Adrenergic Influences on the Distal Purkinje System of the Canine Heart

By Lura Ann Harrison, John Wittig, and Andrew G. Wallace

ABSTRACT

The purpose of these experiments was to examine the effects of norepinephrine and propranolol on distal Purkinje fibers of the canine heart. Previous studies have indicated that action potential duration is normally greatest in distal Purkinje fibers 3–4 mm from the Purkinje-muscle junction. In such preparations, premature beats initiated either proximal or distal to the area of maximal action potential duration may propagate with delay or block. Our experiments were performed on the right bundle branch and the distal Purkinje fibers of dog hearts and used standard microelectrode techniques. Premature beats with a coupling interval comparable to the duration of action potentials at the area of maximal duration were conducted with delay. Earlier beats were confined to fibers proximal to the area of maximal action potential duration. Norepinephrine (1 × 10^{-6}M) increased action potential duration in some fibers, consistently prolonged the functional refractory period of distal Purkinje fibers, and produced a marked delay in the propagation of early premature beats. Propranolol (0.25–1.0 mg/liter) shortened action potential duration, shortened the functional refractory period of distal fibers, and reduced or abolished conduction delay and block of early premature beats. These observations suggest that the unique properties of the Purkinje-muscle junction may contribute to the genesis of arrhythmias and that this region is an important site of action of propranolol. The action of propranolol on the Purkinje-muscle junction was dose dependent.

KEY WORDS
cardiac denervation
electrophysiology
norepinephrine
propranolol
sympathetic nerves
arrhythmias

Changes in the activity of the autonomic nervous system exert an important influence on cardiac rhythm. Early studies by Del Castillo and Katz (1) and by Hutter (2) demonstrated that sympathomimetic amines increased the slope of spontaneous diastolic depolarization in the sinus node. A similar effect of catecholamines on the rhythmicity of normal Purkinje fibers was noted by Hoffman and Cranefield (3, p 183). In addition to these effects on isolated automatic cells, several studies also demonstrated that sympathetic nerve stimulation or injections of epinephrine could induce ectopic rhythms in either normal hearts or hearts with experimental myocardial infarction (4, 5). Other investigators reported that removal of the thoracic sympathetic nerves reduced the incidence of arrhythmias following occlusion of a coronary artery (6, 7); subsequent studies in dogs and in man (8–12) confirmed this influence of cardiac sympathectomy. Despite these data, the mechanism(s) by which catecholamines produce disturbances of cardiac rhythm and the mechanism(s) of the protective action of antiadrenergic influences remain to be clarified. The purpose of this report is to illustrate certain features of the distal Purkinje network which might be important to the genesis of reentrant arrhythmias. A second objective is to describe the effects of norepinephrine and propranolol on this region in normal and catecholamine-depleted tissues.

Methods

Adult mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv). The dogs were subjected to a right thoracotomy, and the excised heart was immediately placed in oxygenated Tyrode's solution. The right ventricle was then opened to permit dissection and removal of tissue containing the right bundle branch, the anterior papillary muscle, accompanying branches of the Purkinje system, and a portion of the right ventricular wall. The muscular junction between the papillary muscle and the right ventricular wall was divided, leaving a Purkinje strand as the sole...
connection between the bundle branch and the muscle. The tissue was then pinned in a silver tissue bath, perfused with modified Tyrode’s solution which was equilibrated with a mixture of 95% O₂-5% CO₂ and maintained at 37.5°C. The millimolar composition of Tyrode’s solution was: NACl 137, KCl 5.4, CaCl₂ 1.8, MgCl₂ 1.05, NaH₂PO₄ 0.42, NaHCO₃ 11.9, and dextrose 5.5.

Glass microelectrodes were pulled with a Koří vertical pipette puller and filled with 3M KCl. Electrodes having a tip resistance of 10—20 megohms were selected for use. Microelectrodes were held in Bioelectric Instrument MHI holders and mounted on Prior micromanipulators. Signals from the electrodes were amplified with a unity gain voltage follower and displayed on a Tektronix RM564 storage oscilloscope. Photographs were obtained with a Tektronix C-12 Polaroid camera.

The preparations were stimulated through two silver wires, using a Grass model S-4 pulse generator and isolation unit. The stimulating electrode was positioned over the proximal right bundle branch. Stimuli 2—3 msec in duration and approximately two times threshold were delivered at a basic cycle length of 1,000 msec. The Grass stimulator was triggered by a series of Tektronix 161 pulse generators. A dividing circuit interposed between two pulse generators provided a test pulse which could be delivered after every sixth basic pulse and with any desired coupling interval between the last basic pulse and the test pulse.

In each experiment the preparation was first paced at a frequency of 60 beats/min from the right bundle branch. One microelectrode was used to impale a Purkinje fiber in the proximal right bundle branch, and the action potential from that cell was used to monitor the stability of the preparation. A second microelectrode was then moved in steps of 1—2 mm from the proximal right bundle branch, along the free-running strand of Purkinje tissue, and over the distal strand until it penetrated the subendocardial surface of the right ventricular free wall. At each position action potential duration was measured. These measurements were used to construct a map of the distribution of action potential durations over the length of the preparation (Fig. 1). Premature test pulses were then introduced to determine the functional refractory period of the free-running strand. The interval between the upstrokes of the two action potentials was used to estimate conduction time across the strand. The interval between the upstrokes of the two action potentials was used to estimate conduction time across the strand.

Following these control observations, normal Tyrode’s solution was replaced with a perfusion medium containing norepinephrine (1 × 10⁻⁷ M). After the preparation stabilized the preceding measurements were repeated. Subsequently, norepinephrine was washed out with normal Tyrode’s solution, and the perfusion medium was then changed to a solution containing propranolol at concentrations ranging from 0.25 to 1.0 mg/liter. The preceding observations were again repeated.

Special studies were performed in three previously sympathectomized dogs to determine whether the effects of propranolol observed in normal tissue were attributable to blockade of beta receptors. Approximately 1 week prior to study, these dogs were given 6-hydroxydopamine¹ (20 mg/kg, iv) to deplete their stores of myocardial catecholamines. At the time of death 1 week later, cardiac catecholamine depletion was confirmed by (1) the failure of myocardial contractile force (Walton-Brodie strain-gauge arch) or heart rate to respond to stimulation of the stellate ganglia and (2) the reduction of myocardial catecholamine stores to less than 10% of normal. Catecholamine determinations were made by a modification of the trihydroxyindol method. Tissues removed from these dogs were prepared and studied by the same procedures except that the responses to propranolol were always examined without prior administration of norepinephrine.

Results

Figure 1 shows a photograph of the preparation used for these studies; the block of tissue on the left is a portion of the right septal surface containing the right bundle branch. At the base of the anterior papillary muscle the right bundle branch emerged from beneath the endocardium to become a free-running strand or a “false tendon.” The false tendon continued for a variable distance before dividing into several branches, and these smaller branches then inserted into the trabeculated endocardial surface of the right ventricular wall. As noted in the Methods, all connections other than the false tendon under study were divided. The bottom of Figure 1 is a plot of action potential durations at 25 sites between the stimulating electrode and the right ventricular muscle. A characteristic finding in all preparations was that action potential duration increased as cells were impaled sequentially from the proximal right bundle branch to the distal segments of the false tendon. The region of maximal action potential duration was always located within the false tendon and usually was 2—4 mm from its insertion into the endocardial surface of the right ventricle. As Purkinje fibers of the false tendon penetrated the endocardial surface of the free wall, action potential duration decreased abruptly. Action potentials with the shortest duration were always obtained from muscle cells.

The discrepancy between the action potential duration in the right bundle branch and that in the

¹Merck Institute generously supplied us with 1 g.

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false tendon was accompanied by parallel differences in the absolute refractory periods of those cells. Thus, it was always possible to initiate a premature beat sufficiently early in the proximal right bundle branch to cause block as cells in the false tendon with longer action potentials and refractory periods were encountered. In each preparation premature beats were introduced in the right bundle branch with progressively shorter coupling intervals while action potentials were recorded from cells proximal and distal to the area of maximal action potential duration. As the coupling interval was reduced to a critical level, a response could be elicited in the proximal cell which failed to propagate across the false tendon to the distal cell. The false tendon thus operated as a "gate." The minimum interval between action potentials distal to the gate in response to stimuli delivered to the proximal right bundle branch was defined as the "functional refractory period of the gate."

Table 1 summarizes the effects of norepinephrine on the action potential duration, the functional refractory period of the gate, and the delay of the earliest propagated premature beat. Action potentials were recorded simultaneously from Purkinje cells proximal and distal to the gate during a control period and after exposure to norepinephrine (1 × 10^{-5} M). The effects of norepinephrine in seven successful preparations are shown in the table. Norepinephrine increased action potential duration of proximal cells in four of seven preparations and of distal cells in three of seven preparations. These changes were not statistically significant (paired t-test). Norepinephrine prolonged the functional refractory period of the gate in five of seven preparations, and this effect was statistically significant. Norepinephrine caused a marked delay in the
propagation of the earliest conducted premature beat in all seven preparations.

The effects of propranolol on the action potential duration, the functional refractory period of the gate, and the delay of the earliest propagated premature beat are summarized in Table 2. The results from ten satisfactory studies are presented. Propranolol decreased the action potential duration of proximal cells in eight of nine preparations and of distal cells in nine of ten preparations. Propranolol reduced the functional refractory period of the gate in all eight preparations in which this parameter was determined, and it either reduced or abolished the delay in propagation of the earliest conducted premature beat in all seven preparations in which delay was observed before propranolol was given.

Figure 2 shows the effects of propranolol on action potential duration and a typical dose-response curve. Propranolol decreased the duration of action potentials in the distal right bundle branch and in the false tendon, but not in the ventricular muscle. The effect of propranolol was greatest at the area of maximal action potential duration. Thus, one effect of propranolol was to reduce the discrepancy between action potential durations in proximal and distal regions of the false tendon. An easily detectable decrease in action potential duration was observed with propranolol at a concentration of 0.25 mg/liter. Progressively greater

| Table 1 |

Effects of Norepinephrine (1 × 10⁻⁶M) on Action Potential Duration, Functional Refractory Period of the Gate, and Conduction Delay across the Gate

<table>
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<th>Proximal NE</th>
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<th>Distal NE</th>
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All measurements are in msec. C = control, NE = norepinephrine, proximal = action potential duration proximal to the gate, distal = action potential duration distal to the gate, and FRPG = functional refractory period of the gate.

| Table 2 |

Effects of Propranolol (1 mg/liter) on Action Potential Duration, Functional Refractory Period of the Gate, and Conduction Delay across the Gate

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All measurements are in msec. P = propranolol; all other abbreviations are as in Table 1.
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**FIGURE 2**

Dose-response curves for the effects of propranolol on action potential duration (APD). Horizontal axis is distance along the conduction system from the proximal right bundle branch (RBB) on the left to the distal fibers and the muscle of the right ventricle on the right.

Effects were observed at concentrations of 0.50 and 1.0 mg/liter.

Figure 3 shows a plot of the functional properties of the gate before and after exposure to norepinephrine. Premature stimuli of progressively shorter coupling intervals were introduced into the right bundle branch, and the intervals between the upstrokes of the last basic beat ($P_1$) and the premature response ($P_2$) are shown on the horizontal axis. The corresponding intervals between the basic beat ($D_1$) and the premature beat ($D_2$) in a distal cell are plotted on the vertical axis. During control observations this plot was nearly a straight line, with only minimal evidence of delayed conduction at short $P_1P_2$ intervals. The functional refractory period of the gate was 250 msec. After exposure to norepinephrine the plot was a straight line at wide $P_1P_2$ intervals. However, at short $P_1P_2$ intervals there was evidence of marked conduction delay across the gate (i.e., the $D_1D_2$ interval was much longer than the corresponding $P_1P_2$ interval because of slow conduction across the gate). The functional refractory period of the gate after norepinephrine was 300 msec.

Figure 4 shows a similar plot of the functional properties of the gate before and after exposure to propranolol. The functional refractory period of the gate was reduced from 300 to 255 msec by propranolol. In all preparations in which delayed conduction of early premature beats was observed during the control period, the evidence of conduction delay was reduced or abolished by propranolol. This effect of propranolol on the delayed propagation of early premature beats is also evident in Figure 4.

Figure 5 shows recordings which illustrate certain of the effects of norepinephrine. In A, a premature beat with a coupling interval of 247 msec propagated across the gate without delay. In B, a
FIGURE 5
Effect of norepinephrine on conduction of premature beats. In A-F, the first action potential is the last of a series of beats at a cycle length of 1,000 msec and the second is a response to premature stimulation of the right bundle branch. Responses labeled P were recorded in a Purkinje cell proximal to the gate, and those labeled D were recorded distal to the gate; corresponding P_1P_2 and D_1D_2 intervals are noted. A-C show control responses, and D-F show effects of norepinephrine.

A premature beat with a coupling interval of 230 msec propagated across the gate with a 5-msec delay. This was the earliest premature beat which would propagate, and the D_1D_2 interval of 235 msec defined the functional refractory period of the gate. Data from the same preparation after exposure to norepinephrine are shown in D-F. In D, a premature beat with a coupling interval of 285 msec propagated across the gate without delay. In E, a premature beat with a coupling interval of 270 msec propagated across the gate with a delay of 10 msec. The D_1D_2 interval of 280 was the shortest D_1D_2 interval observed after exposure to norepinephrine and thus defined the functional refractory period of the gate. When the coupling interval was further reduced to 245 msec, the premature beat propagated across the gate with a delay of 98 msec. Premature beats with shorter coupling intervals failed to propagate across the gate. Thus, under the influence of norepinephrine marked delay in the conduction of early premature beats was observed.

The effect of propranolol on propagation of premature beats is illustrated in Figure 6. In A, a premature beat with a coupling interval of 290 msec propagated across the gate without delay. In B, a premature beat with a coupling interval of 254 msec propagated across the gate with a reduced upstroke velocity and a 10-msec delay. A premature beat at 248 msec elicited an action potential proximal to the gate (C) but failed to propagate to the distal cell. D-F show that propranolol reduced action potential duration. The functional refractory period of the gate was reduced to 235 msec. After propranolol, the earliest premature action potentials were initiated from a higher resting membrane potential, and each had an upstroke velocity and a propagation velocity better than those before exposure to propranolol. Thus, propranolol shortened the functional refractory period of the gate and reduced conduction delay on early premature beats.

Finally, we were interested in determining if the effects of propranolol on action potential duration and on the functional properties of the gate were related to its antiadrenergic activity or to a direct membrane effect. To answer this question, studies were performed on preparations obtained from three of five dogs with myocardial catecholamine stores depleted by the administration of 6-hydroxydopamine prior to the studies. In the five dogs that
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FIGURE 6
Effect of propranolol on propagation of premature beats. Action potentials were recorded simultaneously from Purkinje cells proximal (P) and distal (D) to the gate. The first action potential in A–F is the last of a series of six basic beats (1,000-msec cycle length) and the second is a response to an early stimulus introduced into the right bundle branch. A–C are control tracings, and D–F are recordings from the same cells after exposure to propranolol.

Discussion
Stimulation of sympathetic nerves to the heart can produce ventricular fibrillation after experimental coronary artery occlusion (5), and even in a normal heart it can reduce the threshold for ventricular fibrillation (13). On the other hand, removal of sympathetic nerves to the heart reduces the incidence of ventricular ectopic activity after coronary occlusion (8–10) and raises the threshold for inducing ventricular fibrillation. These observations demonstrate that, by a mechanism which remains to be clarified, the probability that an appropriately timed premature beat will lead to multiple reentrant responses and fibrillation is influenced importantly by the level of sympathetic nerve activity.

An insight into at least one of the factors which may influence vulnerability of the heart to premature excitation was provided by Han and Moe (14). They demonstrated that several agents which made the ventricle more or less vulnerable to fibrillation produced a corresponding increase or decrease in the discrepancy of refractory periods in adjacent areas of myocardium. They called this discrepancy "temporal dispersion of recovery of excitability." They reasoned that, if an impulse was initiated at
one site when adjacent regions were in a non-homogeneous state of recovery, the impulse would propagate more rapidly in some directions than it would others and might block in some regions. This setting of slow uneven propagation with areas of block would thus provide the conditions for fragmentation of the wave front and subsequent reentry (15). Cardiac sympathetic nerve stimulation was among the interventions which Han et al. (13) demonstrated to increase temporal dispersion of recovery of excitability and to decrease the threshold for fibrillation. Their observations in an intact heart made it reasonable to search for a model of nonuniform recovery in isolated cardiac tissues and to explore more fully the influence of alterations in sympathetic activity.

In 1970, Myerburg et al. (16) demonstrated that action potential duration was longer in distal Purkinje fibers than it was in either proximal portions of the bundle branch or ventricular muscle. Previous reports had shown that action potential duration was longer in Purkinje tissue than it was in muscle (3 [p 176], 17) and had suggested that the safety factor for conduction at the Purkinje-muscle junction might be unusually low (18). Myerburg et al. (16) showed that the refractory period of distal Purkinje fibers was long and that it was possible to initiate premature beats on either side of this segment because of its longer refractory period. He termed this phenomenon the “gating mechanism.” It should be noted that, whereas Han and Moe (14) observed differences in the refractory periods of adjacent regions of epicardial muscle in the range of 10 to 20 msec, Myerburg et al. (16) and the results of our study indicate differences in action potential duration between proximal and distal Purkinje fibers in the range of 100 msec. Furthermore, in his original article, Myerburg noted that early premature beats would conduct across the gate with delay and that at critical rates of stimulation 2:1 block could be induced. Subsequent studies have shown that interventions which modify refactoriness or conduction in one branch of a branching network of distal Purkinje fibers can lead to repetitive reentrant beats (19). Thus, work by others suggested to us that the gating mechanism of false tendons near their insertion into ventricular muscle might serve as a useful model in which to explore the influence of adrenergic agents on the response to premature stimuli.

Several reports concerned with the electrophysiological effects of epinephrine or norepinephrine and propranolol have shown that these agents prolong and shorten, respectively, the plateau phase of the action potential in Purkinje fibers (3, 20). In our experiments, norepinephrine prolonged the action potential in some, but not all, preparations, although the refractory period was consistently prolonged. The mechanism by which catecholamines prolong action potential duration and recovery of excitability is not known, but there is some evidence that they may increase a slow inward sodium current, calcium current, or both during the plateau (21, 22). There is also evidence that catecholamines may decrease the potassium conductance of the cell membrane (23). To our knowledge there are no data concerning the mechanism by which propranolol shortens the action potential, although this effect has been observed consistently (20, 24). A finding of particular interest in our study, however, was that propranolol exerted its most marked effect on action potential duration at the region of the longest action potentials. A consequence of this action was that the spatial discrepancy of action potential duration along the false tendon and at the Purkinje-muscle junction was attenuated.

When premature beats were introduced into the proximal right bundle branch with coupling intervals which were only a few milliseconds longer than
the functional refractory period of the gate, propagation of the premature beat across the gate was delayed. When the distance between proximal and distal microelectrodes and the interval between phase 0 of the two action potentials were used to estimate conduction velocity in the false tendon under control conditions, values of approximately 2 m/sec were obtained for basic beats. Under these same conditions, early premature beats propagated across the gate with a conduction velocity of approximately 1.0 m/sec. Whenever the conduction velocity of an early premature beat was slow, this delay was reduced by propranolol. A similar finding was observed by Davis and Tente (20).

Norepinephrine not only prolonged the functional refractory period of the gate, but it produced a marked delay in the conduction of early premature beats across the gate. Under the influence of norepinephrine, estimated conduction velocities of 0.1–0.2 m/sec were observed on premature beats. The effects of norepinephrine on propagation of early premature beats could always be reversed by replacing Tyrode’s solution containing norepinephrine with normal Tyrode’s solution. Thus the extraordinarily slow conduction of these early beats could not be ascribed to an irreversible structural change in the Purkinje strand. We did not systematically impale cells within the region of delay under the influence of norepinephrine. In cells proximal and distal to the gate, however, we never observed any noteworthy change in resting membrane potential after the addition of norepinephrine. We did not differentiate the upstroke of the action potentials to compute the rate of rise of the action potential (dV/dt), but a marked decrease in dV/dt on premature beats which propagated with delay was easily appreciated by simple inspection of some records. Conduction velocities of 5 or 10% of normal and even less have been observed in Purkinje fibers in which resting membrane potential has been depressed by a localized increase in extracellular potassium concentration (25). The mechanism of such slow conduction is difficult to explain (19), but the fact that it can occur under the influence of norepinephrine certainly lends credence to the validity of the reentry hypothesis of adrenergically induced alterations of vulnerability.

Because of the opposite effects of norepinephrine and propranolol on the duration of the action potential, the functional refractory period of the gate, and the conduction of premature beats across the gate, we initially attributed the actions of propranolol to its property of being a beta-blocking agent. However, the fact that propranolol exerted a qualitatively and quantitatively similar action on tissues obtained from catecholamine-depleted dogs is against this interpretation. Furthermore, current studies in our laboratory indicate that the dextroisomer of propranolol, which is not a beta-receptor antagonist, also shortens action potential duration. Thus a racemic mixture of d- and l-propranolol, which is a potential clinical antiarrhythmic agent (26, 27), exerts important actions which are not attributable solely to beta-receptor antagonism. The actions we have described are not quinidineline; rather, they resemble the effects of lidocaine. These actions include shortening of action potential duration, the well-known antiarrhythmic effect, and a lack of effect on the upstroke of the action potential (28, 29). The effects of propranolol on action potential duration demonstrated dose-response kinetics and were observed at concentrations of 0.25 mg/liter. The range of plasma levels reported to exert antiarrhythmic effects in man is 0.04 to 0.13 mg/liter (30, 31).

It is generally accepted that the inherent duration of the action potential in Purkinje fibers is substantially longer than that in ventricular muscle. Mendez et al. (32) have demonstrated clearly that at the Purkinje-muscle junction there is a continuous gradation between the longer action potential of the specialized fibers and the shorter action potential of the muscle fibers. They also provided clear evidence of electrotonic interactions at this junction. It is interesting to speculate that the "hump" in maps of action potential duration in the false tendon (Fig. 1) may reflect a relative absence of electrotonic interactions with muscle at this region of a free-running strand. The shorter action potentials at either end of the preparation might reflect electrotonic interaction between Purkinje and muscle cells at the base of the papillary muscle and the right ventricular free wall, respectively. If this hypothesis is correct, then it follows that maximal action potential duration and the functional refractory period of various gating segments would be influenced by the length of the free-running strand and, for any given length, would be influenced by whether the intercellular connections between Purkinje and muscle offer a high or a low resistance to current flow. Such a system would allow for considerable nonhomogeneity of action potential duration and functional properties on

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anatomic grounds. Furthermore, if propranolol increased the space constant of the false tendon, such an action would allow for more electrotonic interaction with neighboring fibers and reduce the discrepancy of action potential duration. Although an action on the space constant is by no means established from the current results, it represents a plausible and testable hypothesis regarding mechanisms which might explain the ability of propranolol to shorten action potentials in the false tendon while exerting a much smaller effect on the proximal right bundle branch, the Purkinje fibers distal to the gate, and the muscle.

In conclusion, this preparation of Purkinje tissue and attached ventricular muscle seems to represent a useful model for studying factors which may influence the characteristics of the action potential and the propagation of early beats through a system with nonhomogeneous rates of recovery of excitability. We have demonstrated that alterations of the catecholamine background in this preparation affect the action potential duration and the propagation of premature beats in a manner which may contribute to our understanding of adrenergic and antiadrenergic influences on ventricular vulnerability. Finally, our observations suggest that a racemic mixture of propranolol exerts important and potentially arrhythmogenic actions on this preparation, but that these effects although directionally opposite to those of norepinephrine, are not solely attributable to beta-receptor antagonism.

References


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ADRENERGIC EFFECTS ON PURKINJE TISSUE


Adrenergic Influences on the Distal Purkinje System of the Canine Heart
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doi: 10.1161/01.RES.32.3.329

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/32/3/329

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