

Physiological changes in ventricular filling alter cardiac electrophysiology in patients with abnormal ventricular function

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Objective: To explore the hypothesis that patients with abnormal ventricular function have an altered electrophysiological response to physiological changes in ventricular filling which is not evident in people with normal ventricles.

Design: The influence of an acute alteration in ventricular filling on dispersion of repolarisation, measured as QT dispersion, was examined in subjects with normal ($n = 9$) and abnormal ventricles ($n = 9$). A physiological reduction in ventricular filling was achieved using dual chamber atrioventricular (AV) pacing in two different modes—AV pacing: atrial activation 120 ms before ventricular activation such that atrial contraction occurred normally in late diastole; and VA (ventriculoatrial) pacing: atrial activation 50 ms after ventricular activation, such that atrial contraction occurred after closure of the AV valves. The absence of effective atrial contraction was confirmed by echocardiography. Ventricular cycle length and sequence of excitation through the ventricle was constant throughout both VA and AV sequences within each patient.

Results: During AV pacing (normal ventricular filling) there was no significant difference in QT dispersion between the two groups. In contrast during VA pacing, when the atrial component to ventricular filling was abolished, there was an immediate and consistent increase in QT dispersion compared with baseline in subjects with abnormal ventricular function ($p < 0.001$) but not in those with normal ventricles.

Conclusions: An abrupt change in ventricular filling, within the physiological range, increased QT dispersion in subjects with abnormal ventricular function but not in subjects with normal ventricles. The findings suggest an altered electrophysiological response to ventricular load in patients with abnormal ventricular function.

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Sudden arrhythmic death continues to account for up to 50% of deaths in patients with abnormal ventricular function,¹ both regional and global. The reasons for this remain unclear. There has been much interest in the tendency for mechanical perturbations of the myocardium to produce transient electrophysiological changes, which might predispose to arrhythmias. This mechanoelectric feedback² is thought to be particularly important in patients with abnormal ventricles, where stress-strain relations may be distorted.³ To date, evidence for a pathological role remains elusive.

In this paper we present data supporting the hypothesis that physiological changes in ventricular loading induce electrophysiological changes in patients with either regional or global impairment of ventricular function, but not in their normal counterparts. The study was undertaken using a dual chamber pacing protocol that allowed the timing of atrial systole to be varied relative to ventricular systole. The timing and sequence of ventricular excitation was held constant throughout. QT dispersion was used as a measure of the inhomogeneity of repolarisation. This allowed the electrophysiological consequences of removing effective atrial contraction to be explored and compared with baseline in each patient. A consistent increase in QT dispersion was found in patients with abnormal ventricles but not in those with normal ventricular function.

METHODS

Patients

Patients were recruited from those undergoing elective cardiac catheterisation for the investigation of known or suspected coronary artery disease or cardiomyopathy. The study was

approved by the local ethics committee, and all patients studied gave their written informed consent. Patients in atrial fibrillation and those on antiarrhythmic treatment other than β adrenergic blockers were excluded. Usual drug treatment was otherwise continued.

Eighteen subjects were studied: nine had normal ventricular function—that is, no evidence of global or regional wall motion abnormalities (mean ejection fraction 74%, range 65–85%)—while nine had evidence of impaired left ventricular function. This group comprised eight patients with evidence of regional wall motion abnormalities spanning a range of ejection fractions (16–58%, mean 36%) and one patient with no regional wall motion abnormality but globally impaired function, with an ejection fraction of 30%.

Pacing protocol

Following the diagnostic cardiac catheterisation, bipolar temporary pacing wires were positioned in the right atrium and right ventricular apex. Atrioventricular (AV) pacing, with an AV interval of 120 ms, was begun at 5–10 beats above the resting heart rate for at least two minutes to achieve a steady state, and was designed to maintain the atrial contribution to ventricular filling. The pacing was then abruptly changed to ventriculoatrial (VA) pacing (VA interval 50 ms) for three beats, which maintained the ventricular cycle length but delayed the atrial contraction so that this occurred after the closure of the atrioventricular valves. This was designed to remove the atrial component of ventricular filling. Twelve lead ECGs were recorded at 50 mm/s using a simultaneously acquiring MAC VU system during steady state AV pacing and immediately after the change to VA pacing.

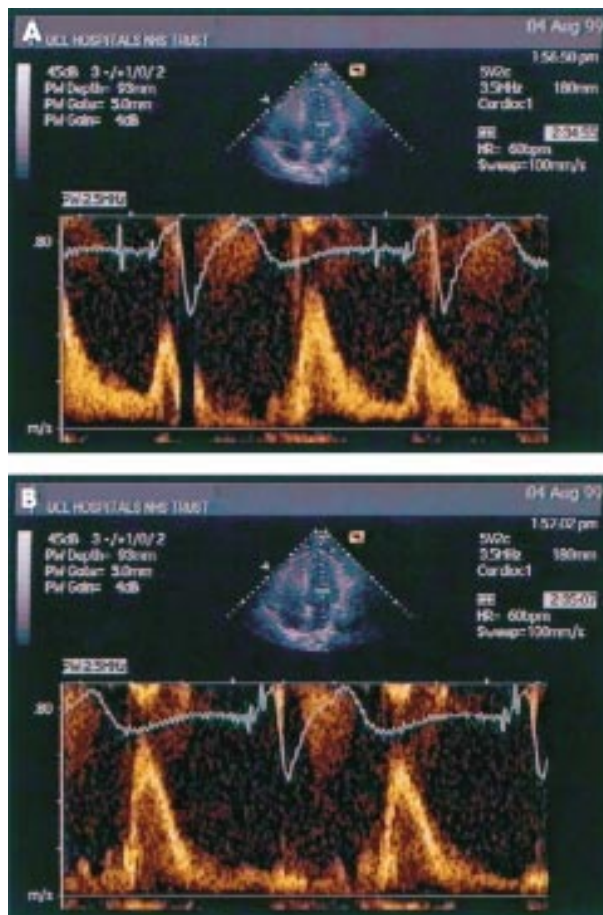


Figure 1 Pulsed wave Doppler sampling of the left ventricular inflow during atrioventricular (AV) pacing (panel A) and ventriculoatrial (VA) pacing (panel B). (A) During AV pacing, the flow is biphasic, comprising the E wave of early ventricular filling followed by a period of diastasis and then the A wave of atrial systole. (B) During VA pacing, the E wave of early ventricular filling only is seen. The A wave of atrial systole is lost because atrial contraction occurs against a closed mitral valve.

Transthoracic echocardiography

We used transthoracic echocardiography to confirm the anticipated loss of effective atrial contraction with the switch from AV to VA pacing. Left ventricular inflow was examined by pulsed wave Doppler. This confirmed the presence of both the E wave, corresponding to early filling, and the A wave of atrial systole (fig 1A) during AV pacing and loss of the A wave with the switch to VA pacing (fig 1B). These changes were confirmed using M mode echocardiography (not shown).

QT dispersion measurement

Individual QT intervals were measured manually by a single investigator in three consecutive beats during AV pacing and in the three beats during VA pacing. QT dispersion was calculated as the greatest interlead difference in the QT interval for each beat⁴ and the average of three beats was calculated. A sample of ECG tracings was assessed by another observer (blinded to the protocol and its rationale) to assess interobserver variability. The mean interobserver difference in QT dispersion was 3.6 ms.

Ventricular function and regional wall motion abnormality

We assessed the presence or absence of a regional wall motion abnormality from the ventriculogram at angiography, but formal scoring of regional wall motion was not undertaken. We

Table 1 Individual patient details

Patient	CAD	Regional wall motion abnormality	Ejection fraction
<i>Normal group</i>			
1	2 vessel	Nil	0.74
2	2 vessel	Nil	0.81
3	Nil	Nil	0.73
4	1 vessel	Nil	0.67
5	2 vessel	Nil	0.65
6	2 vessel	Nil	0.72
7	2 vessel	Nil	0.78
8	1 vessel	Nil	0.75
9	1 vessel	Nil	0.85
<i>Abnormal group</i>			
1	3 vessel	Inferior akinesis	0.58
2	2 vessel	Anterior hypokinesis	0.51
3	3 vessel	Anterior hypokinesis, inferior akinesis	0.28
4	3 vessel	Anterior hypokinesis	0.17
5	3 vessel	Anterior hypokinesis	0.32
6	Nil	Global hypokinesis	0.30
7	2 vessel	Anterior hypokinesis, inferior akinesis	0.40
8	2 vessel	Inferior akinesis	0.47
9	3 vessel	Anterior hypokinesis	0.16

CAD, coronary artery disease.

calculated the ejection fraction at the time of angiography using Simpson's method. Echocardiography was undertaken at the time of the studies to verify the absence of the atrial component of ventricular filling during the test beats in the pacing protocol.

Statistical analysis

For statistical analysis we used the parametric two sample *t* test and the non-parametric Mann-Whitney test. As the results were similar for both analyses, probability values using the parametric method are presented. A value of $p < 0.05$ was considered to be significant.

RESULTS

At baseline there was no difference in QT dispersion between subjects with evidence of impaired function and those with normal ventricles (45.9 v 44.4 ms, NS) (fig 2). The abrupt physiological alteration in ventricular filling was then induced by changing the timing of atrial relative to ventricular contraction such that atrial contraction was delayed until after the closure of the AV valves, thereby removing the atrial component of ventricular filling and the likely reduction in ventricular filling. This was confirmed on echocardiography by loss of the A wave, seen during baseline AV pacing, with the switch to VA pacing. This manoeuvre resulted in an immediate increase in QT dispersion (compared with baseline values) in

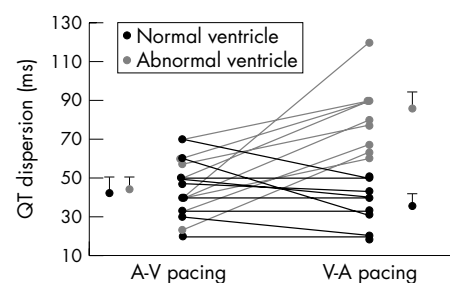


Figure 2 When load changes within the physiological range are employed using VA pacing to abolish atrial transport, QT dispersion increases in subjects with abnormal left ventricular function but not in those with normal function ($p < 0.001$). Mean data are shown, with standard errors.

the group of subjects with abnormal ventricles (from 45.9 to 81.9 ms, $p < 0.001$) but not in those with normal ventricles (44.4 to 36.2 ms, NS) (fig 2). There was no significant difference in QT dispersion between beats 1, 2, and 3. The differential responses of the two groups to the load change was consistent and significant ($p < 0.001$) (fig 2). There was no evidence of wall motion abnormality in any of the subjects in the normal group. In contrast, eight of the subjects in the abnormal group had regional wall motion abnormalities. The remaining patient had severe global impairment (patient 6, table 1).

DISCUSSION

In this study we showed that an abrupt change (presumed reduction) in ventricular filling consistently produced increases in QT dispersion in subjects with abnormal ventricular function but not in those with normal function. The study was designed to explore the hypothesis that patients with abnormal ventricular function may show an altered electrophysiological response to physiological changes in ventricular filling. In order to investigate this, we employed a dual chamber pacing protocol that enabled the atrial component of ventricular filling to be manipulated on a beat by beat basis, thereby reducing ventricular filling on selected beats. We suggest that the likely explanation for the findings is an effect of mechanoelectric feedback.

It has long been established that the atrial contribution to ventricular filling is variable,^{5,6} ranging between 11–40%,^{7,8} and is dependent on ventricular function. Typically it is those patients with abnormal ventricular function who are most dependent upon atrial contraction to complete ventricular filling.^{9,10} It follows that if this component is lost, as for example with the onset of atrial fibrillation¹¹ or with an early ectopic beat, ventricular filling may be significantly reduced. The protocol we used was designed to explore the electrophysiological consequences of this loss to ventricular filling by abruptly removing the atrial component from one beat to the next, and to allow comparison with an electrophysiological baseline during the normal pattern of filling in each patient. The loss of the atrial component was confirmed using Doppler echocardiography (fig 1B). The protocol was intended to ensure that other factors that might influence QT dispersion were absent or minimal. In particular, the ventricular cycle length was held constant throughout the protocol in each patient, at 5–10 beats above the patient's usual resting heart rate, to eliminate cycle length or rate dependent effects on QT intervals (including tachycardia induced ischaemia in patients with coronary artery disease). The ventricular sequence of excitation was also constant in each individual patient. The abolition of atrial transport was effected from one beat to the next and maintained for three beats only. This was designed to ensure that any haemodynamically mediated reflex changes that might have resulted from more sustained manipulations did not contribute to the results, while allowing a mean of three measured values to be obtained.

It is not possible to exclude the contribution of neurogenic reflexes to our results, as an interaction between stretch and autonomic nerve endings and mechanoelectric feedback has been demonstrated,¹² and sympathetic innervation and tone may be altered in abnormal ventricles. Ischaemia would be an implausible explanation for our findings as baseline and test beat measurements were made on consecutive beats during a pacing protocol which maintained the heart rate at a rate only a few beats above the patient's resting rate. While the absence of any quantitative assessment of the changes in ventricular filling limits the interpretation of our findings on a mechanistic level, the results nevertheless show consistent differences between the two groups of patients.

In order to achieve the controlled volume changes associated with the loss of atrial transport, it was necessary to

pace the ventricles throughout the study. Thus all measures of QT dispersion were undertaken during ventricular pacing. To our knowledge there are no published data describing "normal" values of QT dispersion during ventricular pacing. However, it is known that altering activation sequence results in minimal change to local monophasic action potentials and local ECG measures of QT intervals. The value of QT dispersion in our patient groups during baseline (AV) pacing was similar to previous work using atrial pacing.¹³ Furthermore, in this study, QT dispersion at baseline did not differ significantly between the two groups (44.4 v 45.9 ms), in contrast to the dramatic increase in QT dispersion in the abnormal group but not in the control group following altered load (81.9 v 36.2 ms, respectively, $p < 0.001$). The mean interobserver variability of QT dispersion in this study was low compared with our own previous work^{13,14} and that of others in studies where measurements were made during normal sequences of ventricular excitation. This is likely to reflect the greater ease with which it is possible to define the end of the T wave during ventricular pacing.

A possible explanation for our findings is mechanoelectric feedback, whereby changes in myocardial loading alter the electrophysiology.^{2,15} Mechanical perturbations have been shown to either lengthen or shorten action potential duration (or refractory periods), depending on the nature and timing of the stimulus.^{16–20} The underlying mechanisms involve either stretch activated channels or calcium cycling.^{21,22} In humans, mechanoelectric feedback alters action potential duration within one beat of an abrupt change in load,²³ and the effects of load alteration on ventricular repolarisation have been shown to be heterogeneous.¹⁵ An altered dispersion of repolarisation may then be reflected in changes in QT dispersion. Much of the work demonstrating mechanoelectric feedback has involved severe stretch,²⁴ whereas physiological changes in loading in humans²⁵ have resulted in such modest changes in action potential duration that it has been suggested that they may be clinically irrelevant.²⁶ In contrast under pathological conditions, such as in patients with impaired left ventricular function, these changes may be magnified and clinically significant. During changes in ventricular loading, diastolic wall stress is the main determinant of altered action potential.²⁷ Wall stress in the left ventricle is affected by regional differences in circumference, wall thickness, and compliance, any of which may be modified heterogeneously in patients with either global or regional wall motion abnormalities. The regional wall motion abnormalities in our patients were all caused by ischaemic heart disease, and our findings are in keeping with earlier animal work from Calkins and colleagues.²⁸

An important aspect of the present study is that the electrophysiological change, which was only observed in patients with abnormal ventricles, occurred in response to a magnitude of load change that can occur spontaneously in patients. Interestingly these electrophysiological changes occurred in response to a protocol which employed a reduction in filling or "destretch" rather than the more usual strategy of an increase in filling or stretch. However, this approach is not without precedent,^{22,29} and data relating to an earlier study³⁰ showed that during the institution of cardiopulmonary bypass, unloading the ventricle lengthened epicardial action potential duration (P Taggart, unpublished observations).

Extensive experimental evidence links enhanced dispersion of repolarisation with serious and fatal ventricular arrhythmias.³¹ It is possible that the loss of the atrial component to ventricular filling which normally accompanies a premature ventricular beat may increase the dispersion of repolarisation in patients with abnormal left ventricular function but not in those with normal function. Similarly, the development of atrial fibrillation in patients with impaired left ventricular function might be expected to produce beat by beat changes in QT dispersion, and it is of interest that new

onset atrial fibrillation in this patient group heralds a poor prognosis, for reasons that have not been fully explained. In both clinical contexts, an increase in dispersion of repolarisation would enhance the substrate for re-entry. Our results support such a hypothesis and are consistent with the concept of a pathological role for mechanoelectric feedback in patients with impaired left ventricular function.

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C J McMahon, H G El Said, C E Mullins

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occluder to avoid "bunching up" of the device and residual transatrial shunting.

(*Heart* 2002;**88**:e3) www.heartjnl.com/cgi/content/full/88/2/e3

Endovascular stent repair for a dissecting thoracoabdominal aneurysm in the setting of a district general hospital: a multidisciplinary approach

M J S Zaman, V Carre, S Parvin, D Shepherd, J Radvan

A patient presented to a district general hospital with a type B dissection of the aorta. He was deemed too unwell for surgical intervention. An endovascular stent repair was successfully carried out. The case shows that such a procedure can be safely performed by a multidisciplinary team within a district general hospital.

(*Heart* 2002;**88**:e4) www.heartjnl.com/cgi/content/full/88/2/e4