Arrhythmia and prognosis in hypertrophic cardiomyopathy

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KEY WORDS: Hypertrophic cardiomyopathy, sudden death, arrhythmia, amiodarone.

The natural history of hypertrophic cardiomyopathy is characterized by a slow progression of symptoms and by sudden death. Ventricular tachycardia is detected during electrocardiographic monitoring in 20 to 30% of patients; this arrhythmia is a sensitive but non-specific marker of those patients who are at particular risk of sudden death. Other specific prognostic features (e.g. anatomic and haemodynamic) to which preventive therapy could be directed remain to be identified. Episodes of supraventricular tachycardia or paroxysmal atrial fibrillation occur in 40—50% of patients and may cause troublesome symptoms. Propranolol, verapamil and conventional antiarrhythmic agents do not suppress serious ventricular arrhythmias or significantly reduce the incidence of paroxysmal supraventricular arrhythmias. The benzofuran derivative amiodarone was used in 24 patients with refractory arrhythmias. Ventricular tachycardia was controlled in 18 of 19, paroxysmal supraventricular arrhythmias were abolished and sinus rhythm was restored in four of eight patients with long-standing atrial fibrillation. These results were maintained for at least 1 year. Longer observation is required to determine if control of arrhythmia with amiodarone will improve prognosis.

Introduction

Hypertrophic cardiomyopathy is now defined as a heart muscle disorder of unknown cause which is characterized by unexplained left ventricular hypertrophy1,2. Recognition of the condition and understanding of the pathophysiology can be viewed in relation to the techniques available for clinical evaluation. Diagnosis was initially based on the clinical features and catheter demonstration of left ventricular gradients and the goal of medical and surgical therapy was their reduction or abolition3. Subsequently, following the widespread use of M-mode echocardiography, asymmetrical septal hypertrophy was emphasized and was considered to be the pathognomonic feature of the condition4; in addition, previously described abnormalities of relaxation and filling5,6 could be more readily studied. Since the advent of cross-sectional echocardiography the broader spectrum of hypertrophy, which has been appreciated by the pathologist, is now evident to the clinician7,8. From current clinical, cross-sectional echocardiographic and haemodynamic characterization of patients with hypertrophic cardiomyopathy it is apparent that: (1) the pattern of left ventricular hypertrophy is variable (Table 1); (2) left ventricular gradients have several causes (Table 2); (3) severe symptoms are uncommon9 and are associated with a spectrum of haemodynamic abnormalities (Table 3); and (4) serious ventricular arrhythmias are common10—12. Though systolic gradients, diastolic function and arrhythmias have received attention, the risk of sudden death is the most worrisome clinical feature associated with the diagnosis of hypertrophic cardiomyopathy13,14. The major challenge remains to predict those patients at particular risk of sudden death in order to determine preventive medical and/or surgical therapy.

The clinical profile of the high risk patient has been partly ascertained9,11,12. A family history of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patterns of left ventricular hypertrophy determined by cross-sectional echocardiography in patients with hypertrophic cardiomyopathy</th>
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</thead>
<tbody>
<tr>
<td>Asymmetric septal</td>
<td>55%</td>
</tr>
<tr>
<td>Upper anterior septum</td>
<td>15%</td>
</tr>
<tr>
<td>Anterior and posterior septum</td>
<td>30%</td>
</tr>
<tr>
<td>Septum and free wall</td>
<td>55%</td>
</tr>
<tr>
<td>Symmetric</td>
<td>30%</td>
</tr>
<tr>
<td>Distal-ventricular</td>
<td>15%</td>
</tr>
</tbody>
</table>
Table 2 Causes of a left ventricular gradient in hypertrophic cardiomyopathy

- Outflow tract obstruction due to systolic anterior motion of the anterior or posterior mitral leaflet
- Obstruction in the mid cavity with prominent papillary muscles
- End-systolic cavity elimination
- Catheter entrapment

Table 3 Haemodynamic abnormalities in hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>71 patients without ventricular tachycardia</th>
<th>29 patients with ventricular tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Percentage</td>
<td>Number</td>
</tr>
<tr>
<td>Hyperdynamic contraction</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>Impaired contraction</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Impaired relaxation and filling</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>True obstruction</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>6</td>
<td>23</td>
</tr>
</tbody>
</table>

Ventricular arrhythmia

The incidence of arrhythmia was determined from ambulatory electrocardiographic monitoring; in hypertrophic cardiomyopathy this is a more sensitive means than exercise testing for exposing important arrhythmias\(^\text{[15]}\). Twenty-nine of 100 consecutive patients had at least one episode of ventricular tachycardia during 3 days of electrocardiographic monitoring. Of these, the majority had frequent as well as complex ventricular extrasystoles; such arrhythmias were rarely seen in patients who did not have ventricular tachycardia (Table 4). The characteristics of the episodes of ventricular tachycardia were assessed from 135 episodes recorded from 30 patients during an average of 6 days of electrocardiographic monitoring. Most episodes occurred during periods of relative vagotonia, 40% between midnight and 08.00 H. The maximum heart rate was 110 to 220, mean 140 beats/min. The episodes were invariably of short duration (3 to 27 beats, mean 8) and in the 15 patients who experienced more than one episode the morphology was usually multiform (Fig. 1).

An exception to these characteristics was seen in a patient with moderate upper septal and free wall hypertrophy who developed recurrent uniform episodes of sustained rapid ventricular tachycardia. A morphologically identical tachycardia to that recorded during electrophysiological stimulation; the earliest endocardial activation during mapping was from an akinetic area near the apex of the left ventricle. This patient, with symptomatic, sustained ventricular tachycardia arising from a single focus, is unusual in our experience of hypertrophic cardiomyopathy. Most patients with hypertrophic cardiomyopathy

Table 4 Ventricular arrhythmia detected during 72 h ambulatory electrocardiographic monitoring in patients with and without ventricular tachycardia

<table>
<thead>
<tr>
<th>Arrhythmia Type</th>
<th>Number Without Tachycardia</th>
<th>Percentage Without Tachycardia</th>
<th>Number With Tachycardia</th>
<th>Percentage With Tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular extrasystoles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (&lt;30/h)</td>
<td>63</td>
<td>89</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td>2 (&gt;30/h)</td>
<td>8</td>
<td>11</td>
<td>16</td>
<td>55</td>
</tr>
<tr>
<td>3a (multiform)</td>
<td>21</td>
<td>30</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3b (uniform pairs)</td>
<td>12</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 (multiform and pairs)</td>
<td>6</td>
<td>8</td>
<td>23</td>
<td>80</td>
</tr>
</tbody>
</table>
experience episodes of ventricular tachycardia which are multiform and are neither sustained nor associated with symptoms.

As ventricular tachycardia in hypertrophic cardiomyopathy seldom causes symptoms, the importance of this arrhythmia is mainly prognostic. The factors which determine whether ventricular tachycardia will sustain or degenerate into fibrillation are unknown. When the results of two independent prospective studies were combined\(^{(11,12)}\) (Table 5), 13 of 169 patients died suddenly or experienced cardiac arrest during an average follow up of 3 years; of these, nine had ventricular tachycardia. The fact that this arrhythmia was more common in those who died suddenly (\(P<0.001\)) indicates that ventricular tachycardia is a marker of poor prognosis in hypertrophic cardiomyopathy; however, a causal relation between ventricular tachycardia and sudden death has not yet been shown.

**Supraventricular arrhythmia**

Supraventricular arrhythmias are also common in hypertrophic cardiomyopathy. Seven per cent of patients are in established atrial fibrillation at the time of diagnosis. During the next 5 years a further 7% can be expected to develop this arrhythmia\(^{(19)}\); this is a poor prognostic feature, particularly in children in whom it is associated with death due to low output cardiac failure. Though established atrial fibrillation and paroxysmal supraventricular arrhythmias are more common in patients with ventricular tachycardia and in those who die suddenly, the correlations between these arrhythmias and events are weak. Short episodes of supraventricular tachycardia or paroxysmal atrial fibrillation do not usually cause symptoms; however, sustained episodes may be accompanied by systemic emboli or marked haemodynamic deterioration.

The potential for accessory pathway conduction of atrial arrhythmias to initiate ventricular fibrillation has received attention. James and Marshall have noted the persistence of a fetal pattern of AV junctional histology in 13 of 22 patients with asymmetric septal hypertrophy who died suddenly\(^{(16)}\). They have emphasized that such tissue may provide accessory routes for the short-circuiting of atrioventricular conduction. Though the Wolff-Parkinson-White syndrome is rare in hypertrophic cardiomyopathy (approximately 2%), an accessory pathway capable of anterograde conduction may exist in the absence of pre-excitation (i.e. concealed). We have reported such a patient with hypertrophic cardiomyopathy who developed accessory pathway conduction and ventricular tachycardia which degenerated to ventricular fibrillation\(^{(17)}\). At post mortem she had fragmentation of the central fibrous body providing multiple atrioventricular connections. Such patients, however, are rare and rapid atrioventricular conduction is unlikely to be a common mechanism precipitating sudden death.

**Treatment of arrhythmia**

The mortality associated with serious ventricular arrhythmia in hypertrophic cardiomyopathy is
sufficiently high to warrant therapeutic intervention. Vigorous treatment must ultimately be based on the demonstration of improved prognosis following the suppression of ventricular arrhythmia. These arrhythmias are usually asymptomatic and the administration of medications which are associated with unwanted effects would not otherwise be justified. β-Adrenergic blocking agents, which are effective in the treatment of chest pain and dyspnoea, when used in moderate dose (mean 280 mg daily) do not reduce the incidence of ventricular arrhythmia. They may, however, be effective when administered in high dose (mean 460 mg daily) in combination with conventional antiarrhythmic agents.

Recently verapamil has been recommended for the treatment of symptoms in hypertrophic cardiomyopathy. Following the suggestion that some ventricular arrhythmias may be slow channel dependent, the demonstration that verapamil suppressed late depolarizations and triggered activation, we assessed the antiarrhythmic effects of verapamil in 19 patients with refractory supraventricular and ventricular arrhythmia. Three of the patients (16%) developed pulmonary oedema, and there was an increase in the number of patients with frequent and complex ventricular extrasystoles and ventricular tachycardia during verapamil therapy. Haemodynamic deterioration following verapamil has been observed in larger series and it has been difficult to predict which patients are at particular risk from this complication.

In our experience conventional agents (quinidine, mexiletine, disopyramide) when used alone or in combination with moderate doses of β-blockers are poorly tolerated and unsuccessful in achieving a sustained abolition of serious ventricular arrhythmia in patients with hypertrophic cardiomyopathy. Amiodarone is available in Great Britain for the treatment of refractory arrhythmia. We have assessed its efficacy during short- and long-term therapy in 24 patients with hypertrophic cardiomyopathy and refractory arrhythmia. Nineteen of the patients had ventricular tachycardia and had previously failed to respond to conventional antiarrhythmic therapy with either mexiletine, disopyramide or quinidine. Of eight patients with established atrial fibrillation, three had a poorly controlled ventricular rate despite β-adrenergic blockers and digoxin; two further patients had troublesome paroxysmal atrial fibrillation. All received a loading dose of 800–1200 mg daily for 1 week, followed by a maintenance dose of 400 mg daily for 1 month; the optimal dose was then selected based on the presence of side effects and the degree of arrhythmia control as assessed by electrocardiographic monitoring. Eleven continued on 400 mg, 11 received 200 mg and two required 600 mg daily. After 1 week on amiodarone the number of patients with frequent and complex ventricular extrasystoles and the number with ventricular tachycardia was markedly reduced (Fig. 2); these results were maintained at 1 month and were slightly improved after 1 year. Longer observation is required to determine whether suppression of ventricular arrhythmia with amiodarone will prevent sudden death.

Paroxysmal supraventricular arrhythmias were virtually abolished during amiodarone (Fig. 3).

![Figure 2](http://example.com/figure2.png)

*Figure 2* Ventricular arrhythmia detected during 72 h ambulatory electrocardiographic monitoring in 24 patients with and without amiodarone. VES = ventricular extrasystoles.
Episodes of supraventricular tachycardia and of paroxysmal atrial fibrillation were suppressed and sinus rhythm was restored in four of eight patients with long-standing atrial fibrillation. This occurred after 6 months in one and during the loading period in three; in three of the four, sinus rhythm has been maintained with amiodarone 200 mg daily. In those patients who remained in atrial fibrillation, control of the ventricular response was achieved. The beneficial haemodynamic effects of such changes require objective assessment but are of particular interest in hypertrophic cardiomyopathy where diastolic filling is a major determinant of systolic performance. In addition the effectiveness of amiodarone in treating paroxysmal supraventricular arrhythmia suppresses an otherwise troublesome therapeutic problem and if sustained control is demonstrated may obviate the need for anticoagulants. As amiodarone potentiates the effect of warfarin, if patients require anticoagulants careful monitoring of prothrombin time must be performed until steady state amiodarone therapy is achieved. The final warfarin requirement is usually reduced by approximately 50% (24). Amiodarone also interacts with digoxin, increasing plasma digoxin levels, though probably not tissue levels (25). Approximately 15% of our patients with hypertrophic cardiomyopathy receive digoxin for cardiac failure or for the control of the ventricular response in atrial fibrillation. The concomitant administration of amiodarone and digoxin should lead to the reduction of the latter by approximately half.

Unwanted effects during treatment with amiodarone are common. Some of these (corneal microdeposits, photosensitivity and skin pigmentation, sleep disturbance, tremor and elevation of hepatic transaminases) are dose-duration dependent, whereas others (pulmonary alveolitis, clinical thyroid disease and peripheral neuropathy) appear to reflect variable patient susceptibility (26). Though troublesome symptoms, particularly sleep disturbance, tremor and photosensitivity, may develop in up to 30% of patients during the initial 3 months of amiodarone therapy, they can usually be alleviated by reducing the dose without loss of arrhythmia control. Serious clinical unwanted effects are uncommon and are reversible.

Preliminary studies using radionuclide assessment of left ventricular function show that amiodarone does not alter systolic function and may improve indices of filling in patients with hypertrophic cardiomyopathy. Though amiodarone was originally developed and marketed in Belgium and France as an anti-anginal agent, we have observed no consistent symptomatic effect in patients with hypertrophic cardiomyopathy and chest pain. Propranolol is usually our drug of choice for the treatment of dyspnoea or chest pain; when these symptoms coexist with refractory arrhythmia we have used amiodarone and propranolol together without complication. This combination must, however, be used with caution in patients with sino-atrial or atrioventricular node disease; the same constraint also applies to the combination of verapamil and amiodarone.

References

(1) Maron BJ, Epstein SE. Hypertrophic cardiomyopathy: recent observations regarding the


Rothlin I would like to make two points on this very interesting observation on your series. First, in Switzerland we have sun in winter as well as in the summer and we are very used to the fact that British tourists have much more sunburn than the Swiss have. I believe this concerns mainly your Celtic tourists have much more sunburn than the Swiss. Now, concerning your data, I was interested in seeing that your maintenance dose was rather high, with 400 and even 600 mg a day. I wonder whether you could comment a little bit more in detail on how you tried to reduce the dosage and which were your criteria to stay at such a high maintenance dose.

McKenna First of all I would like to make an important correction. Eleven of the 24 patients were on 200 mg a day and 11 on 400 mg, with only two...
receiving 600 mg daily. These patients were treated relatively early on in our experience with amiodarone. Currently we are using a loading dose of 800 mg daily which dramatically reduces the sleep disturbance and gastrointestinal problems. In elderly patients we may even reduce the loading dose to 600 mg daily. The selection of an appropriate maintenance dose is on somewhat of a trial and error basis. We evaluate patients after 1 month on 400 mg daily. If the arrhythmia persists, then we would prefer to add another drug (usually a class 1B agent) rather than increase the dose of amiodarone. In our experience most of the clinically important side effects occur in patients receiving 600 mg or more of amiodarone daily.

Kuhn First, what is your policy now? Could we go on to treat patients with amiodarone or should we wait first for results of a control trial? Secondly, have you observed patients who developed severe arrhythmia under amiodarone therapy because of a side effect, as was described in the literature, and did you look for pulmonary fibrosis?

McKenna I will respond to your question regarding the side effects of amiodarone first. We have over 200 patients who have received amiodarone for at least 1 year, and in none of these have we observed exacerbation of supraventricular or ventricular arrhythmia. At the recent American Heart Association meeting, however, McGovern presented four patients who appeared to develop incessant ventricular tachycardia while on amiodarone therapy. I am unable to recall the specifics of these cases and whether or not these arrhythmias were actually made worse on amiodarone. In one patient with ventricular tachycardia who received amiodarone we have observed incessant VT following programmed stimulation. However, the tachycardia was much slower, though of identical morphology to that observed during control studies. We have never observed worsening of ventricular arrhythmia which we could attribute to amiodarone.

The association of pulmonary alveolitis in a minority of patients receiving amiodarone is confusing. The English experience in a large number of patients followed over the past 3 to 5 years would suggest that pulmonary alveolitis is extremely rare. However, the recent American literature has included reports suggesting up to a 10% incidence. The reason for this discrepancy is unclear but may relate to differences in the patient populations receiving amiodarone and to marked differences in the dosage used. In general American experience has been with much higher doses (e.g. 600 to 1000 mg daily) and many of the patients who have developed pulmonary alveolitis have also been in cardiac failure with high filling pressures. This association, however, is important and requires further evaluation. From a practical point of view we perform baseline chest X-rays and pulmonary function tests, but we would not repeat them serially unless some clinical indication developed.

Your question regarding a controlled trial is important. Our preliminary data suggests that in patients with hypertrophic cardiomyopathy and ventricular tachycardia amiodarone may improve prognosis. The ethics and the need for a controlled trial in such patients depends upon one’s interpretation of the existing data. Briefly summarized, this data shows control of ventricular tachycardia in 32 of 33 patients with amiodarone therapy. On the basis of a predicted annual mortality in such patients of 10%, five or more deaths would have been expected; none have occurred. The extrapolation of this data to other ‘high risk’ patients with hypertrophic cardiomyopathy is also important and has wide ranging implications. We are at present in the process of organizing a controlled, randomized study comparing propranolol and amiodarone therapy in such patients.

Knleriem In one of your diagrams concerning the mechanism of arrhythmia, in cases of hypertrophic cardiomyopathy, you mentioned the role of the conduction system and said there are only a few patients observed and studied thoroughly. So far we have studied five cases of cardiomyopathies and of those three cases with hypertrophic cardiomyopathy. We found that the sinus node was involved in the disarray of the myofibre disturbance. We have seen only minor changes in the AV node and in the bundle of His. I would like to ask if these findings could be confirmed by your group?

McKenna Michael Davies, the pathologist at St George’s Hospital in London, would, I am sure, agree with your postmortem findings, as would James. I do not think that sino-atrial disease, however, is likely to represent a common antecedent mechanism or cause of sudden death in patients with hypertrophic cardiomyopathy. We analysed three days of ECG recording from 86 consecutive patients and found little evidence of sino-atrial disease in
these patients. Were you also asking about accessory pathways?

Knieriem In our experience, the AV node and the bundle of His are not so often affected and showed only minor changes. I would like to ask again if you had some cases where you could find additional findings in the conduction system?

McKenna I cannot comment on pathological findings in the AV node or His-Purkinje system. In response to the question of rapid atrial ventricular conduction, as you are probably aware, Dr Dennis Krikler has reported such patients who died suddenly. Apart from these we have not seen others.

Rothlin I should like to make another comment to 'the torsade de pointes' ventricular tachycardia. It can occur and it has been observed now five times in a relatively short time. It must be said that usually these patients were on amiodarone combined with additional treatment with mexiletine, disopyramide, pencylamine or quinidine respectively, but never at a very high dosage. In particular, the combination of type 1 antiarrhythmics with amiodarone may lead to this complication. If one is regularly controlling the QT interval, one can probably stop this treatment before the complication occurs because all these patients had a prolonged QT interval (Schweiz med Wschr 1982; 112: 1585).

Borggrefe You mentioned three patients developing tremor while on amiodarone and you treat them with propranolol. Do you think it is safe to put patients on the β-blocker in the presence of amiodarone?

McKenna Yes, presumably you are referring to problems resulting from the sino-atrial and atrioventricular nodal suppression which occurs with both amiodarone and propranolol. As I mentioned, the dose of propranolol which we use for an amiodarone-related tremor is small, usually 20 mg daily. We do, however, have approximately 10 patients who receive amiodarone for the treatment of refractory arrhythmia and who also receive propranolol for the treatment of dyspnoea or chest pain. These patients are receiving between 200 and 400 mg daily of propranolol and in them we have seen no excessive PR prolongation or conduction problems.

Your point, however, is a good one, and the administration of any drug which has antiarrhythmic effects to someone who is receiving amiodarone should be done cautiously. We also have limited experience of the combination of amiodarone and verapamil and this would suggest that the effects of these drugs on the AV node are additive if not synergistic. This, however, is a clinical impression based on a few patients, and more detailed electrophysiological studies are needed.

Perez-Gomez We have experience in two cases, in whom the treatment with amiodarone was responsible for the death of the patients. We use amiodarone very often and like it very much but these were cases with repeated episodes of ventricular tachycardia and with rather early coupling of ventricular ectopic beats. So on treatment with amiodarone and with the prolongation of the QT, this early coupling of the ectopic beats which was not suppressed before the prolongation of the QT. These ectopic beats came just at the end of the T wave. So we believe that probably the prolongation of the QT before the suppression of the ectopic arrhythmias were responsible for the deaths of the patients. They were on amiodarone for just a short time, only 1 or 2 days.

McKenna I would suggest that if they had only been on amiodarone for 2 days that you probably didn't have significant drug effect. As you know, you can get an AV nodal blocking effect with amiodarone within 1 or 2 days, but you will not get repolarization changes so early.

Perez-Gomez But the QT was prolonged, clearly prolonged, and was measured by electrocardiogram before the treatment and 2 days after the treatment, so the QT is prolonged in a short time.

McKenna You are dealing with a drug that has variable bioavailability (20 to 80%) and a long t½ (approx. 30 days). It will therefore take a variable but long time (months) to reach equilibrium. Drug effect will be seen earlier, but in our experience an effect which could be attributed to the class 3 action of amiodarone is usually apparent after 1 week but never after 1 or 2 days. I cannot explain the QT prolongation in your patients, but I think it is unlikely to be due to amiodarone effect.

Breithardt In your first slides you presented the data on the incidence of supraventricular/ventricular tachycardia. But it is just a matter of definition. You defined VT as three or more consecutive beats. How many of these patients had sustained VT; how often
did it occur? The same question also applies to those patients with supraventricular tachycardia. What was the rate of tachycardia, of supraventricular tachycardia; how long did it last; how often did it occur?

McKenna On the electrocardiographic recording which I showed I described the characteristics of the episodes of ventricular tachycardia. Of 45 patients with VT, sustained arrhythmia was seen in only two. Both these patients were studied electrophysiologically and the tachycardia mapped to a single focus in an akinetic area distal in the ventricle. These two patients, however, are the exceptions, and in the remaining 43 patients the characteristics of the ventricular tachycardia were similar. The episodes were slow (mean 140 beats/min); they were typically between 5 and 12 beats and were not sustained; and they occurred during relatively vagal periods, e.g. 40% occurred between midnight and 06.00.

Breithardt Could you induce the VT in those two patients whom you studied electrophysiologically?

McKenna Yes, Paul Curry studied the first one and Edward Rowland the second; in both patients a uniform VT was initiated which was of similar morphology to that detected during ECG monitoring.

Kuhn Could you comment on the significance of programmed ventricular stimulation in patients with hypertrophic obstructive cardiomyopathy, i.e. especially in a patient who is admitted to you with syncope of unknown aetiology. What are you doing with such a patient regarding programmed ventricular stimulation?

McKenna I think my views must be taken in the context of a limited but negative experience which is highly coloured by one of our early studies. This was a young girl undergoing a limited electrophysiological study to assess the feasibility and safety of treatment with verapamil. An atrial premature stimulus induced atrial fibrillation which was conducted down a concealed and hitherto unsuspected accessory pathway and initiated ventricular tachycardia which degenerated into ventricular fibrillation. Direct current cardioversion was administered promptly and though sinus rhythm was restored an adequate cardiac output was not achieved and this patient died.

This is consistent with our broader experience of patients with hypertrophic cardiomyopathy in that when ventricular fibrillation occurs they are usually difficult to resuscitate successfully. We do not feel then, that provocative electrophysiological testing is safe or warranted in patients with hypertrophic cardiomyopathy. There are, however, centres whose practice differs from our own. I believe in Hamburg that between 10 and 15 patients have been assessed with programmed stimulation and that approximately 30 to 40% of these patients have required defibrillation which has been successful in all cases. Is there anyone from Hamburg here who can give further details concerning these studies? Our own approach to the identification of patients with hypertrophic cardiomyopathy who were at particular risk of sudden death is less invasive. We would regard the following patients to be at particular risk: (1) those who present in childhood or adolescence with clinical signs or symptoms of hypertrophic cardiomyopathy; (2) those who present following syncopal episodes; (3) those who have had a first degree relative die suddenly from hypertrophic cardiomyopathy; (4) those with ventricular tachycardia detected during ambulatory electrocardiographic monitoring.

Morgensen I would like to ask you about an answer you gave, when it was enquired of you whether it is now time to recommend amiodarone or whether we should await further trials. In your answer you said that from an ethical point of view, you hesitated regarding further trials.

McKenna The question of whether a clinical trial should be undertaken to assess the effect of amiodarone on prognosis in patients with hypertrophic cardiomyopathy and ventricular tachycardia appears difficult. We have identified a marker (VT) for adults at particular risk of sudden death and we have shown that this arrhythmia or marker can be suppressed with amiodarone. In addition, preliminary uncontrolled data suggests that such treatment will improve prognosis. Obviously there are problems with the interpretation of such data. The numbers are small, follow-up short (mean 2-3 years) and the comparison is based on an expected mortality from previous experience and not from a 'control' population. Nevertheless this clinical experience is valuable and suggests to me that we can improve prognosis by treating the VT patients with amiodarone. The question which you pose forces me to ask: is it ethical to withhold treatment in patients with VT in order to perform a control trial?
Morgenson  May I turn the question around? Do you feel that a control trial in such patients is ethical?

McKenna  We are discussing the interpretation of clinical experience versus the information which would be provided from a randomized clinical study. The question becomes particularly relevant as ventricular tachycardia in these patients is usually asymptomatic and amiodarone may be associated with unwanted effects. Treatment with amiodarone would then not be warranted unless it can be shown that prognosis has improved. Our preliminary data suggests that this is so, however longer follow up is required.