Clinical Perspectives

What is the role of pacing in dilated cardiomyopathy?

**Introduction**

DDD pacing has proved invaluable in treating patients with disorders of atrioventricular conduction but intact atrial function, although electrical reliability is achieved only with some deterioration in mechanical function. Pacing from the atrial appendix renders right atrial contraction incoordinate and increases atrioventricular delay by an unpredictable amount. Pacing from a right ventricular site, especially from the apex, leads to abnormal activation, and thus, again, to incoordinate contraction of both ventricles. Since intrinsic atrial and ventricular function are usually well preserved in most patients needing DDD pacing on conventional grounds, these indirect mechanical effects are of little practical consequence. It has been suggested, however, that DDD pacing may also be useful on haemodynamic grounds in patients with end stage dilated cardiomyopathy with intact atrioventricular conduction. At first sight, benefit would seem unlikely; if it were to occur it would probably be because the pathophysiology of dilated cardiomyopathy differed so greatly from normal that the limitations described above do not apply.

**Atrial function in dilated cardiomyopathy**

Left atrial function is often abnormal in patients with dilated cardiomyopathy. Restrictive filling is common, with an increase in the height of the E wave as measured by transmitial Doppler, and a reduction in A wave amplitude. In extreme cases, there is no forward flow with atrial systole, in spite of a pressure wave corresponding to atrial contraction and retrograde flow in the pulmonary veins. In a minority of patients, no left atrial function can be detected at all, although right atrial contraction persists. Atrioventricular interrelations may thus be very disturbed in dilated cardiomyopathy and normal conditions cannot be expected to apply.

**Atrioventricular conduction in dilated cardiomyopathy**

PR interval, as measured on the standard 12 lead ECG, is often prolonged in patients with late stage dilated cardiomyopathy. This predisposes to late diastolic mitral regurgitation detectable by continuous wave Doppler. While this puts negligible volume load on the left ventricle, prolonged regurgitation prevents forward flow across the mitral valve. Since the duration of regurgitation changes little with RR interval, when heart rate is high, ventricular filling time is correspondingly shortened. Similarly, tricuspid filling time may be limited by presystolic tricuspid regurgitation.

**Ventricular activation in dilated cardiomyopathy**

QRS duration is often increased in dilated cardiomyopathy, and when this reaches 120 ms or more, complete left bundle branch block is usually diagnosed. Normal frequency analysis of QRS duration in dilated cardiomyopathy, however, shows a unimodal distribution, with no evidence of the expected discontinuity at 120 ms. This finding suggested that activation disturbances in dilated cardiomyopathy might be more complex than usually considered.

Wiggers wrote in 1927 that coordinate left ventricular contraction depended on normal activation. Disturbed activation makes contraction prolonged and incoordinate and reduces peak velocities of pressure rise and fall. The mechanical consequences of abnormal activation can be assessed by echocardiography in humans. M-mode shows that in right bundle branch block, the onset of right sided atrioventricular ring motion is delayed, and the left in left bundle branch block. The time course of the high fidelity left ventricular pressure trace is reflected to within 5 ms by that of functional mitral regurgitation, as recorded by continuous wave Doppler. Regurgitation is greatly prolonged in patients with the ECG pattern of left bundle branch block compared with normal activation (Fig. 1), because isovolumic contraction and relaxation times are both increased. With advanced activation abnormalities,
mitral regurgitation may last for 650 ms or more, a value that changes little with heart rate\(^9\). The time available for ventricular filling thus falls below 200 ms when RR interval is 850 ms, corresponding to a heart rate of just over 70 min. A filling time of 200 ms is physiologically significant since it is the minimum achieved on exercise by patients with diastolic disease\(^1\). If the prolonged mitral regurgitation were due to simple left bundle branch block, its onset should be delayed with respect to that of the start of the QRS complex; if the block were more diffuse, this time interval, representing electromechanical delay, would be normal. In fact, electromechanical delay is frequently abnormally short, a finding difficult to explain in terms of classical electrocardiography. Moreover, in individual patients, there is an inverse relationship between a short electromechanical delay and a long PR interval. This finding strongly suggests that the true onset of ventricular activation may be of such low voltage that it is not apparent on the standard 12 lead ECG, a hypothesis confirmed by signal averaged ECG\(^8\). Furthermore, in such cases, M-mode echo shows the onset of both right and left ventricular free wall motion to be delayed with respect to that of the interventricular septum to an extent equal to that seen in complete right or left bundle branch block respectively.

In a significant minority of patients with dilated cardiomyopathy, therefore, ventricular activation is very much more abnormal than is apparent from the standard interpretation of the 12 lead ECG. Effectively, there is bilateral complete bundle branch block with early activation of the whole ventricular mass from high in the septum, the site of earliest detectable motion. The anatomical substrate required to explain this corresponds closely to fibres described by Mahaim and Winter in 1941\(^{11}\), passing from the atrioventricular node or the common bundle of His to adjoining myocardium, with slow myogenic spread to the remainder of the ventricle. If this hypothesis is correct, therefore, and contrary to what is predicted by classical electrocardiography, right ventricular pacing should have clear mechanical effects on left ventricular function in patients with the 12 lead ECG pattern of left bundle branch block by providing an alternative pathway for left ventricular activation. This is indeed the case (Fig. 2): functional mitral regurgitation substantially shortens with right ventricular pacing\(^12\). This occurred in all our patients. It is the rationale for right ventricular pacing in dilated cardiomyopathy.

---

Figure 1 Effect of ventricular activation on functional mitral regurgitation in dilated cardiomyopathy, as recorded by continuous wave Doppler, from patients with left bundle branch block (A) and normal activation (B). The duration of the functional regurgitation is much greater with left bundle branch block. This is because isovolumic contraction (CT) and relaxation (RT) times are both longer. Ejection time (ET) was not different. FT=filling time. (Time markers 40 ms.)

Eur Heart J, Vol. 17, June 1996
Clinical Perspectives 821

Q. Ao

Figure 2  Effect of ventricular pacing on functional mitral regurgitation in a patient with left bundle branch block. Left panel, unpaced; right panel, paced. The duration of the regurgitation falls strikingly with pacing, because isovolumic contraction (interval 2) and relaxation times (interval 3) both get much shorter. Electromechanical delay (interval 1) was also abnormally brief before pacing. (Time markers 40 ms, frequency shift markers 1 kHz.)

Figure 3  Pulsed Doppler record of transmitral flow in a patient with dilated cardiomyopathy and prolonged functional mitral regurgitation. Note that the total duration of forward flow is reduced to approximately 150 ms, and that separate E and A waves are merged into a single pulse. (Time markers 40 ms, frequency shift markers 1 kHz.)

Criteria for patient selection

Based on these findings, selection criteria for DDD pacing are clear: symptomatic patients with prolonged QRS duration, functional mitral regurgitation prolonged to more than 450 ms, and a ventricular filling time of less than 200 ms at rest. In these patients, the normal E and A waves of the transmitial Doppler flow velocity record are superimposed to form a single summation pulse (Fig. 3). Patients can often be recognised clinically from the presence of sinus tachycardia and a summation gallop. On 12 lead ECG computed QRS duration complex is usually more than 140 ms, PR interval increased, and QRS axis is normal. Patients with a simple restrictive filling pattern, i.e. a large or isolated E
wave terminating well before the Q wave of the next beat are unsuitable for pacing. Although presystolic tricuspid regurgitation is also abolished by short atrioventricular delay pacing, filling time on the right side of the heart should probably not be increased if there is already a restrictive filling pattern on the left.

Pacing parameters

DDD pacing is used to allow physiological changes in heart rate to occur and to correct diastolic mitral regurgitation if it is present. Atrioventricular delay must be set to less than the true PR interval, which may be up to 70 ms less than that on the 12 lead ECG in patients with bilateral complete bundle branch block, so that the left ventricle is activated solely from the paced right ventricle and not from a fusion effect. Progressive shortening of atrioventricular delay throughout and below the physiological range leads to corresponding shortening of the duration of mitral regurgitation and lengthening of filling time at constant RR interval. Bearing in mind the normal lack of ventricular filling with atrial systole in many of these patients, we have used a short (70 ms) atrioventricular delay as the standard approach, always checking the effect against the continuous wave Doppler of mitral regurgitation. On two occasions, an atrioventricular delay of 15 ms has increased the severity of mitral regurgitation as assessed by colour flow.

Assessing the results of pacing

We do not believe that resting haemodynamics are adequate to assess the effects of pacing. This approach has proved unreliable in predicting the long-term effects of drugs in patients with heart failure. The main effects of heart failure are to limit exercise tolerance, and with it the quality of life, and to impair prognosis. Our primary aim is to treat the reduced exercise tolerance of these patients, which requires formal testing with measurement of MVO₂. Acute alterations in the duration of mitral regurgitation and filling time have proved reliable markers of the long-term change in ventricular contraction pattern brought about by pacing.

Effects of DDD pacing in dilated cardiomyopathy

In all patients selected according to the criteria outlined above, DDD pacing promptly reduced the duration of mitral regurgitation by a mean of 105 ms and increased filling time by 75 ms, the apparent discrepancy being accounted for by a significant increase in heart rate. This occurred within 1–2 min, as soon as measurements could be made after the pacemaker had been reprogrammed. Exercise time, measured within 24 h, increased acutely by 30% and MVO₂ by 25%. This improvement in functional capacity has been maintained or even enhanced 6 months after insertion, when MVO₂ was 43% and exercise time 40% above baseline. The changes in the duration of mitral regurgitation and left ventricular filling time have persisted, while left ventricular cavity size has begun to fall and shortening fraction to increase. Other studies, not using these selection criteria, have shown no consistent acute or chronic effects of pacing in dilated cardiomyopathy. Indeed, it would have been surprising if they had.

Future developments

We believe that in the clearly defined group of patients with dilated cardiomyopathy we have described, pacemaker therapy can be further refined. It is perhaps a measure of the magnitude of the activation disturbance that even so unsophisticated a measure as pacing from the right ventricular apex leads to functional improvement. It is most unlikely to be the best site. The right ventricular outflow tract and in the longer term, pacing from one or more left ventricular sites should also be considered.

A second problem is that of optimal atrioventricular delay. We initially chose a short atrioventricular delay to ensure ventricular capture and achieve the greatest possible shortening of the mitral regurgitation. This may well be reasonable in the short-term, although improvement occurs at the expense of mechanical function of the left atrium. As suggested above, this latter is probably unimportant when left atrial pressure is high. However, administering angiotensin converting enzyme inhibitors to patients with a restrictive filling pattern due to dilated cardiomyopathy leads to a fall in E wave amplitude and an increase in that of the A wave, along with a striking increase in isovolumic relaxation time compatible with falling left atrial pressure. Thus it may be useful to lengthen atrioventricular delay once initial clinical improvement has occurred, and filling pattern has become stabilised to a restrictive rather than a summation pattern.

Since the patients who benefit from pacing are those with advanced activation disturbances, they are also likely to be at risk from sudden death due to bradyarrhythmia. PACing might thus improve...
prognosis quite independent of any effect on exercise tolerance. Such an effect has been reported by Hochleitner. We have also noted in a retrospective study that prolongation of QRS duration to more than 160 ms, particularly when associated with lengthening PR interval, is a marker of very high risk in patients with dilated cardiomyopathy, and that this may be significantly reduced by pacemaker insertion. There are thus indications that pacing may improve impaired prognosis, another major manifestation of congestive heart failure.

Summary and commentary

(1) DDD pacing is not applicable in the majority of patients with dilated cardiomyopathy. However, in the 10–15% with a QRS duration of more than 140 ms, in whom mitral regurgitation lasts for more than 450 ms, and ventricular filling time is less than 200 ms, we have found DDD pacing to confer significant and prolonged haemodynamic benefit. It appears unimportant whether the underlying aetiology is ischaemic or idiopathic. The patients are usually elderly and so are unlikely to be treated with cardiac transplantation, even though control values of MVO₂ (mean 9 ml·min⁻¹·kg⁻¹) would qualify them for it.

(2) In the patients we have studied, the effects of pacing on left ventricular contraction have been invariable and immediate. In increasing peak dP/dt and in shortening the overall duration of left ventricular systole, its effects are similar to what it was once hoped would be achieved by positive inotropic drugs. However, tachyphylaxis does not seem to occur with pacing, and since the properties of individual myocytes are not affected, it seems unlikely that the other harmful effects of these drugs will become apparent. Prognosis may be improved rather than shortened by pacing.

(3) Patients are initially identified using simple non-invasive methods. PR interval and QRS duration should be determined by built-in software and not measured directly from the standard 12 lead ECG recorded at 25 mm·s⁻¹. On echo-Doppler, the critical determinations are those of time intervals rather than the amplitude of wall motion or the severity of regurgitation. Records must thus be made with this aim in view, on paper at 100 mm/s, and a simultaneous phonocardiogram. Recordings made at slow sweep speed on video tape without physiological markers are suboptimal. Furthermore, mechanical function will probably change with time after pacing has been initiated, implying mechanical as well as electrical follow-up.

(4) Other clearly defined reasons for treating patients with dilated cardiomyopathy by pacemaker may be identified in future. However, there seems little to be gained by the practice of implanting pacemakers into unselected patients with dilated cardiomyopathy in the hope of unspecified benefit. Not surprisingly, the results have been disappointing. Pacemaker manipulation of abnormal electromechanical interrelations is precise and predictable, and represents a new field of therapy for patients with ventricular disease. It must be exploited by careful analysis of the disturbances that it is hoped to treat followed by documentation that these effects have been achieved. Only in this way will it achieve its full potential.

Key points

(1) DDD pacing is not applicable to the majority of patients with dilated cardiomyopathy, and should not be undertaken without specific indication.

(2) In a minority (10–15%), usually those with prolonged PR interval and QRS duration >140 ms, functional mitral regurgitation may be so prolonged (<450 ms) that it occupies up to 90% of the total RR interval, reducing ventricular filling time to less than 200 ms.

(3) In such patients, short atrioventricular delay DDD pacing from right atrial and right ventricular electrodes confers prompt and consistent haemodynamic benefit by reducing the duration of mitral regurgitation. Exercise capacity increases by up to 50%, both short and long term.

S. J. D. BRECKER
D. G. GIBSON
Royal Brompton Hospital, London, U.K.

References


Myocardial hibernation: adaptation to ischaemia

The concept of hibernation

When severely reduced coronary blood flow persists for more than 20 min, myocardial necrosis begins to develop and contractile function is eventually irreversibly lost. When myocardial ischaemia is more moderate, the myocardium can remain viable for a longer period of time, and although contractile function is reduced, it recovers upon reperfusion. In patients with coronary artery disease, chronic contractile dysfunction, which is reversible upon reperfusion, is termed myocardial hibernation.[1]

The term hibernation has been borrowed from zoology and implies that the observed reduction in contractile function is an adaptive and regulatory event acting to preserve viability. The concept of hibernation was developed entirely on clinical grounds, but quickly gained support from experimental studies.

Mechanisms of acute ischaemic contractile dysfunction

Following acute reduction of coronary blood flow, contractile function in the ischaemic region rapidly (within a few cardiac cycles) ceases. However, reduction in myocardial ATP as the underlying mechanism for the rapid reduction in contractile function has been ruled out, since (1) contractile dysfunction occurs prior to changes in myocardial ATP, and (2) the result of myocardial ATP loss should be rigor of the myofibril rather than the observed loss of wall tension. Mechanisms which have been proposed, but not unequivocally proven, include a reduction in the free energy change in ATP hydrolysis, a decreased rephosphorylation rate of cytosolic ADP from creatine phosphate, the development of intracellular acidosis, accumulation of inorganic phosphate or impairment of sarcoplasmic calcium transport kinetics, which again may be pH- or ATP-dependent (for review see[2]).

Transition from an imbalance between supply and demand towards myocardial hibernation

Within the first few seconds following acute reduction of myocardial blood flow, energy demand by the hyperperfused myocardium clearly exceeds the reduced energy supply. However, this imbalance between energy supply and demand is an inherently unstable condition since contractile function and