Response to Single Threshold Stimuli Following Acute Myocardial Infarction[1] (36832)

HANS JENZER,[2] LEIF LOHRBAUER, AND BERNARD LOWN
(Introduced by Fredrick J. Stare)

Cardiovascular Research Laboratories, Department of Nutrition, Harvard School of Public Health and Cardiovascular Service, Department of Medicine, Peter Bent Brigham Hospital, Boston, Massachusetts 02115

A pressing contemporary problem in cardiology is the identification of patients with coronary heart disease who are susceptible to sudden arrhythmic death. This might be facilitated if the myocardium prone to catastrophic arrhythmia could be shown to possess a predisposition to enhanced ectopic activity. Lown (1) has developed a method to unmask increased Purkinje fiber automaticity following digitalization. In the digitalized heart, delivery of an early diastolic low energy pulse to the endocardium results in a multiple rather than a single propagated response. A pertinent question is whether such a repetitive ventricular response (RVR) is also exhibited by the ischemic myocardium. This question was examined in mongrel dogs subjected to ligation of the left anterior descending coronary artery by a modified two-stage Harris technique (2). After ligation, Harris observed two successive distinct phases of arrhythmia: a quiescent period of 4.0 to 8.0 hr in which there was little arrhythmia; and a period of multifocal ventricular tachycardia (VT) persisting for 24 to 48 hr. This investigation examined the occurrence of RVR during the quiescent period after a multistage coronary artery occlusion.

Materials and Methods. These studies were carried out on 11 mongrel dogs weighing between 18 and 24 kg and consisted of three phases: (a) placement of an inflatable balloon around the left anterior descending coronary artery; (b) inflation of the balloon after recovery from operation; and (c) testing for RVR during the postocclusion quiescent period.

Dogs were anesthetized with 30 mg/kg of pentobarbital and ventilated with a Harvard pump through a cuffed endotracheal tube. The chest was opened through a fourth left intercostal space incision and the anterolateral aspect of the heart was exposed. The left anterior descending coronary artery was dissected at the level of the left atrial appendage and a small silastic balloon (3) was placed around the vessel. The polyvinyl tubing connecting with the balloon was fixed to the pericardium, brought out through an intercostal space and then funnelled subcutaneously and externalized in the nape of the neck.

On days 5 to 7 after balloon placement, dogs were reanesthetized with pentobarbital and ventilation was again sustained by means of a Harvard pump through a cuffed endotracheal tube. Coronary artery occlusion was accomplished in the following manner: the balloon was inflated with 1 ml of saline for 1, 2 and 5 min with each period of inflation separated by a 1-min period of deflation. After the last inflation–deflation sequence, the balloon was reinflated and the tubing was tied. This marked the time of onset of occlusion. A Teflon-coated multistrand-wire electrode was introduced through a jugular vein into the right ventricle. Proper position was ascertained by recording a right ventricular endocavitary electrogram and by evoking a propagated ventricular response with a stimulus of less than 0.5 mA in middiastole. The indifferent electrode was attached through a needle fixed in the precordial area. The test stimulus employed was a 2 msec square wave constant current pulse of

[1] Supported in part by Grants HL-14602 and HL-07776 from the National Institutes of Health, U.S. Public Health Service.

[2] Present address: Kantansspital, Aaurau, Switzerland.

adjustable amplitude that could be varied from 0.1 to 10.0 mA with an accuracy of 3%. The stimulus was synchronized to the R wave of the surface electrocardiogram (ECG) and timed in the cardiac cycle through an adjustable delay permitting variations from 10 to 400 msec with an accuracy of ± 3 msec. An ECG lead II was continuously monitored until the emergence of spontaneous VT, defined as three consecutive ventricular ectopic beats. After the occlusion, attempts to evoke RVR were made at hourly intervals. The threshold for a single propagated response was first determined in electrical mid-diastole, and a ventricular stimulus of 2 mA was used for stimulation (approx 4× threshold). The refractory period was then determined by exploring the cardiac cycle. This was accomplished by reducing R-stimulus interval by 10 msec increments until no response could be elicited. Testing for RVR was studied at spontaneous as well as at paced heart rates of 180 and 200 beats/min (bpm).

Atrial pacing was accomplished by means of a Teflon-coated multistrand steel wire electrode introduced into the right atrium through a jugular vein. The indifferent electrode was attached to a subcutaneous needle positioned over the precordium. Stimulus intensity was maintained at the threshold required for a propagated atrial response. To permit development of RVR after delivery of right ventricular test stimuli, the atrial pacemaker was electronically short-circuited for an interval just sufficient to block three pacing stimuli.

Results. The quiescent period, characterized by absence of VT, lasted for a mean duration of 7.5 hr. During this interval, RVR could be demonstrated in 10 of the 11 dogs (Fig. 1). The RVR phenomenon was characterized by the emergence of one or more ventricular ectopic beats following the electrically evoked response. The interval between the electrically induced and spontaneously occurring responses was always longer than the underlying cycle interval and RVR never degenerated into ventricular fibrillation.

The mean appearance time of RVR after coronary occlusion was 3.7 hr. Once RVR could be evoked it persisted until development of VT in all but two animals. In one dog, RVR developed 1 hr postocclusion, disappeared at 2 hr, but reemerged at 3 hr and persisted for an additional 3 hr until development of VT. A similarly transient disappearance of RVR was noted in a second animal.

The diastolic threshold for a single propagated ventricular response did not change as a result of occlusion and never exceeded 0.4 mA (range 0.2 to 0.4 mA).

In six animals the width of the RVR zone was determined at 10 msec intervals within the cardiac cycle throughout the quiescent period. In five dogs the zone of RVR widened progressively and encompassed an extensive period of diastole prior to the onset of VT. The morphology of the RVR complex was unaltered when elicited from different parts of the cardiac cycle. The morphology of the RVR complex usually differed from the response directly evoked by electrical stimulation (Fig. 1). Differing heart rates did not alter the ease of producing RVR, morphology of the QRS complex, or duration of the RVR zone. These attributes of RVR remained unaltered whether the mechanism was sinus rhythm or atrially paced rhythm at rates of 180 or 200 bpm.

Discussion. In the normal animal a single electrical stimulus applied to the heart evokes a single response. The exception is when a large suprathreshold pulse is discharged during the ventricular vulnerable period; ventricular fibrillation may then ensue. Following myocardial infarction, a stimulus inadequate to precipitate ventricular fibrillation when delivered in the vulnerable period may still precipitate VT (4). Within 4 min of occlusion of the LAD coronary in dogs, Han, Goel and Hanson (5) noted that repetitive ventricular responses followed stimulus-induced premature systoles. Kaplinsky, Yahini and Neufeld (6), as well as Sherlag and co-workers (7), noted paroxysms of arrhythmia including ventricular fibrillation to follow rapid pacing. In these experiments (5–7) reentry was presumed to be the basis for arrhythmia. Indeed, Han, Goel and Hanson (5) demonstrated slowed conduction time in the ischemic area, thus permitting recovery of excitability in noninfarcted myocardium in time to accept a reentrant impulse emerging from the

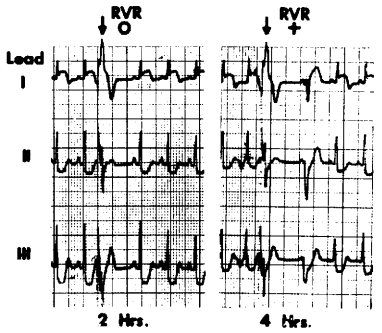

FIG. 1. Two hours after coronary artery ligation an early diastolic stimulus elicits but a single response but no repetitive ventricular response (RVR): (left panel) three limb leads recorded simultaneously. However, within 4 hr following coronary occlusion, an additional response or RVR is provoked (right panel).

ischemic area.

The RVR represents a different category of response. It may be evoked from middiastole and not just from the vulnerable period. A near-threshold stimulus is adequate. It cannot be elicited immediately after coronary artery ligation and requires several hours for evolution of responsiveness. An RVR phenomenon can also be evoked from the digitalized animal where enhanced Purkinje fiber automaticity is the basis of ectopic activity. These factors suggest RVR is due to pacemaker automaticity enhancement. When a coronary artery is abruptly occluded, there is a high immediate incidence of VT and ventricular fibrillation. It would thus appear that following coronary artery occlusion there are two sequential phases of altered excitability: an initial phase with impaired conduction within the ischemic tissue favoring reentrant rhythms including ventricular fibrillation; and a second phase characterized by ever increasing Purkinje fiber automaticity leading to VT. Inded, Kerzner and co-workers (8) also demonstrated two such differing response patterns by utilizing vagal stimulation as the provocative maneuver for exposing changing cardiac excitability following coronary artery occlusion.

Summary. Single threshold stimuli were delivered to the endocardium during early diastole in 11 dogs hourly following multistage balloon occlusion of the left anterior descending coronary artery. RVR could be evoked in all but one animal with a mean appearance time of 3.7 hr after coronary occlusion and preceding onset of spontaneous VT by an average of 2.5 hr. The RVR phenomenon may be helpful in unmasking electrical instability in the presence of coronary heart disease and in providing a simple technique for studying the effects of various interventions on the altered electrophysiologic properties of the ischemic heart.

1. Lown, B., Amer. J. Cardiol. **22**, 251 (1968).

2. Harris, A. S., Circulation **1**, 1318 (1950).

3. Chimosky, J. E., Szentivianyi, M., Zakheim, N., and Barger, A. C., Amer. J. Physiol. **212**, 1025 (1967).

4. Wolff, G. A., Keith, F., and Lown, B., Cardiovasc. Res. **2**, 111 (1968).

5. Han, J., Goel, B. G., and Hanson, C. S., Amer. Heart J. **80**, 778 (1970).

6. Kaplinsky, E., Yahini, J., and Neufeld, H., Cardiovasc. Res. (Abstr. World Congr. Cardiol., 6th, London, Sept. 6–12, 1970, p. 181).

7. Scherlag, B. J., Helfant, R. H., Haft, J., and Damato, A. N., Amer. J. Physiol. **219**, 1665 (1970).

8. Kerzner, J., Wolf, M., Kosowsky, B., and Lown, B., (Abstr.) Circulation **42**, Suppl. III-81 (1970).

Received May 23, 1972. P.S.E.B.M., 1972, Vol. 141.