Effects of Acebutolol on Chronic Stable Angina Pectoris

A Placebo-controlled, Double-blind, Randomized Crossover Study

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SUMMARY We evaluated the effects of acebutolol, a cardioselective β-adrenergic blocking agent, on the anginal pattern and exercise tolerance in 44 patients with chronic stable angina. There were 43 males and one female, with a mean age of 57 years (range 48–73 years).

The study consisted of an initial 4-week, single-blind placebo control phase, followed by a 3-week, single-blind dose-titration phase using increasing doses of acebutolol and by two 5-week double-blind phases that included randomization to acebutolol or placebo and crossover. A 1-week withdrawal schedule followed each treatment phase. All patients kept a diary of anginal frequency and nitroglycerin consumption. Capsule counts of returned medication were made at each visit. Exercise treadmill tests were performed at entry into the study and on the final day of each of the four phases.

Acebutolol produced a significant decrease in the frequency of angina attacks, consumption of nitroglycerin and exercise capacity. Resting and peak exercise values were significantly reduced. Heart rates were reduced by 16% and 18%, respectively (p < 0.002) and rate-pressure products by 17% and 30%, respectively (p < 0.002). At effective antianginal dosages, acebutolol had no significant adverse effects on pulmonary functions. No clinical side effects of acebutolol necessitated drug discontinuance.

Acebutolol is a well-tolerated β-blocking drug that significantly reduces spontaneous anginal frequency, decreases consumption of nitroglycerin and increases exercise capacity in patients with chronic stable angina. It is a useful therapeutic addition to the group of β-adrenergic blocking agents. Further, its lack of deleterious effects on the bronchial smooth muscle suggests that acebutolol may be safely used in patients in whom angina is associated with obstructive pulmonary disease.

THE THERAPEUTIC EFFICACY of propranolol hydrochloride, a noncardioselective β-adrenergic blocking agent, for the treatment of ischemic heart disease and symptomatic angina pectoris has been shown. However, the adverse effects on bronchial and vascular smooth muscle constriction that accompany noncardioselective β blockade have stimulated interest in identifying more cardioselective β-blocking agents. Cardioselective β blockade may be associated with improved exercise capacity and a lower risk of inducing glucose intolerance compared with noncardioselective blockade. Acebutolol, unlike propranolol, has been shown to be cardioselective. It also possesses mild intrinsic sympathomimetic activity, posing a theoretical limitation to its antianginal effects; therefore, careful clinical testing to assess acebutolol for its overall effects in the treatment of angina is crucial.

Studies of this new agent for the treatment of angina pectoris have been limited by a failure to adhere to all of the widely accepted standards for the evaluation of antianginal drugs, including documentation of disease in patients with frequent anginal pain, diaries for recording anginal pain and nitroglycerin consumption, randomization procedures with placebo-controlled, double-blind design, large homogeneous sample sizes and, especially, multistage exercise stress testing. The present study was undertaken to investigate the effects of oral acebutolol...
on the frequency of angina and exercise capacity using a placebo-controlled, double-blind, randomized crossover study design in a large group of patients with chronic stable angina pectoris.

Methods

Subjects

The study group consisted of 44 ambulatory patients (43 males and one female), mean age 57 years (range 48–73 years), from the outpatient clinics of the Veterans Administration Medical Center, Washington, D.C., and the St. Vincent Hospital, Worcester, Massachusetts. Each patient had a primary diagnosis of chronic stable angina pectoris for at least 3 months and signed a consent form approved by the respective institutional review committee before entering the study. A minimum of three episodes of angina during each week with an overall average of five or more episodes of angina per week during the first 4 weeks of the single-blind placebo phase was required; in addition, each patient had to demonstrate an abnormal response to a standardized maximal multistage treadmill exercise test with at least 1 mm of flat or downward-sloping ST segment depression 0.08 second after the J point, associated with anginal limitation to exercise capacity. Pulmonary function testing consisting of spirometry and flow volume loops was performed in 25 patients at various periods during the study.

Exclusion Criteria

Patients who had a myocardial infarction or who underwent cardiac surgery (within 6 months) were excluded. Patients with severe heart failure, atrioventricular block greater than first degree (or PR ≥ 0.30 second), conduction disturbances with QRS prolongation greater than 0.09 second, severe renal insufficiency (serum creatinine ≥ 2 mg%), diabetes mellitus requiring insulin, symptomatic asthma, or signs or symptoms compatible with systemic lupus erythematosus were excluded from the study. Patients judged uncooperative or incapable of completing a standardized maximal multistage treadmill exercise test were also excluded.

Thirty patients in this study (68%) had coronary arterial narrowing confirmed by coronary arteriography; 28 of these (93%) had confirmed multivessel coronary artery obstructions (≥ 70% cross-sectional area in each involved coronary artery) and two patients (7%) had one-vessel disease. Nineteen patients (43%), including eight of the fourteen (57%) patients who did not have coronary arteriography, had clinically documented myocardial infarctions more than 6 months before this study. Only six patients (14%) lacked either angiographic evidence of coronary narrowing or a history of myocardial infarction.

Study Design

During the study, patients were permitted sublingual nitroglycerin tablets (0.6 mg; Eli Lilly) as the only antianginal medication other than test capsules, which were administered three times daily. Nitroglycerin tablets were used when necessary to abort anginal episodes and were not used prophylactically; they were supplied in bottles of 100 tablets and were replaced at each visit to ensure potency. Daily patient diaries of anginal attacks and investigator-confirmed counts of the returned capsules and nitroglycerin tablets were kept. All other medications were kept constant throughout the study. Digitalis, propranolol, long-acting nitrates, and sedative hypnotics were withdrawn at least 2 weeks before entry into the study.

The protocol (fig. 1) consisted of an initial 8-week single-blind phase that began with a 4-week, single-blind, placebo-controlled baseline period. This was followed by a 3-week dose-titration phase to establish the maximally tolerated dose of acebutolol for each patient. During this stage, three weekly increases in the dosage of acebutolol were made (600 mg, 900 mg and 1200 mg/day) provided that patients experienced no side effects, there was no bradycardia (heart rate ≤ 55 beats/min), and standing systolic blood pressure remained greater than 105 mm Hg. Patients incapable of tolerating 600 mg/day were dropped from the study. Acebutolol was given to 40 patients at a daily dose of 1200 mg; two patients received 900 mg/day and two patients received 600 mg/day. After the dose-titration phase, the patients underwent a 1-week drug withdrawal period consisting of twice-daily administration of acebutolol for 2 days and once-daily.

**Figure 1.** Acebutolol study design: 8-week single-blind phase composed of a 4-week baseline phase, 3-week dose-titration phase and a 1-week weaning schedule. The 12-week double-blind phase immediately follows, composed of two 5-week treatment phases separated and terminated by 1 week of weaning. Standardized multistage graded exercise tests (Ex) are shown at points administered. Study drug dosages are indicated for the dose-titration phase.
administration for the next 4 days. The patients then entered a 12-week double-blind comparison phase, during which they took the maximally tolerated dose of acebutolol or an identical placebo for 5 weeks each. During this phase the patients were withdrawn twice from treatment over a 1-week period each time. Patients were seen on at least 13 visits over the 20-week protocol; daily diaries, nitroglycerin tablets and capsule consumption, supine and standing vital signs and an ECG were reviewed at each visit. Randomization during the double-blind and crossover phase was accomplished through coding and prepackaging of the capsules before shipment to the investigator.

A complete laboratory profile, a complete blood count, erythrocyte sedimentation rate, platelet count, urinalysis, blood sugar, BUN, creatinine, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, uric acid, serum sodium, potassium and calcium and flourescent antinuclear antibody titer, was obtained before entry and at the end of each treatment in the double-blind phase.

Exercise tests were done before entry and on the final day of each phase of the study (fig. 1). The data from the exercise tests at weeks 4, 7, 13 and 19 were used for comparisons.

Exercise Protocol

Each exercise test consisted of identical sequential 3-minute stages of increasing work load, speed and elevation on a calibrated, motor-driven treadmill according to Bruce.44 The exercise protocol was modified to comply with recommendations for a slow application of work load to further encourage reproducibility44 (table 1). At rest, before exercise testing and during the last minute of each stage, indirect arm blood pressures were determined by the cuff method. Tests were done at approximately the same times and on the same day of the week for each patient in the postabsorptive state and at least 2 hours after the ingestion of any medication. Patients in the initial 4-week single-blind baseline phase were maximally exercised to the development of moderately severe anginal pain and at least 1 mm of flat or downward-sloping ST-segment depression 0.08 second after the J point. Moderately severe anginal pain was defined as chest pain of increasing intensity as reported by the patient. Patients who showed physical exhaustion, hypotension, light-headedness, clinically important arrhythmia or who attained 85% of their age-predicted maximal heart rate on exercise testing were dropped. Exercise tests were always performed in the presence of one of the physician investigators. Subsequent exercise tests were stopped when the patients developed either moderately severe anginal pain or physical exhaustion.

The last minute of each stage of exercise was analyzed for the heart rate, systolic and diastolic blood pressures, ST-segment displacement, arrhythmia and rate-pressure product ([systolic blood pressure × heart rate]/105). Each test was analyzed for the maximum heart rate, systolic blood pressure, rate-pressure product, peak stage of exercise, total exercise duration (seconds), ST-segment displacement (mm), and reason for exercise limitation. The exercise work, expressed in kilopond meters (kpm), was calculated from the formula work (kpm) = sin x speed (m/sec) × body weight (kg) × exercise time (seconds) divided by 10α, where α is the angle of inclination of the treadmill.

Statistics

The data were statistically analyzed using the paired t test (two-tailed). During the single-blind phase, resting heart rate frequency of angina and consumption of nitroglycerin (fig. 2) for different sample sizes were compared only for patients who were evaluated at different dosages. During the double-blind phase, the lack of carry-over, sequence and period effects allowed application of an analysis of variance to the data (paired t test). Further, a large sample size also justified the use of this statistical method.

Comparison of the ST-segment response during the double-blind phase was evaluated using a uniformly most powerful unbiased test for trinomial distribution (Lehmann45). Probabilities were taken from standard distribution tables and considered statistically significant if they achieved the 0.05 level. Levels of significance were not expressed beyond the 0.002 level.

Results

Effects of Nitroglycerin on Frequency of Angina and Consumption (table 2)

During the initial 4-week, single-blind baseline period, the average frequency of angina with placebo treatment was 12.3 ± 1.9 (mean ± SEM) attacks per week for the group (n = 44); this was reduced to 7.7 ± 1.4 attacks per week (p < 0.01) at the maximal dose of acebutolol established in the dose-titration phase. The average number of nitroglycerin tablets consumed for these same periods decreased from 14.7 ± 2.8 per week with placebo to 9.3 ± 2.1 per week with the maximal dose of acebutolol (p < 0.01).

The 3-week dose-titration phase permitted an evaluation of the effects of increasing dosages of acebutolol on the frequency of angina and the number of nitroglycerin tablets consumed. The results (fig. 2)
clearly show a progressive and statistically significant decline in the frequency of angina and nitroglycerin tablet consumption after acebutolol in dosages of 600–1200 mg/day.

During the 12-week double-blind phase of the study, the average frequency of anginal attacks with placebo was 7.6 ± 1.4 per week (n = 40). Patients who were taking acebutolol (mean dose 1155 mg/day) during this period had fewer attacks of angina (6.0 ± 1.4; p = NS) and lower consumption of nitroglycerin (8.5 ± 1.9 tablets/week with placebo vs 6.7 ± 1.8 with acebutolol; p = NS). Four patients who developed unstable angina during the double-blind phase were dropped from the study. None of the patients had serum enzyme or electrocardiographic evidence of myocardial infarction. The medication code was broken and all of them were found to be taking placebo. Because these patients had significantly more anginal attacks with placebo (> 50 per week) and because none of them completed the 5-week placebo phase, their results were not included in the analysis of the double-blind phase. Acebutolol therapy was instituted in these patients at the previously established maximal dose, with prompt resolution of anginal pain in each case.

**Placebo Effects (table 2)**

The weekly frequency of anginal attacks during the 5-week double-blind placebo phase (7.6 ± 1.4) did not return to that during the 4-week single-blind placebo baseline period (12.3 ± 1.9); the difference between the two was significant (p < 0.01). Similarly, the weekly consumption of nitroglycerin tablets during the above phases was 8.5 ± 1.9 and 14.7 ± 2.8, respectively (p < 0.01). No carry-over period or sequence effects were observed.

**Effects on Resting Hemodynamics**

**Heart Rate**

The resting heart rate in 44 patients during the single-blind placebo phase was 77 ± 2 beats/min. During the dose-titration phase, acebutolol produced a significant reduction in the resting heart rate to 69 ± 1 beats/min (p < 0.01, table 2). No further decline in the resting heart rate occurred despite increasing daily dosages of acebutolol (fig. 2). This is in distinct contrast to the effect of acebutolol on anginal attack pattern and nitroglycerin consumption during this phase (fig. 2).

The resting heart rate during the 5-week, double-blind placebo phase (81.0 ± 2.0 beats/min) was reduced to 68.0 ± 2.0 beats/min (p < 0.002) with acebutolol. The resting heart rate during the double-blind placebo phase had returned to the baseline value observed during the single-blind placebo period, indicating a complete washout of the β-blockade effect (table 2).

**Rate-Pressure Product**

The resting rate-pressure product showed similar significant decreases after acebutolol during both the dose-titration and the double-blind phases (p < 0.002). The return of the rate-pressure product during the double-blind placebo to the baseline level indicates a washout of acebutolol effects during the later phase (table 2). Although the study population was normotensive, a slight but statistically significant decrease in resting systolic blood pressure occurred in the acebutolol group (table 2).

**Effects at Maximal Exercise**

**Heart Rate**

During the 4-week, single-blind placebo phase, the heart rate at peak exercise was 127 ± 2 beats/min. The exercise heart rate after administration of acebutolol during the dose-titration phase was 101 ± 2 beats/min (p < 0.002). A similar β-blocking effect was observed during the double-blind phase (table 2).
Rate-Pressure Product

A corresponding decrease in the rate-pressure product at maximal exercise was produced by acebutolol in both the dose-titration and double-blind phases (p < 0.002, table 2). The systolic blood pressure at peak exercise decreased significantly after acebutolol treatment (table 2).

Maximal ST-segment Displacement (table 2)

The maximal ST-segment depression below the resting level on the multistage treadmill exercise test during treatment with acebutolol was smaller in both single-blind (1.3 ± 0.1 mm with placebo vs 0.9 ± 0.1 mm with acebutolol; p < 0.01) and double-blind periods (1.1 ± 0.1 mm with placebo vs 0.9 ± 0.1 mm with acebutolol; p = NS). The change in maximal ST-segment depression during the double-blind comparison did not correlate with either the absolute or the percentage change in peak rate-pressure product (both r = 0.1) or the total exercise time (r = 0.2).

During the double-blind comparison, 10 patients had ≥ 1 mm more ST-segment depression with placebo compared with acebutolol. Four patients had ≥ 1 mm less ST-segment depression with placebo compared with acebutolol (p = NS). The remaining 26 patients had < 1 mm ST-segment change from acebutolol to placebo.

Exercise Capacity (table 2)

Exercise capacity as assessed by the total exercise time and total exercise work on standardized treadmill exercise testing improved significantly during acebutolol treatment in both single- and double-blind comparisons. The double-blind comparison (fig. 3) showed increases in total exercise time (516 ± 22 seconds with acebutolol vs 454 ± 23 seconds with placebo; p < 0.01) and total exercise work (3.0 ± 1.6 kpm with acebutolol vs 2.5 ± 1.7 kpm with placebo; p < 0.05).

During the double-blind phase of the study, 27 patients (68%) had an increase in total exercise time of at least 30 seconds with acebutolol compared with placebo, nine patients (22%) had at least a 30-second increase in total exercise with placebo compared with acebutolol and four patients (10%) had no change (fig. 3).
were broken, and therapy with acebutolol was reinstituted, resulting in prompt resolution of angina, without electrocardiographic or serum enzyme evidence of myocardial infarction. Nine days after completing the study, one patient suffered a small, uncomplicated inferior wall myocardial infarction when he was without access to nitroglycerin and ignored the initial symptoms of angina. While taking acebutolol, one patient developed fatigue, weight gain and edema that required an increase in his daily diuretic. A patient with back pain was not considered to have a drug-associated side effect. One patient noted moderate fatigue while taking placebo. No patient developed bronchospasm with acebutolol or placebo. No drug-associated laboratory abnormalities were identified by the complete laboratory profile.

Despite a previous report of the development of fluorescent antinuclear antibody titers during treatment with acebutolol, all titers remained negative after 8 weeks of therapy (3 weeks during the dose-titration phase and 5 weeks during the double-blind phase). Several of these patients have continued on long-term acebutolol (over 6 months), and their fluorescent antinuclear antibody titers are being followed.

Discussion

This study shows the antianginal efficacy of oral acebutolol in patients with chronic stable angina pectoris evaluated both subjectively through observations of angina attack frequency and nitroglycerin tablet consumption and objectively by an improvement in exercise capacity assessed by maximal multistage treadmill exercise testing (fig. 4). Using a more complete study design than has been previously employed, this study included placebo controls, double-blind and randomization techniques, a large diagnostically and symptomatically homogenous patient sample. The results obtained give strong support to the previous clinical observations of the therapeutic efficacy of acebutolol.

Why Investigate Another \( \beta \)-blocking Agent for Angina Pectoris?

Beta-adrenergic receptor antagonists have improved both the short-term\(^1\) and long-term\(^4\) medical management of angina pectoris. In the U.S., this has been most clearly documented for propranolol, a noncardioselective \( \beta \)-blocking agent.\(^4\) However, the pharmacokinetics, comparative effectiveness and side effects of the \( \beta \)-blocking agents differ, significantly affecting the selection of the appropriate agent for clinical use.\(^8\) Pharmacologic properties of particular importance include cardioselectivity, presence of partial agonist activity, and properties unique to the specific agent. Acebutolol was tested for its antianginal efficacy because, unlike propranolol, it is cardioselective,\(^2\) has mild partial agonist activity\(^2\) and may have unique advantageous properties.\(^8\)

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**FIGURE 3.** Effects of acebutolol (mean dosage 1155 mg/day) compared with placebo on the duration of maximal exercise assessed by a standardized multistage treadmill exercise protocol. Results for each of 40 patients show an overall improvement in the mean duration of exercise with acebutolol (516 ± 22 vs 454 ± 23 seconds, \(p < 0.01\)). Nine patients lowered maximal exercise duration on acebutolol. Four patients (not shown) who could not tolerate placebo therapy had a lower mean exercise capacity on placebo (383 ± 56 seconds) and a higher mean exercise capacity on acebutolol (551 ± 101 seconds) than the others as obtained from their single-blind comparison of treatments.

**Pulmonary Function Testing**

In 25 patients studied during the double-blind phase, the forced vital capacity, forced expiratory volume in 1 second, the ratio of forced expiratory volume to forced vital capacity, peak expiratory flow and maximum midexpiratory flow rate were not statistically different on acebutolol and placebo (DiBianco et al.\(^3\)).

**Adverse Reactions**

During the double-blind phase, four of 44 patients (9%) had a progressive increase in the severity of frequency of symptoms compatible with unstable angina while taking placebo; no patient had such symptoms while taking acebutolol. These events occurred 8, 10, 11 and 25 days after the acebutolol was given according to a 6-day dose-tapering (weaning) schedule. In each instance, the study was terminated, drug codes...
Cardioselectivity

Beta-blocking agents possessing a higher potency for the antagonism of cardiac than of noncardiac β receptors are termed cardioselective and may provide increased clinical safety in patients with bronchospasm, glucose intolerance, and, possibly, peripheral arterial insufficiency. Acebutolol has shown cardioselective properties in both experimental and clinical settings and therefore may have a wider therapeutic utility than propranolol. In addition, beneficial effects of cardioselective agents may extend to advantageous redistribution of myocardial blood flow to the ischemic zones, further supporting the continued interest in identifying and characterizing cardioselective β-blocking agents.

Partial Agonist Activity

Because acebutolol possesses intrinsic sympathomimetic activity, it may, in principle, exacerbate angina or decrease exercise capacity in coronary patients by increasing myocardial oxygen demand. Therefore, we investigated this theoretical limitation to the antianginal efficacy of acebutolol.

During incremental weekly therapy with acebutolol (fig. 2) in the dose-titration phase, patients evidenced a significant and progressive decrease in anginal frequency and consumption of nitroglycerin tablets (p < 0.01). The lack of a progressive bradycardic response to higher dosages of acebutolol supports the presence of mild agonist activity. A progressive decline in anginal frequency with higher dosages of acebutolol fails to support the theoretical concern regarding a limitation of antianginal efficacy secondary to particular agonistic activity. The improved exercise capacity with maximal doses of acebutolol lends no support to the position that this higher heart rate represents compensation for lowered cardiac performance. A practical clinical advantage of acebutolol may be its lower risk of inducing symptomatic bradycardia; 40 of 44 patients in this study (91%) were able to tolerate the peak dosage of acebutolol (1200 mg/day) without excessive bradycardia (≤ 55 beats/min).

Beta-adrenergic Blocking Agents and Ischemia

The mechanisms by which β-blocking agents reduce ischemia remain uncertain. Many investigators believe that decreased oxygen requirements resulting from negative chronotropic and inotropic actions of β blockade improve myocardial oxygen debt. However, recent experimental evidences from studies of regional myocardial blood flow suggest that alterations in the distribution of myocardial flow during β blockade may account for the increased blood flow to ischemic areas. Alterations in myocardial flow distribution, independent of the commonly recognized hemodynamic effects of β blockade have also been shown. Whether increased flow to ischemic myocardium is related to or independent of cardioselective blockade is unknown. Joye et al. showed that acebutolol, unlike propranolol, does not increase peripheral vascular resistance and suggest that lowered myocardial oxygen requirements resulting from a lower afterload burden contribute to the benefit of acebutolol treatment. The effects of acebutolol on regional myocardial blood flow have not been fully elucidated. However, it is conceivable that its effects on myocardial flow are similar to those observed with other β blockers.

Despite the significantly higher work loads attained by patients taking acebutolol during the single-blind phase (table 2), there was a significantly lower maximal ST-segment shift (p < 0.01) and fewer patients (24 of 44 with acebutolol vs 44 of 44 with placebo) had angina during exercise testing. This could be either secondary to the lower rate-pressure products at each level of exercise, redistribution of regional myocardial blood flow in these patients or an overall improvement in transmural flow distribution with reduced ischemia with acebutolol treatment at peak exercise. During the double-blind acebutolol phase, despite significantly higher work loads and fewer patients developing angina during exercise testing (22 of 40 taking acebutolol vs 29 of 40 taking placebo), there was no
significant change in the maximal ST shift. The reason for this discrepancy is unclear.

Objective vs Subjective Criteria in Anginal Studies

During the double-blind placebo phase of this study, the objective variables, such as heart rate (resting and peak exercise), rate-pressure product, maximal ST-segment depression during peak exercise, exercise duration and exercise work, had returned to the levels seen during the single-blind placebo phase (table 2). The subjective variables, such as number of nitroglycerin tablets consumed and number of anginal attacks, were at a significantly lower level during the double-blind placebo period compared with the single-blind placebo period. The fact that the objective variables had returned to control levels indicates a complete washout of the β-blockade effect. Thus, it is important to give more emphasis to objective than to subjective features when analyzing data from double-blind, well-controlled angina studies.

Comparison with Previous Studies

Suitably designed clinical studies that compare placebo effects with various treatment modalities are essential for the complete evaluation of new treatment forms.31 Benson et al,46 implied that this is especially true for disorders such as angina pectoris, because symptoms may vary considerably with time and placebo effects have been known for more than 40 years. Controlled studies that blind both patient and investigator to the specific type of therapy as well as combined objective testing, namely exercise testing,50-53 are crucial for a complete and accurate evaluation. Controlled studies on acebutolol in concordance with the above guidelines have been lacking.22-28

We conclude that the present study serves as more substantial proof of antianginal efficacy of acebutolol compared with placebo than previous studies.52-53, 56 The comparative effects of acebutolol and propranolol were not assessed in this study; however, the decrease in symptoms and increase in exercise capacity with acebutolol were similar to those with propranolol.46

Acknowledgment

The authors gratefully acknowledge the help of Barbara Wright, Edward Gillus, Eileen Adams, R.N., and Delores Polladino, R.N., in the exercise testing; Ives Laboratories, Inc., New York, for supplying acebutolol and identical placebo for the use in this study; and Darlene Amendola, Gloria Price and Wanda Johnson for secretarial assistance.

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Circulation. 1980;62:1179-1187
doi: 10.1161/01.CIR.62.6.1179

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/62/6/1179.citation

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