The hemodynamic effects of sotalol and quinidine: analysis by use of rest and exercise gated radionuclide angiography

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ABSTRACT This placebo-controlled, double-blind trial compared the hemodynamic effects of sotalol and quinidine with the use of rest and exercise gated radionuclide angiography. Patients had frequent ventricular premature depolarizations (≥ 30 VPDs/hour) and depressed cardiac function (mean ejection fraction 43 ± 15%). Resting left ventricular ejection fraction and stroke volume index increased (p < .002, p < .001, respectively) during sotalol therapy, associated with a concomitant fall in heart rate (p < .001). Quinidine also increased mean left ventricular ejection fraction, but less so than did sotalol (p < .05). Quinidine significantly decreased left ventricular end-diastolic (p < .05) and end-systolic (p < .002) volumes, but had no effect on stroke volume index or heart rate. Neither drug affected cardiac index. Quinidine resulted in no symptomatic deterioration in left ventricular function or serious arrhythmia aggravation. In contrast, five patients on sotalol developed either decompensated congestive heart failure (two patients), arrhythmia aggravation (two patients), or hypotension associated with bradyarrhythmia (one patient). These patients had a unique hemodynamic profile that can be used to identify patients likely to have a poor outcome on sotalol. This profile reflected a lack of cardiac reserve, characterized by an inability to increase stroke volume and cardiac output with supine bicycle exercise.


FREQUENT ventricular premature depolarizations (VPDs) and depressed left ventricular function are independent and additive risk factors predicting increased risk of sudden cardiac death in patients after acute myocardial infarction. Patients with complex ventricular ectopy and idiopathic dilated cardiomyopathy are an additional target population for possible antiarrhythmic therapy. Despite the potential benefit of arrhythmia suppression in these patients, antiarrhythmic drugs may aggravate congestive heart failure. We have recently reported that the outcome of antiarrhythmic therapy may be related to patients' initial hemodynamic status. In that study right heart catheterization was used to characterize baseline hemodynamics at rest and with exercise. However, sequential right heart catheterization is impractical in that it is an invasive procedure with potential complications, whereas gated radionuclide angiography is a noninvasive alternative that can be performed serially to indirectly assess hemodynamics both at rest and during supine bicycle exercise.

Sotalol is a β-blocker with class III antiarrhythmic properties that appears effective in suppressing ventricular arrhythmias, including ventricular tachycardia. There is insufficient data regarding the effect of sotalol on left ventricular function. Likewise, despite the fact that quinidine has been in use for several decades, quantitative assessment of its hemodynamic effects in patients with depressed cardiac function is sparse.

The present investigation was initiated as an ancillary study of a multicenter trial comparing the ventricular antiarrhythmic effects of sotalol and quinidine.
The purpose of this study was to assess the hemodynamic effects of sotalol and quinidine by the use of sequential rest and exercise gated radionuclide angiography.

Methods

Patient population. The study population consisted of 27 patients (18 men and nine women; mean age 56 ± 12 years) with 30 or more VPDs/hour during a 24 hour ambulatory electrocardiographic recording. Cardiac diagnoses were: coronary artery disease (14 patients), cardiomyopathy (four patients), mitral valve prolapse (four patients), and valvular heart disease (one patient), and there was no known cardiac disorder in the remaining four patients. A total of 13 patients had prior myocardial infarction, while nine had a history of congestive heart failure. For inclusion into the trial antiarrhythmic agents and β-blockers had to be discontinued for at least 4 days. The 27 patients had the following arrhythmia frequencies on placebo: 346 ± 72 VPDs/hour (n = 27), 7.4 ± 2.7 couplets/hour (n = 24), and 23 ± 12 runs of ventricular tachycardia daily (n = 15).

Study design. This was a placebo-controlled, randomized, double-blind, crossover trial to assess the hemodynamic effects of sotalol and quinidine. The protocol was approved by the institutional review boards of both Baylor College of Medicine and The Methodist Hospital. Informed consent was obtained before study enrollment. The study design is depicted in figure 1.

Patients enrolled in the study were withdrawn from all antiarrhythmic drugs and had 24 hour ambulatory electrocardiographic monitoring after a washout of 4 days or more. A 1 week placebo period was followed by randomization to either 320 mg of sotalol or 800 mg of quinidine sulfate daily in divided doses for a 4 week period. If ventricular ectopy was not reduced by 75% or more at the end of 2 weeks, the drug dosage was increased to 640 mg of sotalol or 1600 mg of quinidine daily for the next 2 weeks. A second placebo phase followed, lasting 2 weeks, at which time a return of 30 or more VPDs/hour was required to continue in the trial. The patients then crossed over to the other active antiarrhythmic drug with identical stepwise dosage titration for an additional 4 weeks. All rest and exercise radionuclide angiograms were obtained during the final week of each placebo and antiarrhythmic drug phase and were read blinded to the treatment phase of the trial. Each placebo angiogram was obtained after at least 20 half-lives of the preceding antiarrhythmic drug and after plasma levels returned to zero, thus ensuring an adequate comparison.

Assessment of left ventricular function. Gated radionuclide angiograms were obtained with a single-crystal gamma camera with a ½ inch sodium iodide crystal and a low-energy, parallel-hole, all-purpose collimator. The camera’s energy discriminator was set at 140 keV with a 20% window, and all images and data processing were performed by a microcomputer attached to the camera.

All patients were injected through a peripheral vein with stannous pyrophosphate followed by 25 to 30 mCi of 99mTc for labeling of red blood cells in vivo. Images were obtained in the standard anterior, 70 degree left anterior oblique, and the left anterior oblique projection with the best septal delineation. After resting images were obtained, each patient underwent symptom-limited supine bicycle exercise beginning at 100 or 200 kilopond-meters (kpm) for 180 sec per stage with doubling of the workload at 3 min intervals. Each patient was exercised to the identical workload achieved during the initial placebo radionuclide angiographic examination in the three subsequent gated angiographic studies. All studies were acquired on a 64 × 64 matrix with the use of 24 frames per cardiac cycle for volume analysis. Left ventricular volumes were measured by a count-based technique previously validated in our laboratory. The intraobserver variability for volume measurements by this technique is acceptable, with a correlation coefficient of .91.

Indirect assessment of hemodynamics were performed in an identical fashion on the rest and exercise images of all four gated radionuclide angiographic studies blinded to the phase of the trial. To be included in the analysis patients had to be clinically stable between the two angiographic examinations on placebo. Hemodynamic measurements in patients on active antiarrhythmic drug were always compared with the measurements from the immediately preceding placebo period.

Plasma drug levels. Plasma sotalol and quinidine levels were obtained at the time of the gated radionuclide angiogram. Serum trough and peak drug levels were drawn before and 1 hr after the morning dose, respectively. Plasma samples for determination of sotalol levels were collected in 10 ml Vacutainer tubes containing K-3 ethylene diamine tetracetic acid as an anticoagulant, and then they were centrifuged and placed in frozen storage until analysis. All of these samples were analyzed by a fluorometric modification of the high-pressure liquid chromatographic method (Bristol-Myers Inc). Plasma quinidine levels were determined in an identical fashion and analyzed with a Syva EMIT enzyme immunoassay.

Statistical methods. When group hemodynamic variables were of a normal distribution statistical analysis was performed by paired, two-tailed t tests. If normality could not be assumed, Wilcoxon signed-rank tests were used. Baseline hemodynamic variables were compared with subsequent hemodynamic and clinical outcomes by the Fisher exact test. Chi-square analysis was performed for comparison of effects of the two antiarrhythmic drugs with individual dichotomous hemodynamic changes.

<table>
<thead>
<tr>
<th>Washout</th>
<th>Placebo#1</th>
<th>Drug#1</th>
<th>Placebo#2</th>
<th>Drug#2</th>
<th>Placebo#3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks</td>
<td>1</td>
<td>2</td>
<td>3-4</td>
<td>5-6</td>
<td>7-8</td>
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<tr>
<td>24 hour</td>
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<tr>
<td>AECG</td>
<td>*</td>
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<td>Gated</td>
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<tr>
<td>Blood</td>
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<tr>
<td>Levels</td>
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</tr>
</tbody>
</table>

FIGURE 1. Study design comparing the hemodynamic effects of sotalol and quinidine. The asterisk (*) indicates when specific studies were performed. AECG = ambulatory electrocardiogram; RNA = radionuclide angiography.
Plasma drug levels were correlated to drug dosage by linear regression. All data were analyzed as mean ± SD except for arrhythmia data, which are described as mean ± SE.

**Results**

**Group data hemodynamic results.** Twenty-five of the 27 patients underwent rest and exercise gated radionuclide angiographic studies during placebo and quinidine administration, whereas only 23 sotalol-treated patients underwent gated angiographic studies. One patient did not undergo a radionuclide angiographic study while on sotalol due to rapid worsening heart failure and in another cardiac arrest (with successful resuscitation) occurred. The mean baseline left ventricular ejection fraction (LVEF) was 43 ± 15%, with a LVEF of less than 30% in seven patients, of 30% to 39% in four patients, of 40% to 49% in four patients, and of 50% or more in the remaining 12 patients.

Hemodynamic data obtained during active antiarrhythmic drug administration were always compared with those from the immediately preceding placebo period. Because of dropouts at various intervals in the trial, sotalol placebo data included those from two patients not participating in the quinidine trial and the quinidine placebo data included those from four patients not participating in the sotalol trial (table 1).

Sotalol reduced rest and peak exercise heart rate and systolic blood pressure, which were unchanged on quinidine (table 1). The change in LVEF with supine bicycle exercise was comparable during both placebo periods. Sotalol and quinidine increased group resting LVEF (p < .002, p < .05, respectively), whereas the observed increase in exercise LVEF on both active drugs approached but failed to reach statistical significance (p < .084, p < .091, respectively; table 1).

Sotalol significantly increased, whereas quinidine decreased, the resting end-diastolic volume index (both p < .05). Resting stroke volume index (SVI) increased (p < .001) during sotalol therapy, while quinidine induced no change. There was no difference in cardiac index (CI) at rest or during exercise with either antiarrhythmic agent.

**Individual hemodynamic responses.** Individual patients demonstrated marked differences in their hemodynamic responses to quinidine and sotalol when compared with those in the immediately preceding placebo period. Many patients (57%) had a 5% or greater absolute increase in resting LVEF on sotalol, with only one patient demonstrating a 5% or greater absolute decrease (figure 2, A). During administration of quinidine, 24% and 16% of patients had a comparable rise or fall, respectively, in resting LVEF (figure 2, B). The resting left ventricular end-diastolic volume index increased in 65% of patients on sotalol but decreased in 68% of patients on quinidine, a significant difference (p < .02; figure 3). Whereas resting SVI rose in 83% of patients on sotalol, 64% of patients had a drop in resting SVI on quinidine (p < .002; figure 4). There was no significant change in resting or exercise mean CI in patients on either drug compared with placebo, although there was marked variability (figure 5). When patients were stratified for a resting baseline LVEF of less than 40% vs that of 40% or more, no difference in the two groups' hemodynamic response to either drug was observed (all p = NS; figures 2 to 5).

**Relationship of initial hemodynamic assessment to subsequent complications on sotalol.** Five patients had serious complications while on sotalol, whereas no patient had serious complications on quinidine. While taking sotalol, two patients developed decompen-sated congestive heart failure (resting placebo LVEFs of 18% and

**TABLE 1**

Hemodynamic results during two placebo periods and after 4 weeks of sotalol (n = 23) or quinidine (n = 25) therapy

<table>
<thead>
<tr>
<th></th>
<th>PL-Sotalol</th>
<th>Sotalol</th>
<th>PL-Quinidine</th>
<th>Quinidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Ex</td>
<td>Rest</td>
<td>Ex</td>
</tr>
</tbody>
</table>
| HR (BPM)       | 71 ± 11    | 117 ± 21| 55 ± 8\(^a\) | 94 ± 21\(^a\)
| SBP (mm Hg)    | 132 ± 20   | 165 ± 21| 125 ± 14\(^c\) | 154 ± 19\(^c\)
| LVEF (%)       | 47 ± 13    | 52 ± 15 | 51 ± 15\(^a\) | 55 ± 14
| EDVI (ml/m²)   | 111 ± 40   | 114 ± 46| 125 ± 42\(^a\) | 120 ± 40
| ESVI (ml/m²)   | 63 ± 37    | 58 ± 41 | 65 ± 39\(^a\) | 57 ± 33
| SVI (ml/m²)    | 48 ± 11    | 55 ± 15 | 59 ± 15\(^a\) | 63 ± 18
| CI (l/min/m²)  | 3.4 ± 0.8  | 6.6 ± 2.3| 3.3 ± 0.8    | 6.0 ± 2.2
| PL-sotalol, PL-quinidine = placebo period preceding active drug therapy; Ex = exercise; HR = heart rate; SBP = systolic blood pressure; LVEF = left ventricular ejection fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; SVI = stroke volume index; CI = cardiac index.
| \(^a\)p < .001; \(^b\)p < .002; \(^c\)p < .05 (all results compared with immediately preceding placebo values).
A. Sotalol

B. Quinidine

FIGURE 2. Comparison of the absolute change in individual and mean LVEF from the placebo to the sotalol (A) and quinidine (B) periods. PL-S and PL-Q represent the placebo measurements immediately preceding sotalol (S) and quinidine (Q) administration, respectively. The mean is expressed as ± SD in this and the following figures. On this and subsequent figures, individual patient responses are separated by those from patients with resting EF < 40% and those with values ≥ 40%.

23%), and both had end-diastolic volume indexes of greater than 200 ml/m² on placebo. A third patient developed torsades de pointes ventricular tachycardia and presyncope, a fourth suffered cardiac arrest (ventricular fibrillation) and was successfully resuscitated, and the final patient developed syncope associated with hypotension and bradycardia. The resting placebo LVEFs of these patients were 50%, 42%, and 44%, respectively.

The five patients with serious complications during

FIGURE 3. The individual percent change in end-diastolic volume index (EDVI) from the placebo to the sotalol (A) and quinidine (B) periods. The zero line represents the immediately preceding placebo EDVI for each patient.
sotalol administration differed significantly in their initial hemodynamic profiles from the remaining 20 patients who tolerated sotalol well. These five patients were differentiated by a higher resting end-systolic volume index, failure to increase LVEF during exercise, a minimal increase in exercise CI, and a fall in exercise SVI (table 2).

The hemodynamic indicators predictive of subsequent complications on sotalol are summarized in table 3. Patients with severely compromised cardiac reserve (no exercise increase in SVI and a minimal increase in CI < 1.3 liter/min/m²) were most likely to have significant complications on sotalol.

Analysis of serum drug levels. The mean peak and trough sotalol levels were 1874 ± 1099 and 1545 ± 835 ng/ml, respectively, at a mean oral sotalol dose of 5.9 ± 2.30 mg/kg/day. The correlation between blood levels and oral sotalol dosage was represented by r = .53 (p < .01). The peak and trough quinidine levels were 2.8 ± 1.0 and 2.2 ± 0.8 μg/ml, respectively,

FIGURE 4. The individual percent change in SVI from the placebo to the sotalol (A) and quinidine (B) periods. The zero line represents the immediately preceding placebo SVI for each patient.

FIGURE 5. The individual percent change in CI from the placebo to the sotalol (A) and quinidine (B) periods. The zero line represents the immediately preceding placebo CI for each patient.
with a mean oral quinidine dose of 15.6 ± 6.7 mg/kg/day. The correlation between blood levels and oral quinidine dosage was represented by r = .58 (p < .003).

The most recent sotalol blood levels in three of five patients who had complications were 1074, 1904, and 3117 ng/ml. In the remaining two patients, blood samples could not be obtained at the time of complications. This small sample size was considered inadequate to address the issue of whether there was a correlation between sotalol blood levels and serious complications. There was no relationship of sotalol or quinidine blood levels to any measured hemodynamic variable.

Discussion

This study is unique in that it emphasizes the utility of exercise data obtained by radionuclide angiography in the evaluation of the hemodynamic effects of antiarrhythmic drugs. As a result of this investigation, we have identified a hemodynamic profile of patients in whom the administration of sotalol should be avoided and alternative therapies considered.

Hemodynamic evaluations of antiarrhythmic drugs incorporating gated radionuclide angiography have been published but they have substantial limitations. Wisenberg et al.19 reported rest and exercise hemodynamics measured by gated radionuclide angiography in 17 patients with complex VPDs in a randomized, placebo-controlled, sequential evaluation of quinidine, procainamide, and disopyramide. There was no change in mean resting or exercise LVEF with any drug. This study did not include other hemodynamic measurements, and was limited in that nearly all patients had normal LVEF (only four of 17 patients had a resting LVEF < 50%). In contrast to the Wisenberg study, the present study included a majority of patients with depressed left ventricular function.

Sami21 recently published his observations on encaïnide in 25 patients with complex VPDs and depressed cardiac function (LVEF < 45%). The major limitation of his hemodynamic observations was the lack of any exercise data. He found no change in mean resting LVEF, stroke volume, or end-diastolic volume in patients on encaïnide compared with placebo measurements. Sixteen of 25 patients were still taking encaïnide at 6 months. The author did not report on whether the individual baseline hemodynamics were related to outcome.

The results of the present study indicate that the hemodynamic effects of sotalol and quinidine are quite disparate. Sotalol decreased both heart rate and systolic blood pressure. Left ventricular end-diastolic volume rose during administration of sotalol in the majority of patients. This was probably due to the indirect effect of bradycardia, which increased diastolic filling time, although a direct effect on left ventricular compliance could not be ruled out. The observed rise in SVI may have been due to a direct inotropic effect, but more likely resulted from changes in preload (increased left ventricular end-diastolic volume) and afterload (decreased systolic blood pressure). Although the mean CI was unchanged, values in individuals varied depending on the differential rise and fall in stroke volume and heart rate, respectively.

In a single-dose intravenous sotalol trial, Thumala et al.17 observed that there was no change in blood pressure, but there was a significant drop in CI that was not corrected by pacing, and they concluded that sotalol possessed significant negative inotropic effects. In contrast, in this oral dosing study we found no fall in SVI, probably because of the combined effects of reduced afterload (systolic blood pressure) and increased preload (end-diastolic volume index) that may have masked a smaller direct myocardial depressant effect.

During administration of quinidine resting end-dia-

### TABLE 2
Hemodynamic profile of patients with and without serious complications on sotalol

<table>
<thead>
<tr>
<th></th>
<th>No complications (n = 20)</th>
<th>Complications (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest (Ex)</td>
<td>Rest (Ex)</td>
</tr>
<tr>
<td>ESVI</td>
<td>60 ± 37 (59 ± 43)</td>
<td>102 ± 57 (91 ± 51)</td>
</tr>
<tr>
<td>LVEF</td>
<td>48 ± 13 (53 ± 15)</td>
<td>35 ± 14 (36 ± 14)</td>
</tr>
<tr>
<td>CI</td>
<td>3.4 ± 0.8 (6.8 ± 2.2)</td>
<td>3.2 ± 1.0 (4.6 ± 1.4)</td>
</tr>
<tr>
<td>SVI</td>
<td>49 ± 11 (57 ± 14)</td>
<td>48 ± 13 (44 ± 10)</td>
</tr>
</tbody>
</table>

Abbreviations as in table 1.

* p < .05; ** p = .051.

### TABLE 3
Sensitivity, specificity, and predictive value of baseline hemodynamic measurements in determining serious complications of sotalol treatment

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Fisher’s exact test (p value)</th>
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<tr>
<td>ΔLVEF &lt;5%</td>
<td>100</td>
<td>45</td>
<td>31</td>
<td>100</td>
<td>.12</td>
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<tr>
<td>ΔSVI &lt;0</td>
<td>80</td>
<td>85</td>
<td>57</td>
<td>94</td>
<td>.01</td>
</tr>
<tr>
<td>ΔCI &lt;1.3</td>
<td>80</td>
<td>90</td>
<td>67</td>
<td>95</td>
<td>.006</td>
</tr>
<tr>
<td>ΔSVI &lt;0 and ΔCI &lt;1.3</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>95</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations as in table 1.

Δ = change from rest to exercise while on placebo preceding sotalol.
stolic and end-systolic volume indexes decreased, which resulted in a clinically insignificant decline in SVI. Mean resting LVEF increased in patients on quinidine, although at less individual magnitude than with sotalol. Whether the drop in end-diastolic volume index was secondary to effects on compliance or a decrease in preload from quinidine-induced venodilation is speculative, although the drug is known to cause direct vasodilation and α-adrenergic blockade of both venous and arterial vascular beds.22, 23

Similar hemodynamic effects have been reported after intravenous administration of quinidine in heart transplant recipients.24 Mason et al.24 studied five patients, 8 to 20 months postoperatively, after they had received quinidine at a dose of 10 mg/kg. End-diastolic, end-systolic, and stroke volumes decreased by an average of 19%, 26%, and 28%, respectively. Cardiac output decreased in all patients, which correlated directly to a decline in SVI, since heart rate was maintained by constant cardiac pacing.24 In the present study the individual changes in CI in patients on quinidine varied, primarily related to changes in heart rate.

This study extends our observations of the interaction of ventricular arrhythmia and left ventricular function with other antiarrhythmic agents (moricizine,11, 25 cibenzoline.26) In those published trials of patients with nonsustained ventricular tachycardia, sequential resting and exercise hemodynamic measurements were obtained with right heart catheterization. Patients had a poor outcome on moricizine if initial (placebo) hemodynamic assessment revealed decreased cardiac reserve (characterized by the inability to increase CI by > 1.1 liter/min/m²).11 In an extended trial using moricizine, patients with initially lower ejection fractions (LVEF ≤ 30%) were less likely to have suppression of nonsustained ventricular tachycardia.25 In a similar patient population taking cibenzoline,26 lack of cardiac reserve at baseline identified patients unlikely to be hemodynamically tolerate the drug. Observations supporting these studies have been made in multicenter trials of flecainide in which patients initially identified as having left ventricular dysfunction had poorer outcomes: either inefficacy or proarrrhythmia.27, 28 The initial report documenting that antiarrhythmic drugs may potentially “aggravate” existing ventricular arrhythmia was made in a patient population in which most individuals had prior myocardial infarction and left ventricular dysfunction.29 Thus, a growing body of evidence suggests the use of certain antiarrhythmic drugs in patients with left ventricular dysfunction may be inappropriate.

The present trial identified a hemodynamic profile of patients unlikely to benefit from sotalol. Since either aggravation of arrhythmia or further depression of left ventricular function may prove to be more life-threatening than the increased risk posed by the presenting arrhythmia, knowing which patients are unlikely to benefit from specific antiarrhythmic drugs is clinically relevant. The resting hemodynamic data were imprecise in identifying these patients likely to have an adverse outcome on sotalol. For instance, only one-third of the patients with a resting LVEF of less than 30% developed clinical congestive heart failure or arrhythmia aggravation. Although resting LVEF is the calculation routinely performed to assess left ventricular function by radionuclide angiography, additional exercise hemodynamic variables were helpful in identifying patients likely to have a poor outcome on sotalol. This hemodynamic profile reflected inadequate cardiac reserve and consisted of a lack of rise in SVI, and only a minimal increase in CI (< 1.3 liter/min/m²) during supine bicycle exercise.

We express our gratitude for the secretarial assistance of Debbie Picot.

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_Circulation_. 1987;76:324-331
doi: 10.1161/01.CIR.76.2.324

_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

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