Haemodynamic and catecholamine response to simulated ventricular tachycardia in man: effect of baseline left ventricular function

T M Kolettis, E Psarros, Z S Kyriakides, C S Katsouras, L K Michalis, D A Sideris

Heart 2003;89:306–310

See end of article for authors' affiliations

Correspondence to:
Dr T M Kolettis, University
of Ioannina, University
Campus, 1 University
Avenue, 45110 Ioannina,
Greece; thkolet@cc.uoi.gr

Accepted 28 August 2002

Objective: To examine the effects of baseline left ventricular function on the haemodynamic and catecholamine responses to ventricular tachycardia.

Design: Experimental cohort study.

Setting: Cardiac catheterisation laboratory in tertiary referral centre.

Subjects: 24 patients (19 male, 5 female; mean (SD) age, 59 (10) years) without coronary artery disease, divided into two groups with normal or impaired left ventricular function: group A, ejection fraction > 65% (n = 10); group B, ejection fraction < 45% (n = 14). Other medical and demographic factors were similar in the two groups.

Interventions: Ventricular tachycardia was simulated with rapid pacing at 150 beats/min for 10 minutes.

Main outcome measures: Arterial blood pressure; venous plasma catecholamine concentrations.

Results: During rapid pacing, blood pressure was lower in group B (with impaired left ventricular function) than in group A: systolic blood pressure, 102 (11) v 115 (9) mm Hg (p = 0.005); mean blood pressure, 79 (6) v 85 (6) mm Hg (p = 0.02). The ejection fraction correlated with the lowest systolic blood pressure (r = 0.64, p = 0.0006). Although the rise in adrenaline was comparable between the two groups, the rise in noradrenaline was more pronounced (p < 0.05) in patients in group B.

Conclusion: At low rates and in selected patients, the underlying state of left ventricular function affects haemodynamic tolerance of ventricular tachycardia. Patients with impaired left ventricular function have a lower blood pressure during ventricular tachycardia, despite an exaggerated noradrenaline release.

Ventricular tachycardia is a common arrhythmia with a poor prognosis.^{1,2} It is characterised by eccentric ventricular activation at a rapid rate. Sustained ventricular tachycardia produces significant alterations in left ventricular haemodynamics, but the resultant change in arterial blood pressure varies widely, from a minimal fall to severe collapse and death.² Although several factors predicting a syncope response have been implicated,³ the exact pathophysiological mechanisms of haemodynamic embarrassment during ventricular tachycardia are not fully understood.

Patients with poor left ventricular function from coronary artery disease or idiopathic dilated cardiomyopathy are at risk of sustained ventricular tachycardia. In clinical practice, it is often assumed that the more impaired the function of the left ventricle, the more severe the hypotension occurring during the arrhythmia. However, this assumption is not supported by clinical or experimental data.

During ventricular tachycardia, various compensatory mechanisms come into play and may explain the differences in the hypotensive response. One such mechanism is the liberation of catecholamines into the blood circulation. However, previous studies on the pattern of catecholamine activation during and after ventricular tachycardia have produced contradictory results.^{4–8} This probably reflects the heterogeneity of the patient populations and differences in the mode of termination of the tachycardia in the various studies.

We aimed to investigate the effect of baseline left ventricular function on haemodynamic responses and catecholamine activation during and after sustained ventricular tachycardia in a homogeneous patient population.

METHODS

Patients

We screened patients who were on the waiting list for diagnostic cardiac catheterisation and electrophysiological study for their suitability for study. Potential candidates were identified as those in sinus rhythm who fell into one of two categories, based on echocardiography within the preceding three months: those with normal left ventricular function (group A) and those with impaired left ventricular function but without any history of myocardial infarction (group B). Patients in New York Heart Association (NYHA) functional class IV were excluded, as were those who had been on amiodarone or a β blocker within one month of entry to the study. Patients with diabetes mellitus, autonomic neuropathy, hypertrophic cardiomyopathy, or valvar heart disease were also excluded.

All drugs were discontinued 24 hours before the study. Informed consent was obtained before recruitment, and the protocol was approved by the hospital ethics committee.

All patients underwent contrast left ventriculography, coronary arteriography, and electrophysiological study, as clinically indicated. The indications for electrophysiological study were: supraventricular tachycardia (1), tachycardia-bradycardia syndrome (6), sinus pauses and/or sinus bradycardia (7), idiopathic ventricular fibrillation (1), dizziness with atrioventricular conduction abnormalities (5), and non-sustained ventricular tachycardia (4). Atropine or isoprenaline (isoproterenol) were not used and no patient required cardioversion during the procedure.

All studies were undertaken in the fasting state, without the use of premedication. The standard percutaneous Seldinger technique was used to gain access to the femoral

vein and femoral artery. Patients with significant coronary artery disease were excluded from the study. For the purposes of this study, "significant coronary artery disease" was defined as any degree of stenosis in the left main stem, or stenosis of over 50% in the diameter of any other coronary vessel.

Patients were enrolled in the study if they had a left ventricular ejection fraction above 65% (group A, normal left ventricular function), or below 45% (group B, depressed left ventricular function). Left ventricular ejection fraction was measured from contrast ventriculography in the 30° right anterior oblique projection. Left ventricular silhouettes at end diastole and end systole were traced from digital images, and the ejection fraction was calculated using computer assisted analysis (Hycor TOP, version 1.5, Siemens, Munich, Germany). When extrasystoles were present, care was taken to analyse a cardiac cycle at least two beats after the last extrasystole.

Protocol

Fifteen minutes after completion of the cardiac catheterisation and the electrophysiological study, a 30 second ventricular pacing burst was given at a rate of 150 beats/min. As atrio-ventricular synchrony is an important determinant of the haemodynamic response during ventricular tachycardia,^{7,9} patients with intact ventriculoatrial conduction at that rate were excluded from the study. In patients with atrioventricular asynchrony after this initial test, continuous rapid pacing was then applied from the right ventricular apex at a rate of 150 beats/min for 10 minutes. Arterial blood pressure was recorded from the arterial sheath and venous blood was obtained from the indwelling sheath for measurement of plasma catecholamines. Data were obtained at baseline, at the first, fifth, and 10th minute of pacing, and at the first, fifth, and 10th minute after termination of pacing. Blood samples for measurement of plasma noradrenaline (norepinephrine) and adrenaline (epinephrine) concentrations were collected in lithium heparin tubes, centrifuged immediately, and stored at -20°C until assayed by high performance liquid chromatography with electrochemical detection.¹⁰ The normal limits of circulating noradrenaline and adrenaline in rested supine volunteers in our laboratory are 275–413 pg/ml and 77–115 pg/ml, respectively.

At the first, fifth, and 10th minute after termination of pacing, a three lead ECG was recorded at a paper speed of 100 mm/s, and the RR interval calculated from the average of three consecutive intervals.

"Steady state" values of systolic and mean blood pressure during (simulated) ventricular tachycardia were calculated as the average of values at the first, fifth, and 10th minute of rapid ventricular pacing. Steady state recovery values of systolic and mean blood pressure were calculated as the average of the values at first, fifth, and 10th minute after termination of pacing. The peak hypotensive response was calculated as the percentage of the maximum fall in systolic blood pressure during rapid pacing with respect to baseline.

Statistics

Differences between two variables were compared using Student's *t* test for independent variables, while differences between three or more variables were compared using analysis of variance for repeated measures followed by Tukey's HSD multiple comparisons test. Linear correlations between variables were determined and Pearson's correlation coefficient was calculated. All statistical analyses were performed using "Statistical" software (version 5, 1998 edition, StatSoft Inc, Tulsa, Oklahoma, USA). Values are expressed as mean (SD). Significance was defined at an α level of 0.05.

RESULTS

Patient population

We studied 24 consecutive patients who fulfilled the entry criteria. The normal left ventricular function group (group A) consisted

Table 1 Baseline characteristics of the two patient groups

	Normal LV (n=10)	Depressed LV (n=14)	p Value
Age (years)	56 (14)	61 (6)	NS
Sex (male/female)	8/2	11/3	NS
Ejection fraction (%)	69 (3)	28 (8)	0.0001
Noradrenaline (pg/ml)	408 (165)	474 (113)	NS
Adrenaline (pg/ml)	92 (26)	130 (77)	NS

Values are mean (SD) or n.
LV, left ventricle.

of 10 patients (eight men, two women; mean (SD) age 56 (14) years), mean ejection fraction 69 (3)%. The *impaired left ventricular function* group (group B) consisted of 14 patients (11 men, three women; age 61 (6) years), mean ejection fraction 28 (8)%. The discharge diagnosis in all group B patients was idiopathic dilated cardiomyopathy. In this group, one patient was in NYHA functional class III, six were in class II, and seven were in class I. Apart from the ejection fraction, the baseline characteristics were comparable between the two groups (table 1). As probably anticipated, patients with depressed left ventricular function tended to have higher resting heart rates (lower RR interval) and lower arterial blood pressure. However, none of these differences reached significance.

Blood pressure

During rapid ventricular pacing, no patient from either group experienced dizziness or syncope. However, the blood pressure response to simulated ventricular tachycardia differed significantly between the two groups (fig 1). Systolic blood pressure immediately (by the first minute of rapid ventricular pacing) became lower in group B (with impaired left ventricular function) than in group A. This difference remained significant throughout rapid pacing until the fifth minute after the termination of pacing. Similarly, mean blood pressure was significantly lower during rapid ventricular pacing in group B than in group A; this difference became non-significant at the first minute after the termination of pacing.

Steady state systolic blood pressure during simulated ventricular tachycardia also differed between the two groups, at 115 (9) mm Hg in group A v 102 (11) mm Hg in group B ($p = 0.005$); equivalent values for steady state mean blood pressure were 85 (6) mm Hg in group A and 79 (6) mm Hg in group B ($p = 0.02$).

During rapid ventricular pacing, the maximum per cent fall in systolic blood pressure—that is, the peak hypotensive response—was 7 (4)% in group A and 14 (5)% in group B ($p = 0.001$).

Figure 1 Systolic and mean blood pressure response (at first, fifth, and 10th minute of simulated ventricular tachycardia, and the first, fifth, and 10th minute post-termination), in patients with normal left ventricular function (filled circles) and impaired left ventricular function (empty circles). *Significant difference between the two groups ($p < 0.05$). LV, left ventricular; p, post.

Figure 2 Correlations between ejection fraction and systolic blood pressure for all study patients. (A) Correlation between ejection fraction and lowest recorded systolic blood pressure during simulated ventricular tachycardia. (B) Correlation between ejection fraction and maximum hypotensive response, expressed as per cent fall in systolic blood pressure compared with baseline. (C) Correlation between ejection fraction and “steady state” systolic blood pressure (see text for explanation). EF, ejection fraction; max, maximum; SBP, systolic blood pressure; sVT, simulated ventricular tachycardia.

During the recovery phase, blood pressure was not significantly different between the two groups. Steady state recovery values for systolic blood pressure were 133 (10) mm Hg in group A and 124 (12) mm Hg in (group B) ($p > 0.05$). The corresponding values for mean blood pressure were 96 (5) and 92 (6) mm Hg, respectively ($p > 0.1$).

Blood pressure versus ejection fraction

The blood pressure response correlated significantly with the left ventricular ejection fraction (fig 2). There was a significant positive correlation between the ejection fraction and the lowest systolic blood pressure recorded during simulated ventricular tachycardia (fig 2A). Expressed in a different way, there was a significant negative correlation between the ejection fraction and the peak hypotensive response (fig 2B). Similarly, there was a significant positive correlation between the ejection fraction and the steady state values of systolic blood pressure during simulated ventricular tachycardia (fig 2C).

Catecholamines versus ejection fraction

There was a negative correlation between the changes in noradrenaline (expressed as per cent increase with respect to baseline) and the ejection fraction. This correlation was significant at the first minute after the onset of simulated ventricular tachycardia ($r = -0.43$, $p = 0.031$) and at the fifth minute of recovery ($r = -0.45$, $p = 0.024$). In contrast, no significant correlation was found between the changes in adrenaline and the ejection fraction.

RR interval

The mean values for RR interval at the first, fifth, and 10th minute after termination of the rapid pacing were as follows: group A (normal left ventricular function), 723 (102) ms, 803 (91) ms, and 860 (77) ms, respectively; group B (impaired left ventricular function), 715 (59) ms, 757 (77) ms, and 799 (84) ms, respectively. Although there was a trend towards a

lower mean RR interval (higher heart rate) in group B by the 10th minute after termination of pacing, none of the observed differences in the RR interval reached significance.

Plasma catecholamine concentrations

These data are given in table 2.

Adrenaline

With respect to baseline values, plasma adrenaline concentrations showed a significant rise during simulated ventricular tachycardia in both groups (overall effect: $F = 5.18$, $p = 0.00007$; group A: $F = 4.27$, $p = 0.001$; group B: $F = 3.04$, $p = 0.01$). There were no significant differences in adrenaline concentrations between the two groups at any time point during the study (fig 3A).

Noradrenaline

With respect to baseline values, plasma noradrenaline concentrations also showed a significant rise during simulated ventricular tachycardia in both groups (overall effect: $F = 12.80$, $p < 0.00001$; group A: $F = 9.77$, $p < 0.0001$; group B: $F = 7.54$, $p < 0.0001$). Both during and after rapid ventricular pacing, plasma noradrenaline values were higher in group B (with impaired left ventricular function) than in group A ($p < 0.05$). This difference was evident at the fifth minute of simulated ventricular tachycardia and was present until the 10th minute of recovery (fig 3B).

DISCUSSION

Ventricular tachycardia is a malignant arrhythmia, but, unlike ventricular fibrillation, its occurrence is not invariably associated with haemodynamic collapse.^{1,2} Some patients tolerate sustained ventricular tachycardia long enough for them to receive appropriate medical care, while in others syncope occurs immediately after the onset of the arrhythmia. Thus haemodynamic tolerance of sustained ventricular tachycardia determines arrhythmic mortality.

Table 2 Plasma catecholamine values (pg/ml) at baseline and during and after simulated ventricular tachycardia

		Duration of tachycardia (min)			Time after discontinuing tachycardia (min)		
	Baseline	1	5	10	1	5	10
<i>Adrenaline</i>							
Group A	92 (26)	109 (25)	132 (28)*	127 (17)*	133 (20)*	129 (32)*	112 (28)
Group B	130 (77)	157 (69)	189 (95)*	188 (114)*	179 (94)	147 (36)	148 (53)
<i>Noradrenaline</i>							
Group A	408 (165)	389 (180)	470 (142)	481 (106)*	482 (85)*	393 (87)	384 (137)
Group B	474 (113)	533 (189)	632 (202)*	644 (218)*	625 (201)*	574 (133)*	530 (119)

Values are mean (SD).

* $p < 0.05$ v baseline values.

Group A, normal left ventricular function; group B, depressed left ventricular function.

Figure 3 Plasma catecholamine concentrations (pg/ml) (at the first, fifth, and 10th minute of simulated ventricular tachycardia, and the first, fifth, and 10th minute post-termination), in patients with normal left ventricular function (filled circles) and impaired left ventricular function (empty circles). *Significant difference between the two groups ($p < 0.05$). (A) Plasma adrenaline. (B) Plasma noradrenaline. LV, left ventricular; p, post.

Although the rate of the tachycardia has been identified as the most important determinant of haemodynamic stability,^{2 3 11 12} symptoms can vary widely in different patients with identical tachycardia rates. Thus a constellation of other variables plays an additional role. These include “central” factors (that is, variables related to the heart) and “peripheral” factors (variables involved in arterial vasoconstriction)).^{2 3 7 13}

Effect of baseline left ventricular function on ventricular tachycardia tolerance

Central variables include the temporal relation between atrial and ventricular systole, the severity of valvar regurgitation, the severity of myocardial ischaemia, and the extent of ventricular asynchrony during the tachycardia.^{2 7 9 12 14 15} In contrast, the importance of baseline left ventricular function on the haemodynamic tolerance of ventricular tachycardia has been debated.^{2 3 11}

We compared the haemodynamic response to simulated sustained ventricular tachycardia in two groups of patients: a group with normal left ventricular function (with an ejection fraction above 65%) and a group with depressed left ventricular function (with an ejection fraction below 45%). Our results show that baseline left ventricular function has a significant effect on the haemodynamic tolerance of ventricular tachycardia, in that patients with depressed left ventricular function had a lower blood pressure than patients with normal function during a simulated ventricular tachycardia of 150 beats/min. Although this is in accord with common clinical belief, surprisingly it has never been demonstrated before.

Two previous reports have failed to show a significant impact of baseline left ventricular function on the response to sustained ventricular tachycardia.^{3 11} Hamer and colleagues reported a lack of significant correlation between the resting left ventricular ejection fraction and blood pressure during ventricular tachycardia³; however, a direct comparison between patients with preserved and impaired left ventricular function was not undertaken, as all the patients they studied had structural heart disease with an ejection fraction of less than 50%. Lima and colleagues,¹¹ in a cohort similar to ours, reported comparable blood pressure responses in the two groups. To explain their findings, they elegantly showed that distinct mechanisms of hypotension occur, depending on left ventricular function in sinus rhythm: in patients with normal left ventricular function, incomplete relaxation during ventricular tachycardia is the dominant mechanism, while in patients with impaired left ventricular function, hypotension occurs because of incoordinate contraction. We feel that our results are not incompatible with those of Lima and colleagues, for two reasons. First, in our study the rate of ventricular tachycardia was much lower than in Lima's study, and it can be assumed that at higher tachycardia rates differences in blood pressure responses between patients with different degrees of left ventricular function would be smaller. Second, differences between the two groups did exist in Lima's study: the “impaired left ventricular function” group had a comparable blood pressure response but at a significantly lower tachycardia rate (193 v 235 beats/min).

Catecholamine release during ventricular tachycardia

The peripheral responses to sustained ventricular tachycardia consist of two phases^{4-7 13 16}:

- a rapid initial phase, which comes into play during the first 30 seconds of ventricular tachycardia; this phase is probably mediated by arterial baroreflexes and results in stimulation of α adrenoreceptors
- a more gradual, catecholamine dependent response, involving not only α mediated vasoconstriction, but also “central” β adrenergic positive inotropic stimulation.

In response to any physiological stress, liberation of catecholamines occurs into the circulation. Although the significance of catecholamine activation during ventricular tachycardia is well established, previous studies have yielded contradictory results.⁴⁻⁸ They showed increases in adrenaline or noradrenaline alone,⁴⁻⁶ in both catecholamines,⁷ or in neither.⁸ The main reason for this discrepancy appears to be the variable use of cardioversion as a means of tachycardia termination.⁸ For this reason it was our aim to examine the neuroendocrine response to ventricular tachycardia without the confounding effects of sympathetic stimulation post-cardioversion. We used rapid ventricular pacing, which produces equivalent haemodynamic changes to spontaneous or induced ventricular tachycardia,¹² and can be immediately terminated without overdrive pacing or external countershock.

We report significant increases in both catecholamines in both groups of patients. Such increases were evident at the fifth minute after the onset of tachycardia and returned to baseline values by the 10th minute post-termination of pacing. We believe that our results add to the current understanding of the haemodynamic response to ventricular tachycardia because—in contrast to previous reports⁴⁻⁸—first, all our study patients were in a drug-free state, and particularly were off amiodarone and β blockade; second, apart from differences in left ventricular function which were present by study design, all our patients were carefully selected to form a population with relatively uniform characteristics; and third, the use of rapid ventricular pacing as a simulator of ventricular tachycardia not only obviates the need for cardioversion, but also confers identical tachycardia characteristics, namely the heart rate and site of origin.

Our study also addressed the relation between left ventricular function and the magnitude of catecholaminergic activation during ventricular tachycardia. We report significantly higher plasma noradrenaline concentrations in patients with impaired left ventricular function. Patients with heart failure have increased adrenergic nerve outflow and raised plasma noradrenaline.^{17 18} More importantly, during comparable levels of exercise, much greater increases in circulating noradrenaline have been reported in patients with heart failure than in normal subjects.¹⁹ Our study indicates that a similar phenomenon may occur as a result of hypotension caused by ventricular tachycardia.

The lack of significant differences in plasma adrenaline between our two groups is more difficult to explain. It can be postulated that, as a response to ventricular tachycardia, the adrenal medulla is activated to a similar extent in patients

with varying left ventricular function, and hence that the plasma adrenaline concentrations are comparable. In contrast, the more pronounced rise in plasma noradrenaline during ventricular tachycardia in patients with poor left ventricular function may be the result of an increased release²⁰ and a reduced uptake²¹ of noradrenaline from adrenergic nerve endings, and its consequent spillover into the plasma.

Study limitations

Some limitations to our study are apparent. First, it was performed with the patients in the resting, supine position; thus our findings may not apply to patients with an episode of sustained ventricular tachycardia in the erect position or during exercise. Second, pacing was undertaken at relatively low rates, because it was felt that rapid pacing at higher rates would have increased the risk of induction of ventricular fibrillation. Third, the effects of rapid atrial pacing were not examined. It would have been interesting to compare the neuroendocrine response during atrial and ventricular tachycardia at identical rates. Fourth, our study examined only the plasma catecholamines, as they have a central role in the neurohumoral reflexes during ventricular tachycardia. However, other substances, such as atrial natriuretic factor, brain natriuretic factor, dopamine, and cortisol, may also be involved.^{5,6} The effects of these agents during ventricular tachycardia have not been well established and should be the subject of future research. Finally, only patients with dilated cardiomyopathy were examined. However, the haemodynamic response to ventricular tachycardia may be different in patients with segmental wall motion abnormalities caused by previous myocardial infarction.

Clinical significance

In recent years, several trials have indicated that in patients with a past history of sustained ventricular tachyarrhythmias, implantable cardioverter-defibrillators offer a better prognosis than medical treatment.²² More importantly, data from those studies have shown that the more depressed the left ventricular function, the greater the benefit from the defibrillator.^{23,24} These data are being validated in primary prevention trials—that is, in patients without a history of sustained ventricular arrhythmias.²⁵ Our results, extrapolated to patients with poor left ventricular function, provide further arguments in favour of the prophylactic implantation of cardioverter-defibrillators. It can be inferred that patients with depressed left ventricular function are not only at greater risk of having an episode of sustained ventricular tachycardia, but in that event, they are also at greater risk of syncope and death. However, further research is necessary before clinical recommendations can be made. Furthermore, the effects of vasodilators, β blockers, and antiarrhythmic drugs—which may alter the haemodynamic response to ventricular tachycardia—need to be evaluated.

Conclusions

The haemodynamic consequences of sustained ventricular tachycardia occur through several mechanisms. Our results indicate that, at relatively low tachycardia rates, the underlying state of left ventricular function affects the haemodynamic response to the arrhythmia. Patients with impaired left ventricular function have a lower blood pressure during ventricular tachycardia, despite an exaggerated noradrenaline release.

ACKNOWLEDGEMENTS

We acknowledge the invaluable help of Mr Anastasios Papalambrou RN in relation to the data collection.

.....

Authors' affiliations

T M Kolettis, C S Katsouras, L K Michalis, D A Sideris, Department of Cardiology, University of Ioannina, Ioannina, Greece
E Psarros, Z S Kyriakides, Onassis Cardiac Surgery Centre, Athens, Greece

REFERENCES

- 1 Josephson ME, Horowitz LN, Spielman SR, et al. Electrophysiologic and hemodynamic studies in patients resuscitated from cardiac arrest. *Am J Cardiol* 1980;**46**:948–55.
- 2 Steinbach KK, Merl O, Frohner K, et al. Hemodynamics during ventricular tachyarrhythmias. *Am Heart J* 1994;**127**:1102–6.
- 3 Hamer AWF, Rubin SA, Peter CT, et al. Factors that predict syncope during ventricular tachycardia in patients. *Am Heart J* 1984;**107**:997–1005.
- 4 Morady F, Halter JB, Di Carlo LA, et al. The interplay between endogenous catecholamines and induced ventricular tachycardia during electrophysiologic testing. *Am Heart J* 1987;**113**:227–34.
- 5 Cohen TJ, Liem B. Neuroendocrine responses of ventricular tachycardia in humans. *Am Heart J* 1991;**121**:1816–18.
- 6 Twidale N, Rayner TE, Menadue M, et al. Atrial natriuretic factor release during rapid ventricular pacing: Interplay between autonomic and hemodynamic stimulants. *Am Heart J* 1993;**125**:1638–44.
- 7 Peuhkurinen KJ, Uusimaa PA, Ruskoaho H, et al. Hemodynamic recovery, atrial natriuretic peptide and catecholamines during simulated ventricular tachycardia: effects of ventriculoatrial conduction. *Pacing Clin Electrophysiol* 1995;**18**:75–82.
- 8 Morady F, DiCarlo LA, Halter JD, et al. The plasma catecholamines response to ventricular tachycardia induction and external countershock during electrophysiologic testing. *J Am Coll Cardiol* 1986;**8**:584–91.
- 9 Maloney J, Khoury D, Simmons T, et al. Effect of atrioventricular synchrony on stroke volume during ventricular tachycardia in man. *Am Heart J* 1992;**123**:1561–8.
- 10 Smedes F, Kraak JC, Poppe H. Simple and fast solvent extraction system for selective and quantitative isolation of adrenaline, noradrenaline and dopamine from plasma and urine. *J Chromatogr* 1982;**231**:25–39.
- 11 Lima JAC, Weiss JL, Guzman PA, et al. Incomplete filling and incoordinate contraction as mechanisms of hypotension during ventricular tachycardia in man. *Circulation* 1983;**68**:928–38.
- 12 Saksena S, Ciccone JM, Craelius W, et al. Studies of left ventricular function during sustained ventricular tachycardia. *J Am Coll Cardiol* 1984;**4**:501–8.
- 13 Feldman T, Carroll JD, Munkenbeck F, et al. Hemodynamic recovery during simulated ventricular tachycardia: role of adrenergic receptor activation. *Am Heart J* 1988;**115**:576–87.
- 14 Burkhoff D, Sagawa K. Influence of pacing site on canine left ventricular force–interval relationship. *Am J Physiol* 1986;**250**:H414–18.
- 15 Kolettis TM, Kyriakides ZS, Popov T, et al. Importance of the site of ventricular tachycardia origin on left ventricular hemodynamics in man. *Pacing Clin Electrophysiol* 1999;**22**:871–9.
- 16 Ellenbogen KA, Smith ML, Thames MD, et al. Changes in regional adrenergic tone during sustained ventricular tachycardia associated with coronary artery disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1990;**65**:1334–8.
- 17 Leimbach WN, Wallin BG, Victor RG, et al. Direct evidence from intrarenal recordings for increased central sympathetic outflow in patients with heart failure. *Circulation* 1986;**73**:913–19.
- 18 Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the studies of left ventricular dysfunction (SOLVD). *Circulation* 1990;**82**:1724–9.
- 19 Colucci WS, Ribeiro JP, Rocco MB, et al. Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization. *Circulation* 1989;**80**:314–29.
- 20 Hasking GJ, Esler MD, Jennings GL, et al. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation* 1986;**73**:615–21.
- 21 Liang CS, Fan TH, Sullebarger JT, et al. Decreased adrenergic neuronal uptake activity in experimental right heart failure. A chamber-specific contributor to beta-adrenoceptor downregulation. *J Clin Invest* 1989;**84**:1267–75.
- 22 Cappato R. Secondary prevention of sudden death: the Dutch study, the antiarrhythmics versus implantable defibrillator trial, the cardiac arrest study Hamburg, and the Canadian implantable defibrillator study. *Am J Cardiol* 1999;**83**:68–73D.
- 23 Domanski MJ, Saksena S, Epstein AE, et al. Relative effectiveness of the implantable cardioverter-defibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias. AVID Investigators (antiarrhythmics versus implantable defibrillators). *J Am Coll Cardiol* 1999;**34**:1090–5.
- 24 Sheldon R, Connolly S, Krahn A, et al. Identification of patients most likely to benefit from implantable cardioverter-defibrillator therapy: the Canadian implantable defibrillator study. *Circulation* 2000;**101**:1660–4.
- 25 Klein H, Auricchio A, Reek S, et al. New primary prevention trials of sudden cardiac death in patients with left ventricular dysfunction: SCD-HEFT and MADIT-II. *Am J Cardiol* 1999;**83**:91–7D.