of echocardiographic detection of the optimum VV delay, showing that biventricular sequential pacing with a VV delay determined individually for each patient with the aid of TDI provides an additional benefit in comparison with the simultaneous pacing of both ventricles in patients with severe heart failure and LBBB. These findings were recently verified by Bordachar et al, who found that individually optimised sequential biventricular pacing in patients with heart failure significantly increased ejection fraction and cardiac output, reduced mitral regurgitation, improved all parameters of intraventricular dyssynchrony and significantly enhanced left ventricular reverse remodelling, in comparison with simultaneous biventricular pacing.[57]

For the determination of the optimal VV delay the following parameters should be evaluated: a) transmitral flow; b) the rate of change in pressure within the left ventricle (dp/dt), calculated from the continuous wave Doppler mitral regurgitation spectral signal; c) interventricular dyssynchrony, using TDI of the basal segment of the interventricular septum and the left ventricular lateral wall; and d) the end-expiratory velocity time integral of aortic flow, thus avoiding respiration-related variance of the calculated values.

The contribution of echocardiography to the assessment of the response to resynchronisation therapy

A number of studies have demonstrated the contribution of echocardiography to the evaluation of the clinical result of biventricular pacing, and based on their findings patients have been classified as either responders or non-responders. Ansalone et al[53] found that after biventricular pacing patients showed a reduction in left ventricular end-diastolic and end-systolic volumes, a reduction in isovolumic contraction time and an increase in ejection fraction, narrowing of the QRS complex on the 12-lead surface ECG and an improvement in symptoms and in NYHA functional class. Penicka et al reported an improvement in left ventricular function after six months' biventricular pacing in patients who had TDI-determined inter- or intraventricular dyssynchrony.[31] Kawaguchi et al used contrast echocardiography to show that left ventricular pacing alone in patients with dilated cardiomyopathy improved dyssynchrony in 50% of patients and eliminated the paradoxical motion of the interventricular septum.[58]

It should also be noted that despite the beneficial effects of biventricular pacing on diastolic functional parameters, such as an increase in diastolic filling time and a reduction in isovolumic relaxation time, it has been shown using echocardiography that the improvement in left ventricular performance largely reflects enhanced systolic rather than diastolic function.[53]

TDI has also been used to assess the effect of biventricular pacing on right ventricular function. Cardiac resynchronisation improves left ventricular function without having any adverse effect on echocardiographic indexes of right ventricular systolic or diastolic function, such as the systolic S wave, the diastolic E and A waves during a TDI study of tricuspid annulus motion, isovolumic contraction and ejection time.[59]

As regards the effect of biventricular pacing in patients with atrial fibrillation, the results of the MUSTIC trial showed that twelve months after the implantation of a biventricular pacemaker patients with atrial fibrillation demonstrated a 4% increase in left ventricular ejection fraction and a 50% decrease in mitral regurgitation.[60] Molhoek et al found that patients with heart failure, LBBB and atrial fibrillation showed similar clinical benefit and survival to patients in sinus rhythm.[61] Recent studies have shown the beneficial haemodynamic effects of biventricular and left ventricular pacing in patients who undergo AV nodal ablation for drug-refractory atrial fibrillation.[62] Specifically, left ventricular pacing has been shown to increase ejection fraction and to reduce mitral regurgitation in comparison with right ventricular pacing in such patients, irrespective of systolic function impairment or the presence of LBBB.[63]

Stellbrink et al found that six months after the implantation of a biventricular pacemaker there was a reduction in the diameters and volumes of the left ventricle (end-diastolic and end-systolic) and an increase in ejection fraction, except for patients with a greatly increased initial end-diastolic volume, who showed no reduction in left ventricular volumes.[64] However, biventricular pacing is not contraindicated in patients with greatly dilated hearts, since the initial beneficial haemodynamic effects of cardiac resynchronisation may lead to an improvement in the patients' symptoms in spite of the absence of any reduction in their left ventricular volume.

It should also be mentioned that the use of Doppler echocardiography has led to the recognition of a group of patients who do not benefit from biventricular pacing, even though they show widening of the QRS complex and a reduced initial dp/dt. This category is made up of patients who show symmetrical conduction delay along the interventricular septum and the left ventricular lateral wall.[65]

Finally, using transthoracic and transoesophageal echocardiography it has been found that cardiac resynchronisation results in a reversal of left atrial remodelling, an increase in total left atrial ejection fraction, as well as a reduction in the incidence and intensity of spontaneous echo contrast within the left atrium.[66]

Follow up of patients post-resynchronisation with the aid of echocardiography

The correct management of a patient who has had a biventricular pacemaker implanted presupposes the ap-

Table 1. Echocardiographic indexes of inter- and intraventricular dyssynchrony.

Interventricular dyssynchrony

- Interventricular mechanical delay
- Left ventricular pre-ejection period
- Difference between the time of occurrence of the peak systolic velocity of the basal left ventricular lateral wall and that of the basal right ventricular wall (TDI)

Intraventricular dyssynchrony

- Intraventricular delay: difference between the time of occurrence of the peak systolic velocity of the basal left ventricular lateral wall and that of the basal interventricular septum
- Time interval between the peak inward motion of the left ventricular posterior wall and interventricular septum (assessed by M-mode)
- Standard deviation ($T_{S\text{-}SD}$) of the times of occurrence of the peak systolic velocity of multiple left ventricular segments (TDI)
- Greatest difference between any of two of the times of occurrence of the peak systolic velocity of multiple left ventricular segments (TDI)
- Strain rate parameters

TDI – tissue Doppler imaging

plication of a complex strategy, which includes regular clinical follow-up, optimisation of device programming and pharmacological therapy, continuous education, as well as repeated echocardiographic evaluation of cardiac function.

With the aid of echocardiography it is possible to assess what reduction has been achieved in intra- and interventricular dyssynchrony by calculating the parameters described above (Table 1). In addition, all patients must undergo repeated checks of systolic and diastolic left ventricular function so that any need for a change in the programming of the biventricular pacemaker can be assessed at regular intervals.

Conclusion

An echocardiographic finding of mechanical dyssynchrony appears to be an independent prognostic index—indeed a much more significant one than the electrical dyssynchrony seen on the ECG—and can make a crucial contribution to the correct selection of patients who will respond to cardiac resynchronisation therapy.[67]

The use of echocardiography with the latest Doppler techniques is emerging as an invaluable and essential tool, both in the selection of patients who will respond to resynchronisation therapy in the form of biventricular pacing, and in the setting of individual AV and VV delays during the programming of the biventricular device, in order that the patients may reap the maximum benefit from this vital pacing therapy. In the near future, guidelines from cardiological societies must surely include echocardiographic indexes for the selection of suitable candidates for cardiac resynchronisation therapy. In consequence, this electrical therapy may bring benefit to more patients with heart failure and at an earlier stage.

References

1. Schoeller R, Andresen D, Buttner P, Oezcelik K, Vey G, Schroder R: First- or second degree atrioventricular block as a risk factor in idiopathic dilated cardiomyopathy. Am J Cardiol 1993; 71: 720-726.
2. Wilensky RL, Yudelman P, Cohen AI, et al: Serial electrocardiographic changes in idiopathic dilated cardiomyopathy confirmed at necropsy. Am J Cardiol 1988; 62: 276-283.
3. Baldasseroni S, Opasich C, Gorini M, et al: Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. Am Heart J 2002; 143: 398-405.
4. Gottipaty VK, Krelis SP, Fei L, for the VEST investigators: The resting electrocardiogram provides a sensitive and inexpensive marker of prognosis in patients with chronic heart failure. J Am Coll Cardiol 1999; 145A: 847-854.
5. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF: Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989; 79: 845-853.
6. Xiao, HB, Lee CH, Gibson DG: Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. Br Heart J 1991; 66: 443-447.
7. Xiao HB, Brecker SJD, Gibson DG: Effects of abnormal activation on the time course of the left ventricular pressure pulse in dilated cardiomyopathy. Br Heart J 1992; 68: 403-407.

8. Yu CM, Chau E, Sanderson JE, et al: Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105: 438-445.
9. Jansens JL, Jottrand M, Preumont N, Stoupel E, de Canniere D: Robotic-enhanced biventricular resynchronization: an alternative to endovenous cardiac resynchronization therapy in chronic heart failure. Ann Thorac Surg 2003; 76: 413-417.
10. Morgan JA, Ginsburg ME, Sonett JR, et al: Advanced thoracoscopic procedures are facilitated by computer-aided robotic technology. Eur J Cardiothorac Surg 2003; 23: 883-887.
11. Kleine P, Gronefeld G, Dogan S, Hohnloser SH, Moritz A, Wimmer-Greinecker G: Robotically enhanced placement of left ventricular epicardial electrodes during implantation of a biventricular implantable cardioverter defibrillator system. Pacing Clin Electrophysiol 2002; 25: 989-991.
12. Auricchio A, Stellbrink C, Butter C, et al: Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. J Am Coll Cardiol 2003; 42: 2109-2116.
13. Mair H, Sachweh J, Meuris B, et al: Surgical epicardial left ventricular lead versus coronary sinus lead placement in biventricular pacing. Eur J Cardiothorac Surg. 2005; 27: 235-242.
14. Abraham W, Hayes DL: Cardiac resynchronization for heart failure. Circulation 2003; 108: 2596-2603.
15. Duncan A, Wait D, Gibson D, Daubert JC: MUSTIC (Multisite Stimulation in Cardiomyopathies) Trial: Left ventricular remodeling and haemodynamic effects of multisite biventricular pacing in patients with left ventricular systolic dysfunction and activation disturbances in sinus rhythm: sub-study of the MUSTIC (Multisite Stimulation in Cardiomyopathies) trial. Eur Heart J 2003; 24: 430-441.
16. Abraham WT, Fisher WG, Smith AL, et al: Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group:. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002; 346: 1845-1853.
17. Young JB, Abraham WT, Smith AL, et al: Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators: Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 2003; 289: 2685-2694.
18. Thackray S, Coletta A, Jones P, Dunn A, Clark AL, Cleland JG: Clinical trials update: Highlights of the Scientific Sessions of Heart Failure 2001, a meeting of the Working Group on Heart Failure of the European Society of Cardiology. CONTAK-CD, CHRISTMAS, OPTIME-CHF. Eur J Heart Fail 2001; 3: 491-494.
19. Bristow MR, Saxon LA, Boehmer J, et al: Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators: Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350: 2140-2150.
20. Bradley DJ, Bradley EA, Baughman KL, et al: Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. JAMA 2003; 289: 730-740.
21. McAlister FA, Ezekowitz JA, Wiebe N, et al: Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Intern Med 2004; 141: 381-390.
22. Cleland JG, Daubert JC, Erdmann E, et al: The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352: 1539-1549.
23. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Circulation 2002; 106: 2145-2161.
24. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M: Doppler myocardial imaging in patients with heart failure receiving biventricular pacing treatment. Am Heart J 2001; 142: 881-896.
25. Zardini M, Tritto M, Bargiggia G, et al: The InSync Italian Registry: analysis of clinical outcome and considerations on the selection of candidates to left ventricular resynchronization. Eur Heart J 2000; 2(suppl): J16-J22.
26. Alonso C, Leclercq C, Victor F, et al: Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. Am J Cardiol 1999; 84: 1417-1421.
27. Leclercq C, Kass DA: Retiming the failing heart: principles and current clinical status of cardiac resynchronization. J Am Coll Cardiol 2002; 39: 194-201.
28. Abraham WT, Fisher WG, Smith AL, et al: Cardiac resynchronization in chronic heart failure: Multicenter InSync Randomized Clinical Evaluation (MIRACLE). N Engl J Med 2002; 346: 1845-1853.
29. Nelson GS, Curry CW, Wyman BT, et al: Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000; 101: 2703-2709.
30. Sogaard P, Kim WY, Jensen HK, et al: Impact of acute biventricular pacing on left ventricular performance and volumes in patients with severe heart failure. A tissue Doppler and three-dimensional echocardiographic study. Cardiology 2001; 95: 173-182.
31. Penicka M, Bartunek J, De Bruyne B, et al: Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging echocardiography. Circulation 2004; 109: 978-983.
32. Auricchio A, Yu CM: Beyond the measurement of QRS complex toward mechanical dyssynchrony: cardiac resynchronization therapy in heart failure patients with a normal QRS duration. Heart 2004; 90: 479-481.
33. Yu CM, Lin H, Zhang Q, Sanderson JE: High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003; 89: 54-60.
34. Ghio S, Constantin C, Klersy C, et al: Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. Eur Heart J 2004; 25: 571-578.
35. Bader H, Garrigue S, Lafitte S, et al: Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. J Am Coll Cardiol 2004; 43: 248-256.
36. Bleeker GB, Schalij MJ, Molhoek SG, et al: Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. J Cardiovasc Electrophysiol 2004; 15: 544-549.
37. Bleeker GB, Schalij MJ, Molhoek SG, et al: Frequency of left ventricular dyssynchrony in patients with heart failure and a narrow QRS complex. Am J Cardiol 2005; 95: 140-142.
38. Achilli A, Sassara M, Ficili S, Pontillo D, Achilli P, Alessi C: Long-term effectiveness of cardiac resynchronization therapy

in patients with refractory heart failure and "narrow" QRS. J Am Coll Cardiol 2003; 42: 2117-2124.
39. Turner MS, Bleasdale RA, Mumford CE, Frenneaux MP, Morris-Thurgood JA: Left ventricular pacing improves haemodynamic variables in patients with heart failure with a normal QRS duration. Heart 2004; 90: 502-505.
40. Cleland JG, Daubert JC, Erdmann E, et al: The CARE-HF study (Cardiac REsynchronisation in Heart Failure study): rationale, design and end-points. Eur J Heart Fail 2001; 3: 481-489.
41. Pitzalis MV, Iacoviello M, Romito R, et al: Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol 2002; 40: 1615-1622.
42. Fauchier L, Marie O, Casset-Senon D, Babuty D, Cosnay P, Fauchier JP: Interventricular and intraventricular dyssynchrony in idiopathic dilated cardiomyopathy. A prognostic study with Fourier phase analysis of radionuclide angioscintigraphy. J Am Coll Cardiol 2002; 18: 380-387.
43. Bax JJ, Molhoek SG, van Erven L, et al: Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony before and after biventricular pacing in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2003; 91: 94-97.
44. Bax JJ, Marwick TH, Molhoek SG, et al: Left ventricular dyssynchrony predicts benefit of cardiac resynchronization in patients with end-stage heart failure before pacemaker implantation. Am J Cardiol 2003; 92: 1238-1240.
45. Notabartolo D, Merlino JD, Smith AL, et al: Usefulness of the peak velocity difference by tissue Doppler imaging technique as an effective predictor of response to cardiac resynchronization therapy. Am J Cardiol 2004; 94: 817-820.
46. Brodin LA, Gabella M, Van D, er Linden J: Simultaneous display of tissue velocity and strain: a fast option in evaluation of myocardial function (abstr). J Am Coll Cardiol 2001; 37 Suppl A:410A
47. Sogaard P, Egeblad H, Kim WY, et al: Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. J Am Coll Cardiol 2002; 40: 723-730.
48. Bax JJ, Bleeker GB, Marwick TH, et al: Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004; 44: 1834-1840.
49. Pitzalis MV, Iacoviello M, Romito R, et al: Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy. J Am Coll Cardiol 2005; 45: 65-69.
50. Yu CM, Fung JW, Zhang Q, et al: Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening in the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. Circulation 2004; 110: 66-73.
51. Investigators CIBIS-II, Committee: The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353: 9-13.
52. Bashir JG, Tyers FG, Lampa M, Yamaoka R: Combined use of transesophageal echo and fluoroscopy for the placement of left ventricular pacing via the coronary sinus. Pacing Clin Electrophysiol 2003; 26: 1951-1954.
53. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M: Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. J Am Coll Cardiol 2002; 39: 489-499.
54. Breithardt OA, Stellbrink C, Franke A, et al: Acute effects of cardiac resynchronization therapy on left ventricular Doppler indices in patients with congestive heart failure. Am Heart J 2002; 143: 34-44.
55. Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen B, Hansen PS: Sequential versus simultaneous biventricular resynchronization for severe heart failure. Circulation 2002; 106: 2078-2084.
56. Mortensen PT, Sogaard P, Mansour H, et al: Sequential biventricular pacing: evaluation of safety and efficacy. Pacing Clin Electrophysiol 2004; 27: 339-345.
57. Bordachar P, Lafitte S, Reuter S, et al: Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. J Am Coll Cardiol 2004; 44: 2157-2165.
58. Kawaguchi M, Murabayashi T, Fetics BJ, et al: Quantitation of basal dysynchrony and acute resynchronization from left or biventricular pacing by novel echo contrast variability imaging. J Am Coll Cardiol 2002; 39: 2052-2058.
59. Santos JF, Caetano F, Parreira L, et al: Effects of cardiac resynchronization therapy on right ventricular function – evaluation with Doppler echocardiography. Rev Port Cardiol 2003; 22: 1347-1355.
60. Linde C, Leclercq C, Rex S, et al: Long-term benefits of biventricular pacing in congestive heart failure: Results from the multisite stimulation in cardiomyopathy study. J Am Coll Cardiol 2002; 40: 111-118.
61. Molhoek SG, Bax JJ, Bleeker GB, et al: Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. Am J Cardiol 2004; 94: 1506-1509.
62. Simantirakis EN, Vardas P: Atrial fibrillation, atrioventricular nodal ablation and biventricular pacing: A new concept. Hell J Cardiol 2004; 45: 61-64.
63. Puggioni E, Brignole M, Gammage M, et al: Acute comparative effect of right and left ventricular pacing in patients with permanent atrial fibrillation. J Am Coll Cardiol 2004: 43; 234-238.
64. Stellbrink C, Breithardt OA, Franke A, et al: Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol 2001; 38: 1957-1965.
65. Breithard OA, Stellbrink C, Kramer AP: Echocardiographic quantification of left ventricular asynchrony predicts an acute hemodynamic benefit of cardiac resynchronization theraphy. J Am Coll Cardiol 2002; 40: 536-545.
66. Vural A, Agacdiken A, Ural D, et al: Effects of cardiac resynchronization therapy on left reverse remodeling and spontaneous echo contrast. Tohoku J Exp Med 2004; 202: 143-153.
67. Manolis AS: Cardiac resynchronization therapy in congestive heart failure: ready for prime time? Heart Rhythm 2004; 1: 355-363.