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Electrocardiographic antecedents of primary ventricular fibrillation
Value of the R-on-T phenomenon in myocardial infarction[1]

Nabil El-Sherif, Robert J. Myerburg, Benjamin J. Scherlag, Benjamin Befeler, Juan M. Aranda, Agustin Castellanos, and Ralph Lazzara

From the Division of Cardiology, Veterans Administration Hospital, and the Division of Cardiology, University of Miami School of Medicine, Miami, Florida, U.S.A.

Primary ventricular fibrillation was seen in 20 of 450 consecutive patients (4·4%) admitted within 24 hours after the onset of acute myocardial infarction. Compared with patients without primary ventricular fibrillation, they showed a lower mean age group and a higher incidence of anterior infarction. Warning ventricular arrhythmias preceded primary ventricular fibrillation in 58 per cent of cases. However, warning arrhythmias were also present in 55 per cent of patients without primary ventricular fibrillation. The following mechanisms of initiation of primary ventricular fibrillation were seen. 1) In one patient, it was initiated by supraventricular premature beats showing aberrant intraventricular conduction. 2) In 2 patients, ventricular tachycardia degenerated into primary ventricular fibrillation. 3) In 17 patients, it was initiated by a ventricular premature beat; in 10 of these, the premature beat showed early coupling (RR'/QT<1—the R-on-T phenomenon). However, ventricular premature beats showing the R-on-T phenomenon were also observed in 49 per cent of patients without primary ventricular fibrillation. In 7, primary ventricular fibrillation was initiated by a late-coupled ventricular premature beat (RR'/QT>1); in 2, the very late coupling resulted in a ventricular fusion beat. The study suggests that warning arrhythmias and the R-on-T phenomenon are poor predictors of primary ventricular fibrillation in acute myocardial infarction. The observation that 41 per cent of primary ventricular fibrillation was initiated by a late-coupled ventricular premature beat suggests that ventricular vulnerability during acute myocardial infarction may extend throughout most of the cardiac cycle and is not necessarily confined to the QT interval.

The concept of ventricular vulnerability was first shown in animal models by Wiggers and Wegria (1940) and Wiggers, Wegria, and Pinera (1940). Later, the clinical extrapolation of this concept was highlighted by the phrase 'R-on-T' phenomenon (Smirk, 1949; Smirk and Palmer, 1960). However, a few clinical reports (Mounsey, 1967; Stock, 1970; Lie, Wellens, and Durrer, 1974a; De Soyza *et al.*, 1974) and some recent experimental observations (Scherlag *et al.*, 1974; Williams *et al.*, 1974; El-Sherif, Scherlag, and Lazzara, 1975b) suggested that the arrhythmogenic potentials in acute myocardial ischaemia were not exclusively confined to those extrasystoles exhibiting the R-on-T phenomenon. This report examines the role of the R-on-T phenomenon in 20 cases of primary ventricular fibrillation observed at the Coronary Care Unit during a 2-year period. In addition, we analysed other electrocardiographic characteristics of primary ventricular fibrillation and their potential value as predictors of the arrhythmia. A summary of this report was recently published in abstract form (El-Sherif *et al.*, 1975a).

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Subjects and methods

Studies were made on 450 consecutive patients with acute myocardial infarction admitted to the coronary care unit from November 1972 to October 1974. All patients were admitted within 24 hours of the onset of prolonged chest pain suggestive of acute myocardial

infarction, with a mean arrival time to the coronary care unit of 4 hours. The diagnosis of acute myocardial infarction was based on all the following criteria: 1) a typical clinical history; 2) electrocardiographic abnormalities consisting of either new Q waves or typical evolutionary ST-T changes; and 3) characteristic serial changes in serum enzymes including CK, AST, and LDH. The site of old and acute infarction was determined and defined according to criteria as outlined by Lipman and Massie (1965). Primary ventricular fibrillation was defined as ventricular fibrillation in the absence of congestive failure, pulmonary oedema, and cardiogenic shock (Meltzer and Kitchell, 1966; Lawrie *et al.*, 1967).

In all patients, continuous electrocardiographic monitoring was performed, and in several patients these data were stored on a 24-hour magnetic tape-recorder using the Holter monitoring system. The first episode of primary ventricular fibrillation was always recorded and analysed for the mechanism of initiation. The heart rate immediately preceding the arrhythmia was noted. The prematurity index of the ventricular premature beat that initiated the first and subsequent episodes of primary ventricular fibrillation was determined by dividing the coupling interval of the ventricular premature beat (RR') by the QT interval of the preceding sinus beat. In the present study, to facilitate description and analysis of the results, a ventricular premature beat with prematurity index less than 1 was considered to represent short coupling or the R-on-T phenomenon while a ventricular premature beat with an index of 1 or more was termed long coupling. The time of occurrence of the first episode of primary ventricular fibrillation after the onset of symptoms was noted. All records were analysed for the presence of warning arrhythmias defined as 1) ventricular premature beats with a frequency of more than 5 beats/min; 2) multiform ventricular premature beats; 3) ventricular premature beats in couplets; 4) premature beats falling on the T wave (R-on-T phenomenon); and 5) ventricular tachycardia (DeSanctis, Block, and Hutter, 1972). All patients showing warning arrhythmias received lignocaine infusion at a rate of 2 to 4 mg/min, with an initial bolus injection of 75 to 100 mg intravenously. Procainamide, quinidine sulphate, and phenytoin were given as second choice antiarrhythmic drugs in several patients. None of these drugs was given before the onset of primary ventricular fibrillation, except for one patient in whom the initiating arrhythmia was supraventricular premature beats.

Results

Age, sex, site of infarction, and outcome (Table 1)

Of 450 patients with acute myocardial infarction, 20 developed primary ventricular fibrillation (4·4%). The mean age of these patients was 55 years, being lower than the mean age of 63 years of those patients without primary ventricular fibrillation ($P < 0·05$). The incidence of fibrillation was slightly greater in patients with anterior myocardial infarction (12 of 221 patients) than in patients with inferior infarction (8 of 179 patients) ($P < 0·1$).

TABLE 1 *Age and sex distribution, site of infarct, and outcome*

	Primary ventricular fibrillation	*No primary ventricular fibrillation*
Incidence	20	430
Mean age (y)	55	63
Sex:		
Male	16	335
Female	4	95
Site of infarct:		
Anterior	12	221
Inferior	8	179
In-hospital mortality	2	65

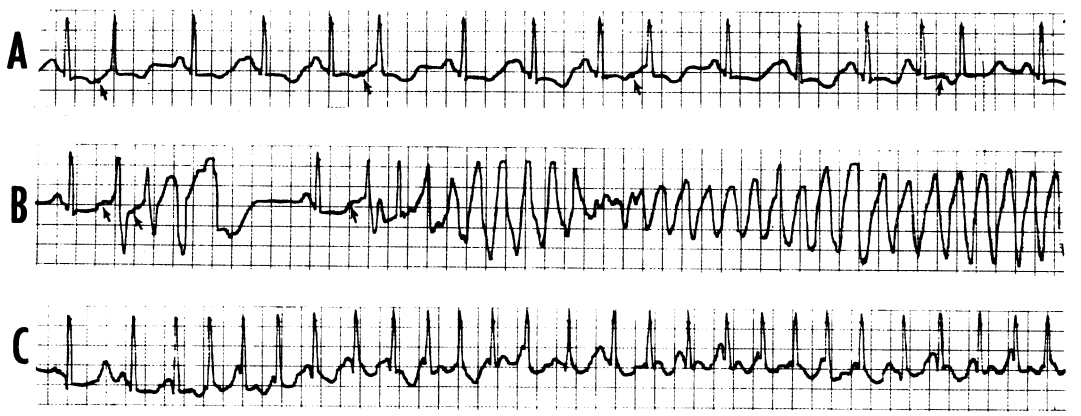

FIG. 1 *Primary ventricular fibrillation initiated by supraventricular premature beats (marked by arrows). See text for details.*

Eight patients were receiving lignocaine. All patients were successfully resuscitated. The in-hospital mortality of 450 patients with acute myocardial infarction was 15 per cent. Of 20 patients with primary ventricular fibrillation, 6 had recurrent episodes (up to 12). One patient died from cardiogenic shock 24 hours after repeated defibrillation. Another patient died on the fifth hospital day from reinfarction and cardiogenic shock. All 18 patients who were successfully cardioverted left the hospital and were still alive for a follow-up period ranging from 3 to 24 months.

Mode of onset of primary ventricular fibrillation

Three different patterns of initiation were observed.

1) In a unique example of a 54-year-old man, the fibrillation was initiated by supraventricular premature beats (Fig. 1). The patient was admitted within two hours from the onset of acute anterior myocardial infarction. The rhythm strip showed frequent supraventricular premature beats, some with short coupling conducted with a slight degree of aberrant intraventricular conduction (Fig. 1, panel A, marked with arrows). The patient was started on oral quinidine, 0·4 g every 6 hours. However, 2 hours after admission, the frequency of supraventricular premature beats was not diminished and, furthermore, the ectopic beats conducted with a high degree of aberrant intraventricular conduction. The first part of panel B of (Fig. 1) shows two supraventricular premature beats conducted with wide QRS followed by two other bizarre ventricular beats before the self-termination of the arrhythmic episode. The second episode in panel B started with an early-coupled supraventricular premature beat which was aberrantly conducted and followed by the onset of ventricular fibrillation. It is difficult to exclude the possibility that more than one supraventricular premature beat was conducted with aberration as in the first episode, before triggering ventricular fibrillation. The patient was successfully defibrillated and started on lignocaine, but continued for the next two hours to show recurrent bouts of ventricular fibrillation initiated by exactly the same mechanism as shown in panel B. After repeated defibrillation, the patient's rhythm changed to atrial fibrillation with rapid ventricular response (Fig. 1, panel C), before reverting spontaneously to sinus rhythm, 8 hours after the onset of symptoms. Analysis of the patient's corrected QT interval showed that it was only moderately prolonged (0·44–0·48 s). Serum potassium and calcium were within normal limits. Review of the patient's previous and follow-up electrocardiograms failed to show any evidence of a pre-excitation syndrome.
2) In 2 patients, a regular ventricular tachycardia for 15 and 40 minutes, respectively, degenerated into primary ventricular fibrillation. The tachycardia was resistant to lignocaine therapy and, in one patient, it failed to respond to cardioversion. In both patients, a predominantly regular tachycardia became irregular; several very early coupled ventricular ectopic beats with different QRS configuration were observed shortly before one of these beats initiated the primary ventricular fibrillation (Fig. 2).
3) In 17 patients, primary ventricular fibrillation was initiated by a ventricular premature beat during sinus rhythm or a high degree AV block. Table 2 shows the prematurity index of the ventricular premature beat that initiated ventricular fibrillation in the 17 patients. In 10 patients, the prematurity index was <1 (short coupling on R-on-T phenomenon) (Fig. 3). Seven patients had a prematurity index of >1 (long coupling). In two patients, the ventricular premature beat that initiated ventricular fibrillation was inscribed so late in the cardiac cycle that it fell after the next P wave, resulting in a ventricular fusion beat (Fig. 4). Panel A shows frequent ventricular premature beats pre-

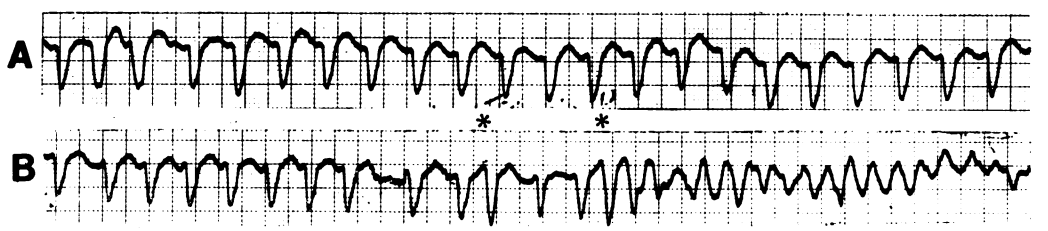

FIG. 2 *Primary ventricular fibrillation initiated by very early coupled ventricular premature beat (marked by asterisk) during course of regular ventricular tachycardia.*

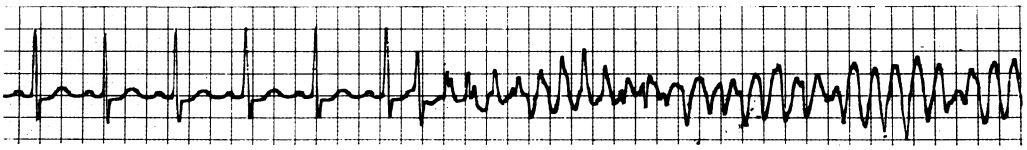

FIG. 3 *Primary ventricular fibrillation initiated by early coupled ventricular premature beat falling on antecedent T wave (R-on-T phenomenon).*

TABLE 2 *Prematurity index of ventricular premature beat initiating first episode of primary ventricular fibrillation in 17 patients (coupling interval RR' divided by QT duration)*

Case No.	*RR'**	QT*	*Prematurity index*
1	28	40	0·70
2	36	44	0·82
3	38	52	0·73
4	46	48	0·96
5	42	56	0·75
6	38	44	0·86
7	42	50	0·84
8	30	36	0·83
9	40	60	0·67
10	32	40	0·80
11	46	38	1·21
12	50	48	1·04
13	62	56	1·11
14	58	42	1·38
15	60	52	1·15
16	56	44	1·27
17	140	60	2·33
Average	49·7	47·7	1·03
SD	25·5	7·5	0·40

*Times are in one-hundredths of a second.

dominantly in a bigeminal rhythm (marked by asterisks). The first ventricular premature beat has a very long coupling interval and probably represents a ventricular fusion beat. Panel B illustrates three ventricular premature beats with long coupling, showing varying degrees of ventricular fusion. The third ectopic beat initiated the episode of ventricular fibrillation. The patient was successfully defibrillated but showed recurrent bouts of ventricular fibrillation and was defibrillated 12 times.

Table 3 shows the relation between the time interval from the onset of symptoms to the occurrence of the first episode of primary ventricular fibrillation and the prematurity index of the ventricular premature beat that initiated the arrhythmia. Five out of seven episodes of ventricular fibrillation that were initiated by a ventricular premature beat with long coupling ($P > 1$) developed within 4 hours from the onset of symptoms. On the other hand, only 2 out of 10 episodes of ventricular fibrillation that were initiated by a ventricular premature beat with short coupling (prematurity index < 1) occurred within

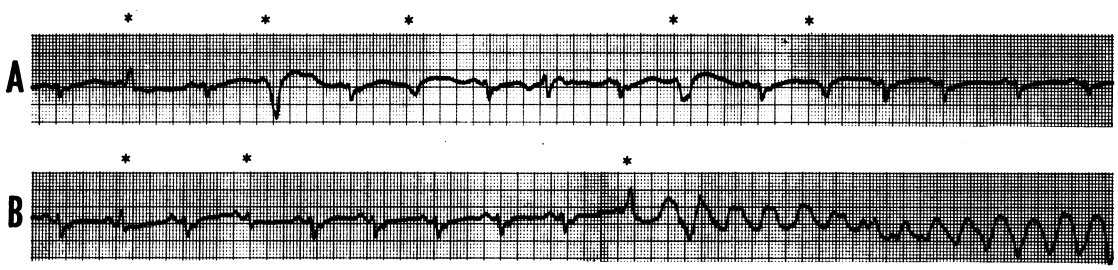

FIG. 4 *Primary ventricular fibrillation preceded by frequent ventricular premature beats (marked by asterisks) occurring predominantly in bigeminal arrangement (panel A). Panel B shows three very late coupled ventricular ectopic beats resulting in ventricular fusion complexes (marked by asterisks), third of which initiated arrhythmia.*

TABLE 3 *Relation between time of onset from start of symptoms of first episode of primary ventricular fibrillation and prematurity index of ventricular premature beat initiating arrhythmia*

Time (h)	*Prematurity index* >1	<1
0–4	5	2
4–8	1	3
8–12	1	2
12–24	—	2
>24	—	1
Total	7	10

4 hours from onset of symptoms. The difference is statistically significant ($P < 0.05$).

The electrocardiograms obtained during the first 24 hours in hospital of 430 patients who did not develop primary ventricular fibrillation were analysed for the presence of ventricular premature beats with a prematurity index < 1. Ventricular premature beats with prematurity index < 1 showing the R-on-T phenomenon were found in 210 patients (49%). This was only slightly lower than the incidence of premature beats with prematurity index < 1 in patients who developed ventricular fibrillation (10 out of 17 patients—59%). Short coupled ventricular premature beats were observed before the onset of the arrhythmia in 5 of the 10 patients in whom fibrillation was initiated by a ventricular premature beat with prematurity index < 1. On the other hand, none of the 7 patients in whom ventricular fibrillation was initiated by a ventricular premature beat with a prematurity index < 1 showed short coupled ventricular premature beats before the onset of the arrhythmia. However, 4 of these patients started to show premature beats with prematurity index < 1 for the first time after being defibrillated, and in 2 patients subsequent episodes of ventricular fibrillation were initiated by such beats with a prematurity index less than 1.

Warning arrhythmias and heart rates preceding primary ventricular fibrillation

Warning arrhythmias preceded primary ventricular fibrillation in 11 out of 19 patients (58%) (excluding the case of ventricular fibrillation initiated by supraventricular premature beats). Eight patients showed no warning arrhythmias. These included three patients with no recognized ventricular premature beats, three with occasional premature beats with prematurity index >1, and two in whom an episode of ventricular bigeminy started 15 and 60 seconds, respectively, before one of the fixed coupled ventricular premature beats started primary ventricular fibrillation (Fig. 5). Table 4 shows the duration of monitoring before onset of ventricular fibrillation. Except for one patient who was monitored for only 30 minutes, patients who showed no warning arrhythmias were monitored for 1 to 6 hours before the onset of ventricular fibrillation. Warning arrhythmias were also present in 236 out of 430 patients (55%) who did not develop primary ventricular fibrillation. The difference between the incidence of warning arrhythmias in patients who developed or did not develop primary ventricular fibrillation was not statistically significant.

The ventricular rates immediately preceding the first episode of ventricular fibrillation are shown in

TABLE 4 *Duration of monitoring before onset of primary ventricular fibrillation*

Time (h)	*With no warning arrhythmias*	*With warning arrhythmias*
0–½	—	2
½–1	1	1
1–2	3	2
2–6	4	4
6–12	—	1
>12	—	1
Total	8	11

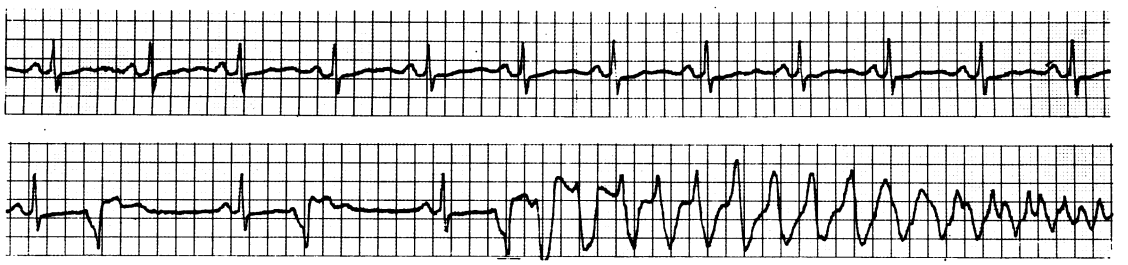

FIG. 5 *Primary ventricular fibrillation preceded by run of ventricular bigeminy for only 60 s before one of fixed coupled ventricular premature beats started arrhythmia.*

TABLE 5 *Ventricular rates immediately preceding first episode of primary ventricular fibrillation*

Heart rate (beats/min)	*No. of patients*
<40	1
40–60	2
60–80	3
80–100	6
100–120	4
120–140	1
>140*	2

*Patients with ventricular tachycardia that deteriorated into primary ventricular fibrillation.

Table 5. Three patients had heart rates less than 60/min. In 2 patients this was the result of sinus bradycardia with a rate of 40 to 60/min. The third patient had a 3:1 AV block with an atrial rate of 110/min after atropine injection. Sinus rhythm with ventricular rates of 60 to 100/min was present in 9 patients, while 5 patients showed sinus tachycardia (100 to 140/min) before ventricular fibrillation.

Discussion

The consistent demonstration of supraventricular premature beats immediately preceding the onset of ventricular tachycardia and fibrillation episodes in the patient whose electrocardiogram is illustrated in Fig. 1 strongly suggests a cause-and-effect relation. However, proof would have required reproducing the ventricular arrhythmia by induced critically timed atrial premature beats, which was obviously not feasible. This example of ventricular fibrillation initiated by supraventricular premature beats represents the first clinical report of its kind in patients with acute myocardial infarction. Ventricular fibrillation induced by supraventricular beats had been described in patients with pre-excitation (Dreifus *et al.*, 1971). One case has been recently reported in which repetitive self-terminating episodes of ventricular fibrillation were induced by supraventricular beats in a 35-year-old woman after cardiac surgery (Sakamoto, Yamada, and Hiejima, 1973): the patient had an unexplained bizarre T wave and an obviously prolonged QT interval. This is different from the present case where the QT interval was only moderately prolonged. Contrary to the obvious rarity of primary ventricular fibrillation initiated by supraventricular premature beats in patients with acute myocardial infarction, in the experimental model, properly timed supraventricular premature beats could induce ventricular fibrillation if ventricular vulnerability is altered secondary to acute ischaemia (Carrol, Ahuja, and Manning, 1965). This probably suggests that a premature beat of any sort can initiate malignant ventricular arrhythmia if it occurs sufficiently early in the presence of altered ventricular vulnerability. Our observation that supraventricular premature beats initiated episodes of primary ventricular fibrillation only when they began to show a higher degree of aberrant intraventricular conduction may suggest that the mechanism of the arrhythmia was re-entry initiated by a striking delay of activation in some part of the ventricular myocardium.

Some of the antiarrhythmic drugs used in this study may have varying effects on the QT interval and coupling intervals of ventricular premature beats. In 42 per cent of patients antiarrhythmic drugs were not given before the onset of ventricular fibrillation because of absence of warning arrhythmias. None of the remaining patients with ventricular fibrillation were given procainamide or quinidine before the onset of the arrhythmia; both drugs are known to prolong both the QT interval and coupling intervals (Giardina and Bigger, 1973). On the other hand, lignocaine seems to have little or no effect on both the QT interval and coupling intervals (Surawicz and Lasseter, 1970). This suggests that the drug regimen used during the study did not influence the observations on the prematurity index of the ventricular premature beats that initiated primary ventricular fibrillation.

An interesting observation was the limited value of warning arrhythmias in predicting the occurrence of primary ventricular fibrillation. Thus, while warning arrhythmias were present in only 58 per cent of patients who developed primary ventricular fibrillation, similar arrhythmias were also present in 55 per cent of those who did not develop fibrillation. Similar observations were previously reported (Dhurandhar, MacMillan, and Brown, 1971; Lie *et al.*, 1974a). These observations strengthen the argument for prophylactic therapy against primary ventricular fibrillation once an acute ischaemic episode is suspected without reliance on the presence or absence of warning arrhythmias. This approach could be further consolidated if the recent preliminary reports (Lie *et al.*, 1974b; Valentine *et al.*, 1974) of the efficacy of lignocaine in the prevention of ventricular fibrillation are upheld by subsequent studies. Antiarrhythmic therapy may be less effective if applied after the onset of warning arrhythmias. Similar observations have been previously reported (Dhurandhar *et al.*, 1971; Lie *et al.*, 1974a).

The most provocative finding in the present report is the reassessment of the role of the R-on-T phenomenon in primary ventricular fibrillation. In 7 out of 17 patients (41%), it was initiated by a ventricular premature beat with prematurity index >1. The demonstration that 41 per cent of fibrillation was initiated by a ventricular premature beat with long coupling (index >1) in addition to the finding that premature beats with short coupling (index < 1) were observed in 49 per cent of patients who did not develop primary ventricular fibrillation strongly suggests that the R-on-T phenomenon may be a poor predictor of malignant arrhythmias in the early phases of acute myocardial infarction. Few previous reports have shown that ventricular tachyarrhythmias in patients with acute myocardial infarction may be initiated by a ventricular premature beat that does not fall on antecedent T waves (Mounsey, 1967; Stock, 1970). In a recent systematic study (De Soyza *et al.*, 1974), the prematurity index of a ventricular premature beat was found to be a poor predictor of ventricular tachycardia during acute myocardial infarction. Assessment of the role of a ventricular premature beat that initiates an episode of ventricular fibrillation is sometimes clouded by the argument that ventricular fibrillation was not initiated by the first long coupled ventricular premature beat but rather by a subsequent beat that has a very short coupling interval. Others avoided this argument by stating that salvos of ventricular premature beats deteriorated into ventricular fibrillation (Lie *et al.*, 1974a). This argument becomes irrelevant if the first premature beat that initiates an episode of fibrillation is viewed as an integral part of an underlying pathophysiological process and represents the first electrocardiographically evident part of this process (El-Sherif *et al.*, 1975b). The data accrued from several recent studies on experimental myocardial infarction (Han, 1969; Waldo and Kaiser, 1973; Boineau and Cox, 1973; Scherlag *et al.*, 1974; Williams *et al.*, 1974; El-Sherif *et al.*, 1975b) have shed light on the mechanism of initiation of primary ventricular fibrillation in the early stages of myocardial ischaemia. Some studies (Scherlag *et al.*, 1974; Williams *et al.*, 1974; El-Sherif *et al.*, 1975b) have shown that most of the malignant ventricular tachyarrhythmias that follow shortly after ligation of a major coronary vessel are initiated by a long coupled ventricular premature beat and not by one that interrupts the antecedent T wave. This observation is explained by a characteristic pathophysiological mechanism whereby an increasing dispersion of ventricular activation results in a re-entrant tachyarrhythmia (Scherlag *et al.*, 1974; El-Sherif *et al.*, 1975b). Williams *et al.* (1974) found that after acute occlusion of a major coronary vessel in the dog, a ventricular premature beat induced so late in the cardiac cycle to result even in ventricular fusion could induce ventricular fibrillation when the underlying dispersion of ventricular activation was great. In the same study, analysis of episodes of ventricular tachycardia leading to fibrillation showed a progressive increase in the degree of dispersion of ventricular activation of successive beats, whereas in those self-terminating episodes it progressively decreased. These observations provide the pathophysiological explanation for the theoretical question of which beat actually initiated the fibrillation.

Our finding that the majority of cases of ventricular fibrillation initiated by a ventricular premature beat with long coupling seem to occur relatively early in the course of acute myocardial infarction as compared with cases of fibrillation initiated by a short coupled beat is of some interest. Several *in vivo* (Scherlag *et al.*, 1974) and *in vitro* studies (Lazzara, El-Sherif, and Scherlag, 1973; Friedman *et al.*, 1973) suggest that ventricular fibrillation occurring early and late in the course of acute myocardial infarction may have different pathophysiological mechanisms. Re-entry caused by obvious disparity of action potential durations (Lazzara *et al.*, 1973), as well as the contribution of enhanced automaticity which can trigger non-homogeneous conduction (Cranefield, 1973), are possible factors in late primary ventricular fibrillation.

Discretion is always required when data from experimental studies are extrapolated to the clinical situation. However, recent experimental studies offer a satisfactory explanation for the clinical observation that primary ventricular fibrillation can be initiated by a ventricular premature beat with long coupling while a ventricular premature beat with short coupling in other patients with acute myocardial infarction is not associated with ventricular fibrillation. Both the clinical and experimental observations call for a reassessment of both the concept of ventricular vulnerability and the R-on-T phenomenon. Though it may be true that, in the normal heart, the vulnerable phase may be limited to the QT interval, in ischaemia with obvious dispersion of ventricular activation, the vulnerable phase can extend throughout most of the cardiac cycle (Scherlag *et al.*, 1974; Williams *et al.*, 1974; El-Sherif *et al.*, 1975b). Our observations should not be construed to mean that ventricular premature beats with short coupling are not clinically significant but rather to point out that the arrhythmogenic potential in acute myocardial infarction is not confined to those extrasystoles showing the R-on-T phenomenon. Furthermore,

at least in our series, the R-on-T phenomenon was a poor discriminator for the occurrence of ventricular fibrillation. This report, as well as others (De Soyza *et al.*, 1974), seems to depart from a widely held view (Lown and Wolf, 1971) that certain characteristics of the ventricular premature beat can serve as predictors of malignant ventricular arrhythmias in the early phase of acute coronary ischaemia.

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Requests for reprints to Dr. N. El-Sherif, Veterans Administration Hospital, 1201 Northwest 16th Street, Miami, Florida 33125, U.S.A.