Acetylcholine-Induced Reversal of Canine and Feline Atrial Myocardial Depression during Stretch, Cardiac Failure, and Drug Toxicity

By Henry Gelband, Robert J. Myerburg, Brian F. Hoffman, and Arthur L. Bassett

ABSTRACT

Microelectrode and isometric recording techniques were used to evaluate the effects of acetylcholine (ACh) on depressed isolated preparations of dog and cat atrial muscle. Atrial muscles were maintained at 36-37°C with warmed Tyrode’s solution and were stimulated at frequencies of 30 or 60/min. Depolarization to resting potentials of approximately -50 mV was noted (1) after excessive stretch was applied, (2) in muscles obtained from cats in overt right heart failure, and (3) during exposure of the muscles to excessive concentrations of acetylstrophanthidin or lidocaine. Depolarized muscles demonstrated action potentials of smaller amplitude and rate of rise. Exposure to ACh (2.7 × 10⁻⁶M) had a minimal effect on resting potential in normal dog and cat atrial muscle and was accompanied by significant negative inotropic actions. The same concentration of ACh markedly increased resting potential and action potential amplitude and induced positive inotropic effects in depolarized muscles; these effects also occurred during beta-adrenergic blockade. We suggest that the positive inotropic effect of ACh in depressed muscles may result from (1) a more synchronous contraction of cells within each muscle, (2) recruitment of previously quiescent cells in contraction, (3) possibly increased calcium inflow in individual cells during depolarizations of greater magnitude, and (4) an increase in the number of interacting sites between actin and myosin after resting potential is improved.

The established effects of acetylcholine (ACh) on normal mammalian atrial muscle include a diminution of active force generation (1-5), an acceleration of repolarization of the transmembrane action potential (1-4, 6), and a modest hyperpolarization of the transmembrane resting potential (6). The ACh-induced increase in resting potential is much more evident in partially depolarized myocardium and may result in an improvement in contractility. In regard to the latter, Marshall (7) has shown that ACh increases resting potential and restores both excitability and mechanical activity in rabbit atrial muscle depolarized by hypothermia. Subsequently, it has been observed that although ACh depresses active force in normal canine atrial muscle the same concentration increases active force in canine atrial muscle preconditioned by exposure to toxic concentrations of acetylstrophanthidin (8, 9).

In the present study, we used a combination of microelectrode and isometric force recording techniques to further characterize and explain the basis for the positive inotropic effect of ACh in acetylstrophanthidin-treated atrium. Moreover, we studied atrial muscle partially depolarized by (1) stretch, (2) cardiac failure, and (3) toxic concentrations of lidocaine to determine the effects of ACh on contractility under these conditions. Our data indicate that ACh has significant positive inotropic effects on active contractile force in the presence of each of these depressant influences through its restorative action on cell membrane electrical polarization.

Methods

Free-running atrial trabeculae were dissected from hearts of normal adult dogs (12-20 kg) and normal adult cats (1.8-3.5 kg) anesthetized by intravenous (dogs) or intraperitoneal (cats) injections of sodium pentobarbital (30 mg/kg). Atrial trabeculae were also obtained from cats with overt right heart failure induced by chronic partial constriction of the main pulmonary artery. A description of this surgical procedure has been published elsewhere (10, 11). Before they were killed, the cats with
right heart failure or sham-operated cats were studied 3–90 days after surgery; they were anesthetized as described earlier and ventilated with room air by intermittent positive pressure. Their chests were opened, and right atrial and ventricular pressures were measured by direct puncture of the appropriate cavities with 22-gauge needles attached to flexible catheters and Statham blood pressure transducers.

Each trabecula was mounted horizontally between a micrometer movement and a transducer in a water-jacketed Lucite myograph. The myograph, transducer, and temperature control system have been described previously (10–12). Temperature was maintained at 36-37°C by flowing (6 ml/min) oxygenated Tyrode’s solution warmed by the water jacket through the tissue chamber. Temperature varied by no more than 0.2°C during the course of each experiment. Drugs were added to the reservoir bottle of Tyrode’s solution or directly to the chamber; adequate mixing of drugs added to the bath chamber was obtained by bubbling 95% O₂-5% CO₂ through a small sintered glass gas dispersion tube in the chamber.

Developed force was measured with an isometric transducer (Statham UC-2). The output of the transducer was amplified (Tektronix 3A10) and displayed on an oscilloscope (Tektronix RM 565, RM 564). Muscle length was adjusted to optimal length so that each muscle developed maximal isometric force. Muscle cross-sectional area (at optimal length) was determined in a previously described manner (10); data are presented from experiments on muscles with cross-sectional areas < 1.0 mm².

The muscles were stimulated at 30 or 60/min with rectangular pulses 2–3 msec in duration delivered through point electrodes. Stimuli were 10–15% above threshold. In several experiments, high-intensity field stimulation was applied via bare silver leads placed parallel on each side of the preparation (13). Glass microelectrodes (10-30 megohms of tip resistance) were used to impale single cells in each muscle preparation. Transmembrane potentials were amplified (Biolectric Instruments, NF1) and displayed on the oscilloscopes. The electrical and mechanical responses were photographed from the cathode-ray tube with a Polaroid camera. Action potential rate of rise was monitored as previously described, and input capacity neutralization was checked via a saw-toothed calibrating signal which was differentiated and displayed on each sweep of the oscilloscope (14). The duration of the action potential at 75% repolarization was also measured. For most experiments, data were obtained by continuously monitoring a single cell. Maintained impalements were not possible during experiments in which muscle length was changed. Control measurements of electrical and mechanical properties were made 1–1.5 hours after the muscle had been mounted in the chamber.

All solutions were made with twice-distilled, deionized water. Drugs used in this study were acetylcholine chloride, acetylstrophanthidin (Eli Lilly and Co.), dl-alpenol hydrochloride (H56/28, AB Hässle), atropine sulfate, lidocaine hydrochloride, and dl-propranolol hydrochloride (Inderal, Ayerst Laboratories). The molecular weight of atropine used to calculate concentrations was taken as 347.4 (atropine [SO₄]₄).

Results

**EFFECTS OF ACh ON NORMAL ATRIAL MUSCLE**

ACh in a concentration of 2.7 × 10⁻⁶ M (0.5 μg/ml) in Tyrode’s solution caused modest increases in resting membrane potential, and action potential duration (measured at 75% repolarization) was consistently shortened (Table 1). These effects were maximum after 1–2 minutes of exposure, persisted as long as the drug was present (usually not longer than 3 minutes), and were consistent with those noted in prior studies (1, 6). A negative inotropic effect of ACh invariably accompanied the altered action potential (Fig. 1); peak isometric force decreased 40–85% in six dog atrial muscles and five cat right atrial muscles during exposure to 2.7 × 10⁻⁶ M ACh.

**EFFECTS OF ACh ON OVERSTRETCHED MUSCLES**

The effects of ACh were different on canine atrial muscles depolarized by excessive stretch (Fig. 1). In four muscle preparations (36°C, 30/min), an

### Table 1

**Effects of Acetylcholine on Transmembrane Electrical Activity of Normal Dog and Cat Atrial Muscles**

<table>
<thead>
<tr>
<th></th>
<th>Resting potential (mV)</th>
<th>Action potential amplitude (mV)</th>
<th>Action potential duration (75%) (msec)</th>
<th>dV/dt (phase 0) (v/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dog</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>81.9 ± 5.9</td>
<td>97.0 ± 9.4</td>
<td>158.0 ± 21.2</td>
<td>165.8 ± 16.1</td>
</tr>
<tr>
<td>ACh</td>
<td>86.1 ± 7.3*</td>
<td>100.4 ± 10.4*</td>
<td>101.5 ± 34.4*</td>
<td>183.6 ± 17.7</td>
</tr>
<tr>
<td><strong>Cat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>67.8 ± 5.8</td>
<td>75.4 ± 3.5</td>
<td>103.8 ± 4.9</td>
<td>115.0 ± 15.8</td>
</tr>
<tr>
<td>ACh</td>
<td>71.0 ± 1.2*</td>
<td>82.2 ± 7.2*</td>
<td>66.0 ± 17.9*</td>
<td>119.0 ± 17.8</td>
</tr>
</tbody>
</table>

Measurements were made at maximal effect of 2.7 × 10⁻⁶ M acetylcholine (ACh). Data are shown as means ± SE and are from maintained single-cell impalpements. The number of experiments is given in parentheses.

* P < 0.01 (paired t-test).
GeneRalex MYERBURG, HOFFMAN, BASSETT

Control

ACh 2.7x10^-6 M

Stnch

ACh 2.7x10^-6 M

30/min 36°C 100 m/sec

FIGURE 1

Effect of acetylcholine (ACh) on overstretched dog atrial muscle. Top Left: Isometric contraction (top trace), control action potential (middle trace), and maximum rate of rise of the action potential preceded by a calibration signal (14) (bottom trace). Top Right: Maximal effect of ACh (2.7 x 10^-6M). A marked shortening of the action potential and a decrease in isometric force can be seen. The resting potential, the action potential amplitude, and the rate of rise of the action potential were not significantly changed. (There was a small decrease in action potential rate of rise for this particular normal cell, but minor variations in the rate of rise frequently occur on a beat-to-beat basis in normal tissue (see Table 1 for summed data). Bottom Left: Records from the same muscle after the length had been increased 110% above control. Note the small membrane response (12 mV) to electrical stimulation (top trace) and the almost complete absence of mechanical activity (middle trace). Bottom Right: Exposure of the overstretched muscle to ACh resulted in an 18-mV increase in resting potential, an increase in the action potential amplitude of the impaled cell, and an increase in isometric contraction; the rate of rise of the action potential was restored to ~40 V/sec.

EFFECTS OF ACh ON MUSCLES FROM CATS IN HEART FAILURE

Overdistention of atrial muscle can occur in heart failure, and we therefore evaluated the action of ACh on atrial muscles removed from sham-operated and pressure-overloaded cat hearts. In preparations from three sham-operated cats, peak force decreased by an average of 47% and resting potential increased by 1.5 mV during exposure to 2.7 x 10^-6M ACh.

Resting potential and action potential amplitude were significantly reduced in right atrial preparations from five cats with chronic right heart failure. Peak active isometric force was 324 ± 62.8 (SE) mg/mm². Exposure of these preparations to ACh was followed by an increase in resting potential (Table 2) and a positive inotropic effect (Fig. 2); peak active force increased to 407.4 ± 72.9 mg/mm². The increase was significant (P < 0.01, paired t-test). In two instances, there was lengthening of the action potential plateau phase, but there were no significant changes in plateau duration in the other three experiments.

The positive inotropic effect of ACh on “failed” atrium was further substantiated in two other experiments on muscles from the right and left atria of cats with pressure overload-induced right heart failure. The same concentration of ACh (2.7 x 10^-6M) induced increases in resting membrane potential and a positive inotropic effect in failed right atrial muscle, but no significant change in membrane potential and a negative inotropic effect occurred in the normal left atrial preparations (Fig. 3).

Table 2: Effect of Acetylcholine on Transmembrane Potentials of Depressed Dog and Cat Atrial Muscles

<table>
<thead>
<tr>
<th>Condition</th>
<th>Resting Potential (mV)</th>
<th>Action Potential Amplitude (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stretch (4)</td>
<td>51.3 ± 2.9</td>
<td>16.5 ± 4.2</td>
</tr>
<tr>
<td>ACh (4)</td>
<td>65.5 ± 3.8*</td>
<td>45.0 ± 10.0*</td>
</tr>
<tr>
<td>AcSt (4)</td>
<td>54.3 ± 5.9</td>
<td>18.0 ± 13.6</td>
</tr>
<tr>
<td>ACh (4)</td>
<td>69.0 ± 5.9*</td>
<td>69.0 ± 10.2*</td>
</tr>
<tr>
<td>Failed (5)</td>
<td>62.8 ± 13.6</td>
<td>53.4 ± 15.2</td>
</tr>
<tr>
<td>ACh (5)</td>
<td>73.0 ± 8.1†</td>
<td>72.6 ± 15.5*</td>
</tr>
<tr>
<td>Lidocaine (4)</td>
<td>53.5 ± 3.4</td>
<td>53.3 ± 6.3</td>
</tr>
<tr>
<td>ACh (4)</td>
<td>69.0 ± 3.2*</td>
<td>81.5 ± 12.5*</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE; note the marked increases in resting potential and action potential amplitude induced by acetylcholine (ACh, 2.7 x 10^-6M) in the depressed preparations. AcSt = acetylstrophanthidin. The number of experiments is given in parentheses. All of the experiments were done on dog atrial muscle except those under “Failed” which were done on cat atrial muscle.

* P < 0.01 (paired t-test).
† P < 0.05 (paired t-test).

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RHF (10 DAY) ACh 2.7 x 10^-6 M

Effect of acetylcholine (ACh) on atrial muscle from a cat with right heart failure (RHF). **Left:** Depressed action potential (top trace) and isometric force (bottom trace) developed by a muscle removed from the right atrium of a cat with right heart failure 10 days after pressure overloading. **Right:** Addition of ACh (2.7 x 10^-6 M) caused a marked increase in resting potential (~18 mV), an action potential of larger magnitude, and an increase in isometric force of approximately 50%. Propranolol (10^-6 M) was present in all of the solutions.

EFFECTS OF ACh ON ACETYLSTROPHANTHIDIN-TREATED MUSCLES

The electromechanical responses to 2.7 x 10^-6 M ACh were studied in atrial muscles exposed to toxic concentrations of acetylstrophanthidin. The concentration of acetylstrophanthidin used in this series of experiments (1.0 x 10^-6 M) resulted within 30-45 minutes in partial depolarization of most cells sampled so that the resting potential was reduced to approximately -50 to -60 mV. At that time, active isometric force was reduced to 5-20% of control, and partial contracture was present (resting force was increased and maintained at 300-700 mg above control). Occasionally, a muscle preparation became inexcitable, even when the mode of stimulation was switched from point stimulation to field stimulation. Addition of ACh to the Tyrode’s solution superfusing acetylstrophanthidin-depolarized muscles while acetylstrophanthidin remained in the solution resulted in an increase in resting membrane potential (range 8 to 25 mV, mean ~15 mV, Table 2). Frequently, a cell that had been made unresponsive to a propagating impulse or that was unexcited because of conduc-

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action block induced by the acetylstrophanthidin demonstrated action potentials coincident with the increase in resting potential after exposure to ACh. However, the action potentials which developed were reduced in magnitude relative to preacetylstrophanthidin values (Fig. 4). Cells maintaining small, slowly rising action potentials during exposure to toxic concentrations of acetylstrophanthidin also developed action potentials of greater magnitude after exposure to ACh, but these action potentials were smaller than those observed in control preparations (Table 2). Simultaneous with the improvements of transmembrane action potential characteristics, there was an increase in active force in poorly contracting muscles and a reappearance of active force in muscles that had previously been inexcitable or that showed marked conduction block (Fig. 4). In control experiments on four additional muscles, superfusion with acetylstrophanthidin-free Tyrode's solution was begun when the resting potential and the action potential amplitude had been reduced to approximately the values shown in Table 2. Three of these preparations stopped generating action potentials despite superfusion with drug-free solution; the remaining preparation showed a transient increase in resting potential of < 4 mv, but eventually it also showed no action potentials in response to stimulation.

For another series of experiments, stimulation was discontinued 20-60 seconds prior to administration of ACh to acetylstrophanthidin-depolarized muscles. ACh (2.7 \times 10^{-6} M) induced a marked increase in transmembrane resting potential and a modest decrease in resting force for unstimulated acetylstrophanthidin-treated dog atrial muscles (Fig. 5). For four such unstimulated preparations, ACh induced a 14-19-mv increase in resting potential and a 20-90-mg/mm² decrease in resting force. The increases in resting potential caused by ACh in stimulated or unstimulated muscles exposed to the toxic concentrations of acetylstrophanthidin were readily reversed by the addition of atropine to the bath or the Tyrode's solution reservoir bottle. Pre-treatment of normal or depolarized atrial muscles with atropine prevented or minimized the effects of ACh.

**EFFECTS OF ACh ON LIDOCAINE-TREATED MUSCLES**

Lidocaine (5 \times 10^{-4} M) exerts a negative inotropic effect on dog atrial trabeculae, and addition of ACh to the superfusate bathing such muscles elicits a positive inotropic response (8). In all 11 experiments of this type, we noted that exposure to lidocaine (5 \times 10^{-4} M) elicited an increase in the voltage necessary to excite the preparation and a decrease in the membrane resting potential; slow action potentials (15, 16) were induced in response to electrical stimulation as the contractile activity diminished (Fig. 6). Muscles with slow potentials progressively developed less force. When ACh (2.7 \times 10^{-4} M) was added to the Tyrode's superfusate of canine atrial fibers partially depolarized by lidocaine and generating slow action potentials, the cells demonstrated a restoration of membrane voltage toward normal values (Table 2) and action potentials of greater amplitude and rate of rise; in addition, the preparations showed an increase in developed force (Fig. 6). In these muscles with slow potentials induced by lidocaine, superfusion with lidocaine-free Tyrode's solution for periods up to 30 minutes did not reverse the electrical effects of the drug. Several muscles had a gradual diminution of slow potential amplitude and eventually demonstrated electrical and mechanical quiescence during exposure to lidocaine. Resting potential was also increased by ACh (5–12 mv) in these muscles, but despite the increase in membrane potential the muscles remained inexcitable.

Many of the experiments on failed, over-stretched, or drug-poisoned muscles were carried out in the presence of beta-adrenergic blocking agents.
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Effect of acetylcholine (ACh) on lidocaine-treated canine atrial muscle. A: Control action potential, isometric contraction, and action potential maximum rate of rise (bottom trace). B: Abbreviation of the action potential and decrease in isometric force brought about by \(2.7 \times 10^{-8}\) ACh. C: Effects of exposing the muscle to lidocaine \((5 \times 10^{-4}\text{M})\) for 25 minutes. Note the slow action potential which arises from a low resting potential. D: ACh \((2.7 \times 10^{-6}\text{M})\) drives membrane potential back toward normal levels, improves action potential amplitude, and increases isometric force in lidocaine-treated muscles. Propranolol \((10^{-6}\text{M})\) was included in all of the solutions.

Discussion

The depression of action potential magnitude and active force generation induced by exposing rabbit atria to cool Tyrode's solution (15-18°C) is reversed by exposure to ACh \((10^{-7}\text{g/ml})\) (7). These data and our results may be complicated by ACh-released endogenous cardiac catecholamines, which may increase resting potential and active force in depressed myocardium (11, 17). Similarly, ACh-induced release of endogenous cardiac catecholamines may be responsible for restoration of spontaneous activity in rabbit atria that cease beating after isolation in Tyrode's solution for 24-30 hours (18). However, the experiments in the present report conducted when beta receptors were blocked indicate that ACh acts directly to increase resting potential in depressed atrium (our experiments do not rule out an alpha-adrenergic blocking effect of ACh-released endogenous catecholamines).

Myocardial intracellular ion concentrations are altered during depolarization induced by exposure to toxic concentrations of digitalis compounds (19) and experimentally produced cardiac failure (20). Ionic changes (i.e., potassium efflux) in dog atria during exposure to lidocaine are rarely evident at concentrations lower than those used in our experiments (21). The membrane and "ionic" actions of ACh on partially depolarized atria were similar to the drug's actions on normal atria, but data on ACh-induced ionic changes in depressed atria are unavailable. In normal atrial cells, ACh may increase resting potential and shorten action potential duration by increasing the membrane permeability to potassium (22) and the outward potassium current (23). However, the effect of the drug may, in fact, be more complicated. High ACh concentrations reduce contractile force and action potential duration in guinea pig atria. Subsequent marked increases in extracellular calcium increase contractile force to above the control level, but increased calcium has little effect on action potential duration (24). Recently, Giles and Tsien (25) have shown that ACh increases membrane conductance in voltage-clamped frog atrial trabeculae at voltages near the resting potential; presumably this action is due to an effect on potassium membrane current. They have also shown that exposure to ACh reduces the slow inward (calcium?) current; they suggest that this phenomenon may directly explain the decrease in action potential duration and the negative inotropic effect of ACh in normal atria. We did not observe a depressant action of ACh on the action potential plateau or amplitude in depressed atria, and we suggest that its effects on potassium conductance, restoration of resting potential, and indirect restoration of sodium conductance predominated.

Diminished action potential amplitude and rate of rise lead to a reduced rate of action potential propagation (26). The partial failure of action potential conduction or the appearance of slowly propagated conduction may reduce peak contractile force (11). More marked decreases in resting potential may also result in inexcitability or conduction block in a portion of the total population of cells; such cells cannot participate in contraction even if gross conduction is maintained. During conduction of partially depolarized myocardium, there may also be a decrease in calcium around the contractile elements, since it is conceivable that, during depolarizations of small magnitude, there may be a reduction in the net inward movement of calcium across the sarcolemma (27). Thus, the calcium available for initiation of excitation-contraction coupling in individual cells may be so
reduced that function is impaired (28). Each of these mechanisms could contribute to a decrease in the active force developed by the isolated myocardium.

The action of ACh on conduction and contraction in cold-depressed rabbit atria (7) apparently occurs as a result of its ability to increase the resting potential and also the action potential rate of rise and amplitude of the population of cells, since the latter properties directly relate to membrane potential at the time of excitation (26). Increased action potential amplitude and rate of rise probably result in increased conduction velocity and greater temporal uniformity of conduction and contraction in the total population of cells and might increase peak developed force in depressed myocardium. For other more markedly depolarized cells, the action of ACh to drive membrane potential toward normal values may restore excitability to these cells and allow them to participate in contraction. In short, the positive inotropic effect of ACh on depressed atrium results from (1) more synchronous contraction of cells within each muscle, (2) recruitment of previously quiescent or conduction-blocked cells, and possibly (3) increased calcium inflow for each individual cell during depolarizations of greater magnitude and, in some instances, increased duration.

Effects on conduction probably do not account for the increased resting force in acetylstrophanthidin-treated muscles. Perhaps in these muscles, the increase in resting force is partially caused by the decrease in resting potential (we recognize that digitalis compounds may have effects on the calcium concentration around the myofibrils which are separate from those induced by the decreased resting potential). This speculative view as to the effect of decreased resting potential on resting force is based on data which suggest that membrane potential may influence myocardial diastolic force (29) and our present finding that, when resting potential is increased, resting force is decreased in unstimulated acetylstrophanthidin-poisoned myocardium. Although the mechanism for the action of ACh on resting force is unclear, the decrease in resting force might result in the increase in the available sites of interaction between actin and myosin during contraction and thus lead to an increase in peak active force.

Epinephrine also exerts a positive inotropic effect on ventricles removed from cats with overt ventricular failure, partly through its restorative action on depolarized cells (11). Our present data further support the concept that partial depolarization contributes to contractile dysfunction in isolated myocardium, since ACh, which usually exerts a negative inotropic action on normal mammalian atria, demonstrates a positive inotropic effect in partially depolarized atria in conjunction with its restoration of resting potential. The significance of partial depolarization to the contractile performance of the in situ heart is uncertain; it is not known whether partial depolarization contributes to alterations in myocardial compliance during cardiac disease in man (30).

References
2. Vaughan Williams EM: Simultaneous measurements of contractions and intracellular potentials in isolated rabbit atria exposed to acetylcholine. J Physiol (Lond) 147:325-332, 1959
3. Furcigott RF, Sleator W Jr, de Gubareff T: Effects of acetylcholine and epinephrine on the contractile strength and action potential of electrically driven guinea pig atria. J Pharmacol Exp Ther 129:405-416, 1960
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18. BÜLBING E, BURN JH: Action of acetylcholine on rabbit auricles in respect to acetylcholine synthesis. J Physiol (Lond) 108:508–524, 1949


23. HARRIS EJ, HUTTER OF: Action of acetylcholine on the movements of potassium ions in the sinus venosus of the heart. J Physiol (Lond) 133:58–59, 1956


27. BEELER GW Jr, REUTER H: Relation between membrane potential, membrane currents and activation of contraction in ventricular myocardial fibers. J Physiol (Lond) 207:211–229, 1970


Circulation Research, Vol. 37, November 1975
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Circ Res. 1975;37:542-549
doi: 10.1161/01.RES.37.5.542

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

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