Arrhythmogenic effect of ventriculography in patients with left ventricular dilation and/or hypertrophy

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ABSTRACT

1. This study examined the effect of an acute injection of contrast medium on generation of arrhythmias in diseased hearts in man.

2. Subjects were 100 patients in sinus rhythm undergoing cardiac catheterization in whom good quality echocardiograms could be obtained. The subjects comprised 78 males and 22 females aged 37–83 years.

3. Arrhythmia induced by left ventricular angiography ranged from nil to brief bursts of ventricular tachycardia. There was a strongly positive relationship between left ventricular internal dimension in diastole (LVIDd) and induced arrhythmia. Out of 26 patients, 25 developed arrhythmia when LVIDd ≥ 5 cm (96%) but only 24 out of 74 patients developed arrhythmia when LVIDd < 5 cm (32%) (P < 0.001). In non-dilated hearts where K⁺ < 4.0 mmol/l, arrhythmia developed in 100% (10 out of 10) of those with left ventricular hypertrophy (LVH), but in only 40% (8 out of 20) without LVH (P < 0.005). Where K⁺ ≥ 4.0 mmol/l, no arrhythmia occurred in patients with LVH but was present in 52% (31 out of 60) of patients without LVH (P < 0.005). There were no relationships with age, end-diastolic pressure, blood pressure, ischaemic heart disease or sex of patient.

4. These data support the view that acute injection of contrast medium in humans induces arrhythmias dependent upon the underlying state of the heart, with potentially complex interplay between left ventricular dimension, hypertrophy and potassium status, supporting similar observations in experimental animals.

INTRODUCTION

There are many factors which contribute to the pathogenesis of ventricular arrhythmia. Ischaemic heart disease is one of the commonest causes but other causes include aortic valve disease, drugs, cardiomyopathies, electrolyte disturbances and autonomic influences, as in the prolonged Q–T syndrome [1]. In some cases clearly more than one factor is responsible; for example, the synergistic action between drugs and electrolytes in the pathogenesis of ventricular tachycardia [2–4]. It is now well recognized that the vulnerability of the heart itself

Key words: arrhythmia, left ventricular dilation, left ventricular hypertrophy, potassium.
Abbreviations: LVH, left ventricular hypertrophy; LVIDd, left ventricular internal dimension in diastole; LVMI, left ventricular mass index.
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may vary [5] while there is also accumulating evidence in both human and animal studies that increases in ventricular loading are arrhythmogenic.

In many cardiac conditions associated with sudden cardiac death, ventricular wall stress is increased [6]. Arrhythmias are highly prevalent in both aortic stenosis and aortic incompetence [7–9] and both of these conditions lead to elevated wall stress [10,11], although by different mechanisms; aortic stenosis by increased intraventricular pressure, and aortic incompetence by left ventricular dilation. Other studies have shown that the mortality rates of coronary heart disease are increased among patients with dilated and poorly contracting left ventricles when compared with patients with more normal left ventricular function [12,13]. Severity of coronary heart disease has not been shown to correlate with occurrence of, or survival from, sudden cardiac death in the absence of left ventricular dilation [14].

In theory, left ventricular hypertrophy (LVH) ought to reduce ventricular wall stress according to the law of Laplace, but LVH is itself a strong predictor of subsequent cardiac events including sudden cardiac death [15]. The work of Loaldi et al. [16] has shown that treatment which lowers wall stress in patients with hypertension can produce a parallel reduction in ventricular arrhythmia. Treatment with potassium-depleting diuretic drugs is a possible causative factor of ventricular arrhythmia and sudden death [17,18]. We have shown previously, in both animal and human studies, that the arrhythmogenic potential of LVH may be dependent on serum cations such as K+ and Mg2+[19,20].

While the effect of increased loading has been studied in a variety of in vitro and in vivo animal experiments [20], there have been very few studies in humans. Taggart et al. [21,22] have shown potentially arrhythmogenic action potential changes produced by increases in wall stress while Sideris et al. [23] showed that ventricular ectopics could be produced by acute increases (metaraminol infusion) and abolished by acute reductions (nitorprusside infusions) in blood pressure. The present study, therefore, was undertaken to further investigate the possible arrhythmogenic effect of an acute left ventricular load in patients with a variety of different cardiac diseases and with various degrees of left ventricular dilation and/or hypertrophy.

**METHODS**

**Subjects**

The study was performed on 100 patients with cardiac disease undergoing cardiac catheterization over a 7-month period. Within this group, 77 had coronary artery disease, 12 had pure aortic stenosis, 4 had pure aortic regurgitation, 4 had mixed aortic valve disease, 2 had mitral regurgitation and 1 had coarctation of the aorta. All patients were considered suitable for the study provided they were not on any specific anti-arrhythmic drugs, although all patients were on a variety of different cardiac drugs including diuretics and angiotensin-converting enzyme inhibitors (24%), nitrates (77%), calcium channel blockers (37%) and β-blockers (26%) but not digoxin. In no patient had any of the drugs, especially β-blockers, been prescribed for anti-arrhythmic indications but rather for hypertension and/or angina. We found no correlation between induced arrhythmia and therapy with any given agent. The protocol was approved by the hospital ethics committee and informed consent was obtained from all subjects.

**Echocardiography**

An echocardiogram was performed on every patient either immediately or, in a few cases to save repetition, within a few weeks before catheterization. Where all the necessary measurements could not be obtained at echocardiography the patients were excluded from the study (approximately 20%). All echocardiograms were performed by an experienced operator and subsequently checked by a consultant cardiac radiologist.

Subjects were studied using standard M-mode echocardiograms. An ALOKA SSD 870 machine with a transducer of 3.5 MHz was used, and in more than 90% of cases two-dimensional imaging using conventional parasternal short- and long-axis views was performed in addition to M-mode studies to make the recordings. In order to obtain accurate measurements of left ventricular internal dimension, part of the mitral valve apparatus was included on the record as recommended by Feigenbaum [24]. Left ventricular wall thickness was measured as the distance between the inner surface of the endocardium and the outer surface of the epicardium. The left ventricular internal dimension (LVIDd) was measured as the distance between the endocardium of the interventricular septum and that of the posterior wall. Both measurements were made in diastole at the onset of the R wave of the ECG. We chose to use echocardiograms for measurements of left ventricular dimensions because left ventricular wall thickness could also be measured at the same time. The subjects remained in stable sinus rhythm throughout the examination.

Left ventricular mass (LVM) was calculated using the modified (Penn convention) formula [25]:

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LVM = 1.04 [(\text{IVST} + \text{LVIDd} + \text{PWT})^3 - \text{LVIDd}^3] - 13.6 \text{ g}
\]

where LVIDd is left ventricular internal dimension in diastole, PWT is posterior wall thickness and IVST is interventricular septal thickness. It has been shown that LVM calculated using the Penn formula correlates closely with necropsy LVM (r = 0.91, P < 0.001). Twenty patients had LVH using this measurement. In addition
we also measured left ventricular mass index (LVMI) in our patients and used upper limits of normal of 134 g/m² for men and 110 g/m² for women [25]. Twenty-seven patients showed an increase in LVMI, of whom seven had left ventricular dilation. Because the Penn formula loses its high correlation with direct anatomical studies when muscle asymmetry, aneurysm formation or right ventricular overload is present, patients with electrocardiographic, echocardiographic or angiographic evidence of significant infarction were excluded. In consequence, left ventricular shape was relatively normal in virtually all the patients in this study.

Cardiac catheterization
All investigations were performed by a single operator and each angiogram was performed in an identical manner in all patients. A right femoral artery approach was used after subcutaneous injection of 10 ml of 2% lignocaine. One hour before the procedure each patient was given diazepam, 10 mg orally. A 6 F angled pigtail catheter was inserted through a sheath. The catheter was advanced to the ascending aorta before being introduced into a stable position in the mid left ventricle. Stable sinus rhythm before injection of the contrast medium was required as a final entry criterion for the patient to be included in the study.

Left ventricular angiograms were performed in approximately the 30° RAO projection with 40 ml of iopamidol (Niopam®) warmed to 37 °C and injected at a rate of 15 ml/s with a 0.5 s rise time. It was, of course, more difficult to cross the aortic valve in patients with aortic stenosis but in no patients were alternative catheters or exchange wire techniques used to insert the pigtail catheter into the appropriate position in the left ventricle. The ECG was continuously recorded on to paper throughout the procedure and any deviation from sinus rhythm taken as arrhythmia. If the pigtail catheter had failed to remain in a stable position during angiography the patient would have been excluded from the study. However, with very careful positioning of the catheter and using a small angled pigtail, no patient had to be excluded for possible mechanical or catheter-induced arrhythmia. The ECGs were analysed in a blind fashion and at a later date to the time of left ventricular angiography or echocardiography. Serum K⁺ was measured using a Hitachi 717 analyser (coefficient of variation 0.9% at a K⁺ concn. of 4.24 mmol/l) and all data were stored for statistical analysis on a personal computer.

Statistical methods
Parametric and non-parametric statistical methods were employed for analysis of results. Differences in the frequencies of discrete variables were tested by χ² tests (with Yates Correction) where numbers were sufficiently large, but where numbers of observations were small Fisher’s exact test was employed. A P value of less than 0.05 was taken as significant.

RESULTS
Forty-nine subjects out of 100 (49%) developed arrhythmia (i.e. any deviation from sinus rhythm) during injection of contrast medium. In those developing arrhythmia a single ventricular ectopic beat occurred in 18%, more than one unifocal ventricular ectopic beat in 26%, and multifocal ventricular ectopics in 40%. Ventricular tachycardia (i.e. four or more consecutive ectopic beats, either monomorphic or polymorphic) was observed in 16% of subjects with arrhythmia. Contrast medium may itself be arrhythmogenic but each patient received exactly the same quantity and method of injection. Iopamidol is a non-ionic contrast medium with a low reported incidence of arrhythmias at cardiac angiography [26].

Relation between LVIDd and arrhythmia
There was a strongly positive relationship between LVIDd and induced arrhythmia. There were 25 patients out of 26 (96%) who developed arrhythmia when LVIDd was equal to or greater than 5 cm, but only 24 patients out of 74 (32%) developed arrhythmia when LVIDd was less than 5 cm (P < 0.001, χ² test). Increased LVIDd predisposed to arrhythmia in patients with both valvular and ischaemic heart disease. All 11 patients with valvular heart disease and LVIDd ≥ 5 cm exhibited arrhythmia. However, none of the 11 patients with valvular heart disease and LVIDd < 5 cm had arrhythmias (P > 0.001, χ² test). Of the patients with ischaemic heart disease, 14 out of 15 (93%) exhibited arrhythmia when LVIDd was ≥ 5 cm, but only 14 out of 62 (23%) had arrhythmia when LVIDd was < 5 cm (P < 0.001, χ² test).

Relationship between serum K⁺, LVH and arrhythmia
Serum K⁺ ranged from 3.1 to 5.1 mmol/l. There were 20 patients who had LVH and 80 who did not have LVH. Of the 20 patients with LVH, 10 (50%) developed arrhythmia while 10 patients had no arrhythmia, (P not significant). Of the patients who did not have LVH, 39 out of 80 (49%) exhibited arrhythmia while 41 out of 80 (51%) showed no arrhythmia (P not significant).

K⁺ was less than 4.0 mmol/l in 10 patients with LVH, and in all 10 of these patients arrhythmia was observed (100%). K⁺ was less than 4.0 mmol/l in 20 patients without LVH but only 8 of these patients exhibited arrhythmia (40%). Data presented in Figure 1 show that the presence of LVH significantly increased arrhythmia...
Of the 27 patients, 16 (59%) exhibited arrhythmia while when $K^+$ was increased, LVMI had arrhythmia while only one did not ($P < 0.005$). NS, not significant.

We chose to separate our patients into those with $K^+ \geq 4.0$ mmol/l or $K^+ < 4.0$ mmol/l because the range 3.7–3.9 mmol/l is the lowest 20% of our laboratory’s normal range (3.7–5.2).

Relationship between LVMI and arrhythmia
LVMI ranged from 60 to 280 g/m$^3$. Twenty-seven patients had an increased LVMI (8 female and 19 male). Of the 27 patients, 16 (59%) exhibited arrhythmia while 11 (41%) did not ($P$ not significant). However, when $K^+ < 4$ mmol/l, 12 out of 13 patients (92%) with increased LVMI had arrhythmia while only one did not ($P < 0.005$). When $K^+ \geq 4$ mmol/l, 4 out of 14 patients (29%) with increased LVMI had arrhythmia while 10 did not (71%) ($P$ not significant). There were no relationships between arrhythmias and age, end-diastolic pressure (either before or after injection of the contrast medium), blood pressure or sex. Coronary artery disease was common in the study patients (77%) but was randomly distributed throughout all groups and varied in severity, e.g., 19 had had previous myocardial infarction, and five previous coronary artery bypass grafting. There was no correlation between arrhythmia and coronary artery disease.

DISCUSSION
The results of this study have shown that during cardiac catheterization, performed in a standardized fashion, arrhythmia is frequently induced. However, arrhythmias do not seem to occur randomly but rather:

(i) in the presence of left ventricular dilation where LVIDd is equal to or more than 5 cm.

(ii) in the presence of LVH or increased LVMI when $K^+ < 4.0$ mmol/l.

We were not able to measure intracardiac pressures simultaneously with injection of contrast and we cannot be certain that the stimulus was identical in all groups. It is possible, for instance, that contrast itself affects dilated hearts differently from normal sized ventricles. Cardiac catheters can also have a direct effect in stimulating the heart but great care was taken to overcome any mechanical influence of the catheter itself. We feel it is probable that arrhythmias were induced in response to stretching of the left ventricle by the injection of contrast and the variation in the arrhythmic response observed was largely dependent on the condition of the hearts, e.g., LVH or left ventricular dilation, or on the level of serum $K^+$.

Previous studies have shown that patients with LVH exhibit more ventricular arrhythmias and that arrhythmias are inversely correlated to serum $K^+$.[18,27–29].

James and Jones [20] found that LVH in the rat heart, although protecting against wall-stress-induced arrhythmia at normal cation concentrations, rendered hearts extremely sensitive to arrhythmia during combined potassium and magnesium depletion, with a high incidence of ventricular fibrillation compared with normal rat hearts. Therefore, both clinical and experimental studies have concluded that arrhythmia is more prevalent in subjects with LVH in the presence of hypokalaemia [29]. Low $K^+$ hyperpolarizes the resting membrane potential and leads to shortening towards normal of the prolonged action potential seen in hypertrophied cells. Lowering $K^+$ may also partially inhibit the membrane Na$^+$–K$^+$ pump, leading to a rise of intracellular sodium which via the membrane Na$^+$–Ca$^+$ exchange will cause an increase of intracellular calcium [30]. Raised intracellular calcium has been widely implicated in arrhythmogenesis.

In this study we did not measure wall stress directly and intra-cavity pressure measurements would be required to do this. However the Law of Laplace states that increasing either intra-cavity pressure or intra-cavity volume increases wall stress. It seems reasonable to assume that wall stress is increased by left ventricular angiography and that, in line with other models, this is arrhythmogenic.

The most important finding of this study was the relationship between LVIDd and the increased susceptibility of hearts to induced arrhythmias. The pathophysiological mechanisms underlying such rhythm changes are unclear. However, Taggart and co-workers have investigated this extensively in animals and also in man [21,22]. They showed that in conscious patients at cardiac catheterization the Valsalva manoeuvre (which leads to increased ventricular loading) could influence myocardial repolarization, and that this was especially...
true if there was abnormal wall motion. In our patients we were not able to study regional wall motion abnormalities but this will form the basis of a future study. In an elegant review, Taggart et al. [31] have discussed the possible interaction between ventricular loading and repolarization in a variety of situations, e.g. where abnormal tissue might propagate electrical wavefronts at different rates to normal tissue when stretched and thus present a potential mechanism for re-entrant circuits. Altered cation levels, such as hypokalaemia, might lead to further changes in the propagation of wavefronts between normal and abnormal myocardium, e.g. ischaemic or hypertrophied tissue. We did look at the possible effect of hypokalaemia on patients with both LVH and dilation, but all patients with LVH, with or without dilated ventricles, developed arrhythmia when the $K^+$ was < 4.0 mmol/l. Similarly there was a high incidence of arrhythmia with dilation whether or not LVH was present. It was therefore not possible to come to any clear conclusion because, in addition, the numbers separated in this way were small.

An unexpected finding of the present study was that obstructive coronary artery disease was not associated with a higher incidence of arrhythmias in response to ventricular loading. This suggests that myocardial ischaemia resulting solely from impaired coronary blood flow may not be the primary mechanism involved. Because there was no overall correlation with ischaemic heart disease we did not subdivide the patients into those with single, two- or three-vessel disease. The clinical relevance, if any, of the present study remains to be determined but there are many physiological conditions associated with acute increases in ventricular loading, such as we have used here. These include coughing, straining, sudden isometric exercise and the abrupt increases in blood pressure associated with waking, REM sleep, or $K^+$ complexes on the EEG. It is of interest that the peak time of day for most cardiovascular events including sudden cardiac death is at around the time of wakening when blood pressure rises rapidly.

These results extend our previous observations in patients with untreated hypertension that, in the presence of LVH, even low normal or mildly hypokalaemic levels of $K^+$ may be clinically important [19].

CONCLUSIONS

In conclusion, catheter-induced arrhythmias were more prevalent in patients with LVH and serum $K^+ <$ 4.0 mmol/l than in patients with LVH and serum $K^+ ≥ 4.0$ mmol/l. The strongest relationship occurred between catheter-induced arrhythmias and cardiac dilation. Increase in LVMI was associated with arrhythmia in the presence of $K^+ <$ 4.0 mmol/l. An acute increase in ventricular loading (and therefore possibly wall stress) appears to be capable of stimulating ventricular arrhythmia regardless of the type of underlying heart disease. It remains to be seen what part more physiologically induced ventricular loading plays in inducing arrhythmias and in the possible aetiology of sudden cardiac death in man.

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