Repetitive ventricular response

Its incidence, inducibility, reproducibility, mechanism, and significance

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SUMMARY Using His bundle electrograms and the ventricular extrastimulus technique (single premature stimulus during sinus rhythm—S₁ method; single premature stimulus during ventricular pacing—S₁ S₂ method; and two premature stimuli during ventricular pacing—S₁ S₂ S₃ method) the occurrence of repetitive ventricular responses was tested in 51 patients. Thirty-two of 51 patients had organic heart disease and 19 of 51 patients (37%) had no evidence of heart disease. No patient had spontaneous or exercise-induced ventricular tachycardia, sudden death, or a recent myocardial infarction (less than six months). Repetitive ventricular responses were induced in 38 of 51 patients. In 33 of 51 patients (65%) the repetitive ventricular responses were reproducible. In 26 patients (51%), they were caused by local re-entry, and in 28 patients (55%) by bundle-branch re-entry. In addition, 16 patients had reproducible repetitive ventricular responses resulting from both bundle-branch and local re-entry. Repetitive ventricular responses caused by local re-entry were induced by the S₁ method in only one patient (4%), by the S₁ S₂ method in seven of 26 patients (27%), and by the S₁ S₂ S₃ method in 24 of 26 patients (92%) and were reproducible in 86% of patients. The incidence of repetitive ventricular responses caused by local re-entry was significantly higher in patients with organic heart disease versus those without organic heart disease. Repetitive ventricular responses caused by bundle-branch re-entry were induced in only one patient (2.5%) by the S₁ method, in 21 of 28 patients (75%) by the S₁ S₂ method, and in 12 of 28 patients (42%) by the S₁ S₂ S₃ method. There was no significant difference between the occurrence of repetitive ventricular responses resulting from bundle-branch re-entry and the presence or absence of organic heart disease. All patients without repetitive ventricular responses have been followed for six to 17 months (average=12 months) with 24 hour ambulatory electrocardiographic recordings. None of the patients with repetitive ventricular responses caused by local re-entry and bundle-branch re-entry has developed ventricular tachycardia and/or sudden cardiac death. Repetitive ventricular responses caused by local re-entry can be induced in a significant number of patients with organic heart disease unlike bundle-branch re-entry; the S₁ S₂ S₃ method is the most sensitive for induction of repetitive ventricular responses caused by local re-entry whereas the S₁ S₂ method is the most sensitive for the induction of repetitive ventricular responses caused by bundle-branch re-entry. The S₁ method is the least sensitive for the induction of both local re-entry and bundle-branch re-entry. Though repetitive ventricular responses caused by local re-entry may suggest electrical instability, our follow-up studies disclosed that it is not a predictor of sudden death.

Despite recent advances in cardiac electrophysiology, sudden cardiac death remains one of the major medical dilemmas of our time. It accounts for approximately 400 000 to 600 000 deaths per year in the United States. Moreover, it is estimated that approximately 100 000 of these deaths occur in individuals less than 65 years of age.¹ Though it remains unclear whether sudden cardiac death is a primary or a secondary arrhythmogenic phenomenon related to acute ischaemia and/or metabolic abnormalities of the ventricular myocardium, recent studies have attempted to identify the patient at risk of sudden cardiac death.²⁻⁴

The ventricular extrastimulus technique has been extensively used in man to study the refractory periods of the ventricular myocardium and the retrograde His-Purkinje system and the effects of cardioactive drugs on the latter.⁵⁻⁷ Its most valuable clinical application, however, has been in the induction and termination of ventricular tachycardia and in the selection of appropriate drug regimens in otherwise drug resistant ventricular tachycardia.⁸⁻¹⁰ In a recent study, Greene *et al.*¹¹ used the response to a single ventricular premature stimulus introduced during supraventricular rhythm as a predictor of sudden cardiac death. This study reported that 79% of patients with a recent myocardial infarction in whom repetitive ventricular responses were induced in response to a single ventricular premature stimulus had symptomatic ventricular tachycardia and/or sudden death or both during a 12-month follow-up period. The authors suggested that the repetitive ventricular response identified patients at risk of developing future life-threatening arrhythmias. The incidence and significance, however, of the repetitive ventricular response in patients without a recent myocardial infarction and without recurrent ventricular tachycardia is unknown. Furthermore, the methods of induction of the repetitive ventricular response, the sensitivity of the various methods, the types of repetitive ventricular responses induced, and their reproducibility and significance have not been systematically studied. Before these important questions are referred to it is probably premature to regard the repetitive ventricular response as a predictor of sudden cardiac death. The purpose of this study was to assess prospectively the incidence, inducibility, reproducibility, mechanism, and significance of the repetitive ventricular response in patients without a recent myocardial infarction, chronic recurrent ventricular tachycardia, and recent or past "sudden cardiac death syndrome".

Patients and methods

Fifty-one male patients ranging in age from 19 to 78

years (average age = 58 ± 3 y) who underwent electrophysiological studies for a variety of reasons were selected for ventricular extrastimulation. Thirty-two of 51 patients (63%) had organic heart disease whereas 19 of 51 patients (37%) had no evidence of heart disease. Of the 32 patients with organic heart disease, 20 patients (63%) had atherosclerotic heart disease while the remaining 12 patients had either cardiomyopathy, valvular heart disease, or hypertensive cardiovascular disease. The presence or absence of organic heart disease was based on: (1) clinical, electrocardiographic, and radiological findings; (2) echocardiography; (3) treadmill exercise testing; and (4) cardiac nuclear scanning. In addition, 15 of 32 patients with organic heart disease and six of 19 patients without organic heart disease had the diagnosis confirmed by cardiac catheterisation. None of the patients had a history or electrocardiographic evidence (24 hour ambulatory Holter electrocardiograms) of recurrent ventricular tachycardia. Twenty-four of 51 patients had frequent premature ventricular contractions (Lown's class III to IVA). None of the patients had an acute or recent (less than six months) myocardial infarction.

Electrophysiological studies were performed in the non-sedated post-absorptive state after explaining the experimental nature of the procedure and obtaining a signed consent. All cardioactive drugs were withheld for at least 48 hours before the study. Two to three quadripolar catheters were introduced percutaneously and positioned in the region of the high right atrium, at the level of the tricuspid valve and in the right ventricular apex, and/or outflow tract. The proximal poles of the catheters were used for recording and the distal poles for stimulation. Stimulation was performed by using a programmable stimulator and an isolated constant current source. The stimuli were rectangular pulses 1.5 ms in duration and twice diastolic threshold.

The procedure for programmed stimulation was as follows.

- (1) Incremental atrial pacing up to rates of 200 beats per minute.
- (2) Premature atrial stimulation during atrial pacing at a fixed cycle length.
- (3) Incremental ventricular pacing up to rates of 240 beats per minute.
- (4) Premature ventricular stimulation.

Premature ventricular stimulation consisted of the following:

- (A) S₁ method: a single premature ventricular stimulus (S₁) was introduced after every eight supraventricular beats (V) at progressively decreasing coupling intervals until ventricular muscle refractoriness.
- (B) S₁ S₂ method: a single premature ventricular

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stimulus (S_2) was introduced after every eight ventricular paced beats ($S_1 S_1$) at decreasing coupling intervals until ventricular muscle refractoriness.

- (C) $S_1 S_2 S_3$ method: double ventricular stimuli ($S_2 S_3$) were introduced during a basic paced ventricular cycle ($S_1 S_1$) starting at an $S_1 S_2$ interval of 30 ms longer than the ventricular effective refractory period and $S_2 S_3$ equal to $S_1 S_2$ interval; the $S_2 S_3$ interval was progressively decreased by 10 ms until S_3 was refractory. $S_1 S_2$ was then shortened and S_3 was reintroduced until S_2 did not evoke a ventricular response. The same sequence of stimulation was used in all patients and all had premature ventricular stimulation performed at two cycle lengths.

Two or more electrocardiograph leads and intracardiac electrograms at filter frequency settings of 40 to 500 Hz were simultaneously displayed on a multi-channel oscilloscope (VR-12) and recorded on a tape recorder (HP No. 3698A) and on thermal paper at speeds of 100 to 150 mm/s.

Statistical analysis was performed by using the χ^2 and the Student t test for paired data. All values represent the mean $\pm$ standard error of mean.

Definition of terms

REPETITIVE VENTRICULAR RESPONSES

These were defined as the appearance of one or more non-stimulated ventricular depolarisations in response to any of the above stimulation methods described.

ZONE OF REPETITIVE VENTRICULAR RESPONSES

This zone is the range of $V S_1$, $S_1 S_2$, and $S_2 S_3$ that resulted in one or more repetitive ventricular responses.

REPRODUCIBILITY OF THE REPETITIVE VENTRICULAR RESPONSE

If one or more repetitive ventricular responses were induced by any of the methods described, stimulation was repeated at the same coupling interval at least three times. The induction of repetitive ventricular responses was considered to be reproducible only if they could be induced on two or more occasions at the same coupling interval and/or if they could be induced successfully at two or more different coupling intervals.

$S_2 S_3/S_3 V_4$

The ratio of these two intervals expresses the relation of the coupling interval that resulted in the repetitive ventricular response to the interval from the initiating premature beat (S_3) to the first complex of the repetitive ventricular response (V_4).

EFFECTIVE REFRACTORY PERIOD (ERP) OF VENTRICULAR MYOCARDIUM

This is defined as the longest $V S_1$, $S_1 S_2$, and $S_2 S_3$ interval that resulted in ventricular refractoriness (that is that did not evoke a ventricular response).

Results

Repetitive ventricular responses could not be induced in any of the patients during incremental atrial pacing, atrial extrastimulation, and incremental ventricular pacing. Reproducible repetitive ventricular responses could be induced, however, in 38 of 51 patients during ventricular premature stimulation. In 33 of 51 patients (64.7%) the repetitive ventricular responses were reproducible. They could be classified into two types: (1) those resulting from local re-entry; and (2) those resulting from bundle-branch re-entry.

REPETITIVE VENTRICULAR RESPONSE CAUSED BY LOCAL RE-ENTRY

These responses demonstrated the following features: (1) they were independent of retrograde His-Purkinje delay (that is $V H_1$, $S_2 H_2$, and $S_3 H_3$ delays); (2) they were not preceded by a His bundle deflection with an HV interval equal to or greater than that of a normally conducted sinus beat; and (3) the QRS complex of the repetitive ventricular response had a different configuration and polarity than that of the paced complex.

REPETITIVE VENTRICULAR RESPONSES CAUSED BY BUNDLE-BRANCH RE-ENTRY^{12 13}

These responses disclosed the following features: (1) they were dependent on the attainment of a critical degree of retrograde His-Purkinje delay; (2) they were preceded by a His bundle deflection with an HV interval equal to or greater than that of a normally conducted sinus beat; and (3) the QRS complex of the repetitive ventricular responses was generally similar in configuration to that of the paced complex.

REPETITIVE VENTRICULAR RESPONSES RESULTING FROM LOCAL RE-ENTRY

Incidence and methods of induction

Repetitive ventricular responses caused by local re-entry could be induced in 26 of 51 patients (51%). The $S_1 S_2 S_3$ method induced repetitive responses in 24 of 26 patients; the $S_1 S_2$ method in seven of 26 patients; and the S_1 method in only one patient. Thus, the $S_1 S_2 S_3$ method was the most sensitive (92%) and the S_1 method the least sensitive (3.8%) in the induction of repetitive ventricular responses. Fig. 1 is a representative example demonstrating the induction of repetitive ventricular responses by the three methods in the same patient. Whereas repetitive ventricular responses were not induced by the S_1 and $S_1 S_2$

Fig. 1 Induction of repetitive ventricular responses by the S_1 method (panel A); $S_1 S_2$ method (panel B); and $S_1 S_2 S_3$ method (panel C). From top to bottom in each panel, $L_1 L_2 V_1$ = surface electrocardiographic leads, HBE = His bundle electrogram, and RVE = right ventricular electrogram. Panel A: a single ventricular stimulus (S_1) is introduced during sinus rhythm at a coupling interval of 290 ms (left-hand panel). The stimulus captures the ventricle but does not evoke repetitive ventricular responses. At a coupling interval of 280 ms, the stimulus (S_1) is refractory (right-hand panel). Panel B: A single right ventricular stimulus (S_2) is introduced at an $S_1 S_2$ interval of 240 ms during a paced ventricular drive ($S_1 S_1$) of 600 ms. S_2 does not evoke repetitive ventricular responses. At a coupling interval of 230 ms (right-hand panel) S_2 is refractory. Panel C: Two sequential extrastimuli ($S_2 S_3$) are introduced during a paced ventricular drive ($S_1 S_1$) of 600 ms. The $S_1 S_2$ interval is 260 ms and the $S_2 S_3$ interval is 230 ms. S_3 evokes three repetitive ventricular responses (V_4, V_5, V_6) which have a right bundle-branch block and left axis morphology, are not preceded by a His bundle deflection, and are presumably a result of local re-entry. At an $S_2 S_3$ interval of 190 ms (right-hand panel), S_3 is refractory. Note that the effective refractory period of the ventricular myocardium is 280 ms as assessed by the S_1 method, 230 ms by the $S_1 S_2$ method, and 190 ms by the $S_1 S_2 S_3$ method.

methods (panels A and B), repetitive ventricular responses were reproducibly induced by the $S_1 S_2 S_3$ method (panel C).

Reproducibility

Repetitive ventricular responses were reproducible in 21 of 26 patients (81%) and non-reproducible in five of 26 patients (19%). Sixteen of 21 patients (76%) with reproducible repetitive responses had two or more repetitive responses whereas all five patients with non-reproducible repetitive responses had a single repetitive response. All patients with reproducible repetitive ventricular responses had a zone of induction 10 to 60 ms in duration (Fig. 2) Of the 21 patients with reproducible repetitive ventricular responses, five patients (24%) had a single response, 13 patients (62%) had two or more responses, and three patients (14%) had sustained ventricular tachycardia (Fig. 3). The latter three patients were successfully cardioverted, two with a praecordial thump and one with electrical D/C cardioversion. Twelve of 16 patients

(75%) with two or more responses had Lown's class IVA ventricular premature contractions; whereas two of five patients (40%) with a single repetitive response had Lown's class IVA ventricular premature contractions.

MORPHOLOGICAL FEATURES OF REPETITIVE VENTRICULAR RESPONSES AND RELATION BETWEEN PREMATURITY OF INITIATING BEAT AND FIRST REPETITIVE RESPONSE

In 15 of 26 patients, the repetitive ventricular responses had a right bundle-branch block pattern; eight patients had a left bundle-branch block pattern; and three patients showed polymorphism. There was an inverse relation between the coupling interval that resulted in repetitive ventricular responses to the interval from the initiating premature beat to the first complex of the repetitive response such that the $S_2 S_3 / S_3 V_4$ ratio decreased significantly (0.76 ± 0.02 to 0.60 ± 0.02 , $p < 0.001$) as the coupling interval of the initiating premature beats ($S_2 S_3$) decreased.

Fig. 2 Induction of repetitive ventricular responses over a zone of coupling intervals. Panel A: The ventricle is paced at a basic drive of 600 ms. Two sequential premature stimuli (S_2 S_3) are introduced at an S_1 S_2 interval of 270 ms and an S_2 S_3 interval of 280 ms. S_3 is followed by repetitive ventricular responses (V_4 to V_7). The repetitive ventricular responses have a right bundle-branch block and left axis deviation QRS morphology. Panel B: Repetitive ventricular responses (V_4 to V_{13}) are reproducibly induced as the S_2 S_3 interval is shortened to 260 ms and the S_1 S_2 interval is constant at 270 ms. Panel C: Decreasing the S_2 S_3 interval further to 220 ms is again associated with induction of repetitive ventricular responses (V_4 – V_8). Panel D: At an S_2 S_3 interval of 200 ms, S_3 is refractory. Thus the zone of repetitive ventricular responses was 60 ms (280 to 220 ms). For abbreviations see Fig. 1.

Fig. 3 The induction of ventricular tachycardia. The right ventricle is paced at a basic drive of 600 ms. Introduction of two sequential stimuli at an S_1 S_2 interval of 300 ms and an S_2 S_3 interval of 290 ms results in ventricular tachycardia. The patient was converted to sinus rhythm by a thump on the chest (solid arrow). HRA, high right atrial electrogram. For other abbreviations see Fig. 1.

Fig. 4 The induction of repetitive ventricular responses resulting from bundle-branch His-Purkinje re-entry and local re-entry. Panel A: The right ventricle is paced at a basic cycle length of 700 ms. Two premature stimuli are introduced at an $S_1 S_2$ interval of 290 ms and $S_2 S_3$ interval of 280 ms resulting in two repetitive ventricular responses (V_4 and V_5). Note that V_4 is preceded by a His bundle deflection with an $H_3 V_4$ interval of 90 ms. In addition, the QRS complex of V_4 has a similar configuration to that of the paced complex. This suggests that V_4 is a result of bundle-branch re-entry. In contrast V_5 is not preceded by a His bundle deflection and has a different configuration and axis from that of the paced beats and V_4 , suggesting that V_5 is the result of local re-entry. Panel B: As the $S_3 S_3$ interval was decreased to 250 ms, repetitive ventricular responses (V_4 – V_7) solely resulting from local re-entry were induced. For abbreviations see Fig. 1.

ORGANIC HEART DISEASE AND REPETITIVE VENTRICULAR RESPONSES

Of the 21 patients with reproducible, repetitive ventricular responses, 18 patients (86%) had organic heart disease whereas only three patients (14%) had no evidence of organic heart disease ($p < 0.005$). Of the latter three patients, however, one had a prolonged QT interval with frequent premature ventricular contractions and the remaining two had high grade (Lown's class IVA) premature ventricular contractions. The incidence of repetitive ventricular responses in patients with organic heart disease was 56% and in patients without heart disease it was 15%.

REPETITIVE VENTRICULAR RESPONSES RESULTING FROM BUNDLE-BRANCH RE-ENTRY

Repetitive ventricular responses caused by bundle-branch re-entry could be induced in 28 of 51 patients (55%). Sixteen of these patients, however, showed reproducible repetitive ventricular responses caused by local re-entry (Fig. 4). Unlike local re-entry, however, bundle-branch re-entry was limited most often to a single re-entrant beat and was generally induced by the $S_1 S_2$ method (21 of 28 patients). The $S_1 S_2 S_3$ method induced bundle-branch re-entry in 12 of 28 patients and the S_1 method in only one patient. Thus, the $S_1 S_2$ method was the most sensitive (75%)

and the S_1 method the least sensitive (2.5%) for the induction of bundle-branch re-entry. The reproducibility of bundle-branch re-entry was not tested in this study since both the consistency and reproducibility of the latter phenomenon have been well documented previously.^{13–14}

ORGANIC HEART DISEASE AND BUNDLE-BRANCH RE-ENTRY

Of 28 patients (60%) with bundle-branch re-entry, 17 had organic heart disease whereas 11 of 28 patients (40%) had no heart disease. This difference was not statistically significant. The incidence of bundle-branch re-entry in patients with organic heart disease was 53% and in those without heart disease it was 58%.

EFFECTIVE REFRACTORY PERIOD OF VENTRICULAR MYOCARDIUM

The effective refractory period of the ventricular myocardium as assessed by the S_1 method (267 ± 4 ms) was significantly longer ($p < 0.001$) than that obtained by the $S_1 S_2$ method (246 ± 2.7 ms) and the $S_1 S_2 S_3$ method (205 ± 3.5 ms). Likewise, the effective refractory period of the ventricular myocardium as determined by the $S_1 S_2$ method was significantly longer ($p < 0.001$) than that obtained by the $S_1 S_2 S_3$ method. Fig. 1 is a representative example showing the differ-

ence in ventricular myocardial refractoriness by the three methods.

FOLLOW-UP STUDIES

The patients with repetitive ventricular responses caused by local re-entry were randomised into two equal groups. One group (11 of 21 patients) received chronic oral antiarrhythmic treatment with the drug that abolished the repetitive ventricular responses during the stimulation study (eight of 11 patients—procainamide, three of 11 patients—quinidine sulphate) and the second group of patients (10 of 21) received no specific antiarrhythmic treatment. The selection of oral treatment was on alternate basis and was not dependent on the number of repetitive ventricular responses. All three patients with sustained ventricular tachycardia received antiarrhythmic treatment. Patients who did not have repetitive responses resulting from local re-entry were not placed on any antiarrhythmic treatment. All patients have been followed for six to 17 months (average=12 months) at three monthly intervals in our arrhythmia clinic. The follow-up consisted of: (1) a questionnaire regarding history of palpitation, dizziness, syncope, and admission to hospital for cardiac related events; (2) 12 lead electrocardiogram; and (3) 24 hour ambulatory continuous electrocardiographic recordings. None of the patients with repetitive ventricular responses from local re-entry developed ventricular tachycardia and/or sudden death. One patient who did not have repetitive ventricular responses had ventricular tachycardia during the acute phase of a myocardial infarction three months after the stimulation study.

Discussion

Since the original description of Wiggers and Wegria¹⁵ that a low intensity electrical stimulus introduced near the apex of the T wave induced ventricular tachycardia or fibrillation in the canine experimental model with conditions predisposing to ventricular electrical instability, several animal studies have attempted to assess ventricular electrical instability by measuring ventricular fibrillation thresholds or by using the repetitive ventricular extrasystole as an index of vulnerability to ventricular fibrillation.^{16–20} Studies in the normal canine heart have shown that the introduction of a single extrasystole of low or medium intensity does not induce repetitive ventricular responses or ventricular fibrillation. Similarly, Fisher and co-workers⁹ have shown that the introduction of up to three programmed extrasystoles delivered at two or four times diastolic threshold with bipolar electrodes and scanning diastole until ventricular myocardial refractoriness does not evoke ventricular tachycardia and/or fibrillation in normal dogs. In con-

trast, the introduction of one or more ventricular extrasystoles of low or medium intensity induces repetitive extrasystoles or ventricular fibrillation in the digitoxic or ischaemic canine heart.^{16–18}

The ventricular extrastimulus technique has been extensively used in man to assess the effects of cardio-active drugs on ventricular myocardial refractoriness and retrograde His-Purkinje conduction and refractoriness.^{5–8} These and other studies^{12–13} have shown that the introduction of a single ventricular premature stimulus during a paced ventricular drive results in the induction of a single ventricular depolarisation in approximately 52 to 62% of human subjects and very rarely in two or more ventricular beats. The former occurred at a critical coupling interval and over a zone of coupling intervals. This ventricular depolarisation has since been well established to be a physiological phenomenon caused by re-entry within the bundle-branch His-Purkinje system^{12–13} as a result of a critical retrograde His-Purkinje delay (that is V2 H2 or S2 H2 delay) and is probably unrelated to the electrophysiological basis of spontaneous ventricular extrasystoles or tachycardia in the majority of patients. Though many of these patients were thought to have clinically normal hearts, none the less none of the patients developed ventricular tachycardia or fibrillation during the stimulation studies. In contrast, in patients with recurrent ventricular tachycardia, the introduction of one or more premature ventricular depolarisations during a paced ventricular drive results in ventricular tachycardia in a significant number of patients.^{8–10}

The findings in this study suggest that repetitive ventricular responses can be induced in a large number of patients without ventricular tachycardia and/or recent myocardial infarction. Repetitive ventricular responses presumably resulting from local re-entry were induced in 51% of patients and those from bundle-branch re-entry in 55% of patients. Repetitive ventricular responses resulting from local re-entry were reproducible in the majority of patients, particularly when two or more responses were induced. That these repetitive responses were possibly caused by re-entry is suggested by the following observations: (1) they were induced only during premature stimulation at a critical coupling interval and over a zone of coupling intervals which favours re-entry as a mechanism; (2) there was an inverse relation between the coupling interval that resulted in repetitive ventricular response to the interval from the initiating premature beat to the first complex of the repetitive response. Though these characteristics suggest re-entry as the mechanism, triggered automaticity cannot be totally excluded.

Of considerable interest was the observation that the induction of repetitive ventricular responses

caused by local re-entry was dependent on the methods used for induction. Thus, though the S₁ S₂ S₃ method induced repetitive ventricular responses in 92% of patients, the S₁ S₂ method induced repetitive ventricular responses in only 27% of the patients and the S₁ method in only 3.8% of patients. This observation may be related to several factors. Since the effective refractory period of the ventricular myocardium is significantly longer as measured by the S₁ method, the critical coupling interval required for attainment of a critical conduction delay and unidirectional block at re-entry site may not be attained. Whereas the ability to shorten significantly the effective refractory period of the ventricular muscle by the S₁ S₂ method and even more so by the S₁ S₂ S₃ method as shown in this study may enable the attainment of coupling intervals that result in sufficient conduction delay and unidirectional block at the re-entry site creating the necessary requisites for re-entry to be manifest. In addition, the introduction of two sequential extra beats may be expected to result in a greater degree of conduction delay within the myocardium and micro-Purkinje system than a single extra beat induced during sinus rhythm. In this regard, it is a well known fact that the introduction of two sequential atrial extrastimuli can induce atrioventricular nodal re-entry when a single extrastimulus fails in patients with atrioventricular nodal re-entrant tachycardia. The introduction of two atrial extrastimuli enables the achievement of the required atrioventricular nodal conduction delay when a single atrial extrastimulus does not.

The findings of Greene and co-workers¹¹ that repetitive ventricular responses could be induced in 19 of 48 patients (40%) by introducing a single ventricular rhythm (that is the S₁ method) are in complete contrast to our observations that repetitive ventricular responses resulting from local re-entry could be induced in only 3.8% of patients by the S₁ method. They did not, however, assess the reproducibility of the repetitive ventricular response induced by the S₁ method nor did they assess the sensitivity of other methods of induction. In addition, they did not qualify the repetitive ventricular response whether caused by bundle-branch re-entry or local re-entry. This differentiation is of considerable importance since, as shown in this study, 16 patients showed both bundle-branch re-entry and local re-entry. Whereas bundle-branch re-entry has been shown clearly to be a physiological phenomenon unrelated to clinical ventricular tachycardia and/or fibrillation, repetitive responses caused by local re-entry may reflect myocardial electrical instability. This is suggested by our observations that a significant number of patients (86%) with repetitive ventricular responses from local re-entry had organic heart disease; whereas repetitive

ventricular responses from local re-entry could be induced in only three patients without organic heart disease. The latter three patients, however, also had conditions predisposing to myocardial electrical instability. In contrast, bundle-branch re-entry could be induced in an equal proportion of patients with and without organic heart disease.

These findings are in agreement with the preliminary observations of Farshidi *et al.* (unpublished) who also found a significantly higher incidence of repetitive responses caused by local re-entry in patients with organic heart disease. In contrast to our findings, however, they observed only a 9% incidence of repetitive responses caused by local re-entry in patients without clinical ventricular tachycardia and fibrillation. Furthermore, they did not assess the clinical significance of the repetitive ventricular response in patients without ventricular tachycardia and/or fibrillation.

CLINICAL SIGNIFICANCE OF REPETITIVE VENTRICULAR RESPONSE

Our short-term follow-up studies suggest that the repetitive ventricular response is not a predictor of sudden death and/or future development of lethal ventricular arrhythmias in patients with and without organic heart disease. These findings are in contrast to the experience of Greene and co-workers¹¹ who showed that 79% of patients who had repetitive ventricular responses had symptomatic ventricular tachycardia or sudden death or both during a 12-month follow-up period. This discrepancy may be related to the following: (1) differences in patient population. Whereas Green *et al.*¹¹ reported their findings in patients with a recent myocardial infarction, none of our patients had a recent myocardial infarction though 63% of our patients had organic heart disease, of whom 63% had coronary heart disease, and 47% had high grade ventricular premature contractions. (2) Whereas Greene *et al.*¹¹ observed repetitive ventricular responses to a single premature stimulus during supraventricular rhythm (S₁ method) we observed repetitive responses caused by local re-entry by the S₁ S₂ S₃ method in the majority of patients. Whether the induction of repetitive responses by the S₁ method connotes a higher degree of ventricular myocardial electrical instability than the induction by the S₁ S₂ S₃ method is not clear at present. It should be noted, however, that several recent studies have indicated that even in patients with recurrent ventricular tachycardia, the ventricular tachycardia is more often induced by the S₁ S₂ S₃ method than by the S₁ S₂ method and even less by the S₁ method.^{9,21}

Since it is not clear whether sudden cardiac death is a primary or secondary arrhythmogenic phenomenon

related to acute ischaemic and/or metabolic abnormalities of the ventricular myocardium the relation of the repetitive ventricular response to the future development of sudden cardiac death is certainly difficult to determine. Perhaps long-term prospective studies in a large number of patients and subgroups of patients will have to be conducted before these questions are answered. Until then the diagnostic and prognostic implications of the repetitive ventricular response remain speculative.

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