Action of sotalol on potential reentrant pathways and ventricular tachyarrhythmias in conscious dogs in the late postmyocardial infarction phase

STUART M. COBBE, M.D., M.R.C.P.,* ELLEN HOFFMAN, ANDREAS RITZENHOFF, JOHANNES BRACHMANN, M.D., WOLFGANG KÜBLER, M.D., AND JOCHEN SENGES, M.D.

ABSTRACT  Sotalol is a β-adrenergic blocker that also prolongs action potential duration and myocardial refractoriness over the short term (class III effect). Its short-term antiarrhythmic effects were compared with those of metoprolol, which has neither short-term class III nor membrane-stabilizing action, on reentrant ventricular arrhythmias produced by programmed stimulation in 17 conscious dogs 3 to 8 days after myocardial infarction. Ventricular arrhythmias were prevented or significantly slowed by sotalol in 11 of 19 studies (58%) compared with one of 14 (7%) studies with metoprolol. Sotalol prolonged refractoriness in the infarct zone, measured from an implanted "composite" electrode, by 41 ± 45% (mean ± SD, p < .01), which was significantly greater than the increases it produced in effective refractory period of the normal ventricle (14.0 ± 5.5%) or QT interval (12.5 ± 7.8%). Metoprolol had no effect on infarct-zone refractoriness. Sotalol differentially increases refractoriness in potential reentry circuits in ischemic myocardium. Its antiarrhythmic effect in this model is not due to β-blockade, and is presumably related to prolongation of action potential duration.

Circulation 68, No. 4, 865–871, 1983.

SOTALOL is unique among currently available β-adrenergic blockers in that it produces short-term prolongation of myocardial action potential duration and effective refractory period (ERP) in vitro.¹ ² According to Vaughan-Williams' classification,³ therefore, sotalol has class III as well as class II antiarrhythmic properties. It has recently been shown that sotalol prolongs monophasic action potential duration in man,⁴ ⁵ and produces acute increases in the ERPs of human atria, ventricles, and ativoventricular accessory pathways.⁶ ⁷

The purpose of this study was to examine the short-term effects of sotalol on reentrant ventricular arrhythmias and epicardial infarct-zone potentials in experimental canine myocardial infarction.⁸ ⁹ The effects of sotalol were compared with those of metoprolol, a cardioselective β-adrenergic blocker that is devoid of short-term class III effect, intrinsic sympathomimetic activity, or membrane-stabilizing properties.¹⁰ We have adapted the experimental model of El-Sherif et al.⁶ and Williams et al.¹¹ to allow recording of epicardial electrograms from a sterilized implanted "composite" electrode. By this technique it has been possible to perform repeated electrophysiologic and drug intervention studies in conscious unsedated dogs.

Methods

Mongrel dogs (11 to 24 kg) were premedicated with morphine and chlorpromazine and anesthetized with pentobarbital (15 mg/kg). After induction of anesthesia, 1 megaunit benzylpenicillin and 30 mg/kg methylprednisolone were given intravenously.⁹ By an aseptic technique a left thoracotomy was performed and bipolar pacing electrodes were sewn onto the left atrial appendage and the posterior wall of the left ventricle. A two-stage ligation of the proximal left anterior descending coronary artery¹² was performed. After total occlusion the epicardial area of cyanosis was determined, and a flexible sterilized composite electrode was sewn into place over the cyanotic area. The electrode was modified from one previously described⁹,¹¹ by the use of Teflon-coated stainless steel wires woven into a flexible sheet of Dacron impregnated with silicone rubber. The electrode measured 6.5 × 6.5 cm and was divided into three parallel components, thus allowing registration of the epicardial signal from three separate areas overlaying the infarct and its border. The pacing electrodes and leads from the composite electrode were exteriorized dorsally and another pair of Teflon-coated stainless steel electrodes were implanted subcutaneously.
to record a stable electrocardiogram (ECG). The chest was closed and the animals were allowed to recover.

Seventeen dogs were studied by programmed stimulation 3 to 8 days after infarction. They were trained to stand unsedated in a sling. Signals from the composite electrode were recorded on an Electronics for Medicine VR12 oscillographic recorder at a gain of 100 µV/cm and a filtering setting of 50 to 500 Hz. During ventricular stimulation a bipolar left atrial electrode (30 to 500 Hz, 1 mV/cm) was recorded, allowing recognition of atrial depolarization and also of ventricular activation from the underlying noninfarcted myocardium. The subcutaneous ECG signal (DC-500 Hz, 1 mV/cm) corresponded to an orthogonal Z lead.

**Pacing protocol.** Pacing was performed with a Medtronic programmable constant-current stimulator with stimuli of 2 msec duration at three times diastolic threshold. The stimulation protocol was as follows: (1) rapid atrial pacing at cycle lengths of from 400 to 160 msec, (2) premature ventricular stimulation with single (V₁) and double (V₂V₃) extrastimuli after every 8 paced beats at basic cycle lengths of 350, 300, and 250 msec, and (3) bursts of four to five ventricular extrastimuli at cycle lengths 220 to 130 msec, with 10 attempts at each cycle length. The end point of the stimulation was development of VT or fibrillation or completion of the full pacing protocol. The ERP of the noninfarcted ventricle (ERPᵥ) was determined and the infarct-zone electrogram analyzed as described below. QRS and QT interval measurements were made during sinus rhythm and constant atrial pacing at a cycle length of 350 msec.

Sustained VT was defined as a stable tachycardia with uniform QRS and epicardial activation patterns that required termination by overdrive pacing or, if necessary, by cardioversion. A nonsustained VT was defined as any self-terminating response of 6 or more pleomorphic ventricular beats. The reproducibility of induction of sustained or nonsustained tachycardia was confirmed three times, except when cardioversion had been necessary.

**Infarct-zone electrogram.** Infarct-zone electrograms were analyzed for the development of fragmented late potentials during sinus rhythm and at all stages of the pacing protocol. The estimation of refractoriness in potential reentrant pathways has been described in a series of reports by El-Sherif et al.,13-15 During the frequency series, the cycle length at which fragmentation first appeared or at which an already fragmented potential showing 1:1 conduction changed to a Wenckebach or 2:1 pattern was recorded. Similarly, during stimulation with ventricular extrasystoles, the V₁V₂ interval at which fragmentation first appeared or at which block of an established late potential occurred was recorded. This V₁V₂ interval was defined as the “refractory period” of the infarct-zone late potential (RPᵢz).

After the control pacing protocol had been performed, an intravenous infusion of either metoprolol (0.45 mg/kg; n = 14 studies) or sotalol (4.5 mg/kg; n = 19 studies) was given over 30 min. These doses were chosen after preliminary experiments because they yielded plasma levels similar to those in clinical use. After a further 20 min the pacing procedure was repeated.

The ERP, RPᵢz, and the QRS and QT intervals were measured as during the control stimulation period. Changes in the refractory periods were expressed as percentages of the control values. If the change in RPᵢz was such that fragmentation was already present at the basic cycle length of 350 msec (see figure 3), the cycle length was increased until a rate was found at which fractionation did not occur, or until competition with sinus rhythm was seen. In the latter case, the RPᵢz was defined as the slowest pacing rate at which fragmentation persisted.

At the end point of the stimulation protocol, the end point was the development of sustained VT or fibrillation or completion of the protocol. If the control stimulation had produced sustained VT, the drug was considered effective if it prevented the induction of sustained VT with the full pacing protocol. An effective response in nonsustained VT was defined as a reduction of the ventricular response to 2 or fewer beats. A drug was considered partially effective if it increased the cycle length of nonsustained or sustained VT by ≥ 25%. Blood samples for determination of drug plasma levels were taken at the end of the procedure. In dogs that underwent study with both sotalol and metoprolol the drugs were tested in random order. Repeat study was performed not less than 24 hr after metoprolol and 48 hr after sotalol administration. A full control stimulation procedure was repeated in each case.

**Statistical methods.** Results are expressed as mean ± SD. Changes produced by the drugs were analyzed by Student’s t test, paired or unpaired as appropriate, and by the chi-squared test with Yates’ correction. Linear regression analysis was used to compare the effects of the drugs on different variables in individual dogs. Two-tailed p < .05 was taken as the level of significance.

**Results**

**VTs: control.** A total of 33 control stimulation experiments and drug studies were performed on the 17 dogs: 19 with sotalol and 14 with metoprolol. Two dogs were studied twice with sotalol; the initial study had failed to produce sustained VT during the control stimulation while a second control stimulation 3 days later induced stable reproducible VT. Control stimulation produced one episode of ventricular fibrillation, 13 reproducible sustained VTs (mean cycle length 185 ± 40 msec), and 19 nonsustained VTs (mean cycle length 140 ± 19 msec). Three cardioversions were necessary, one for ventricular fibrillation and two for fast VT with loss of consciousness. Immediate return of sinus rhythm and consciousness was achieved in all three cases. No sustained tachycardias were induced by atrial pacing or atrial premature beats; of the 13 sustained tachycardias, three were induced by a single ventricular premature beat (V₁V₂), four by two premature beats (V₂V₃V₄), and seven by bursts of four to five ventricular stimuli during sinus rhythm. Sustained VT was associated with a stable pattern of continuous electrical activity bridging diastole on one or more of the infarct-zone electrograms, as previously described13 (figure 1). In contrast, nonsustained VTs had pleomorphic patterns on the ECG and infarct-zone electrogram. Three episodes of nonsustained tachycardia were induced with V₁V₂, 12 with V₂V₃V₄, and three with burst pacing. In assessing nonsustained VT, the response with the shortest mean cycle length obtained during the full pacing protocol was taken for comparison with the postdrug result.

**Sotalol.** The effects of the two drugs on the inducibility of sustained and nonsustained VTs are shown in figures 1 and 2. Sotalol was completely effective in 63% of the sustained and 9% of the nonsustained tachycardias and partially effective in another 45% of
nonsustained VTs. The mean plasma level of sotalol was 2.13 ± 1.45 μg/ml, which is within the therapeutic range. There was no correlation between efficacy and plasma levels between dogs.

**Metoprolol.** The only beneficial effect of metoprolol was that of the complete prevention of one sustained tachycardia (1/6, 17%), and it caused acceleration in two other continuous tachycardias, resulting in degeneration into ventricular fibrillation. Metoprolol was ineffective in nonsustained VT (0/8). The mean plasma level of metoprolol was 0.21 ± 0.09 μg/ml, which should provide effective β-blockade. The overall rate of complete and partial effectiveness with sotalol (11/19, 58%) was significantly greater than with metoprolol (1/14, 7%; χ² = 6.91 with Yates' correction, p < .01).

**ERPv.** The values before and after drug administration are given in table 1. The control values in the two groups were not significantly different, and both drugs caused a significant increase in ERPv over the control value. Sotalol produced a significantly greater percentage increase in ERPv than did metoprolol (14.0 ± 5.5% vs 5.4 ± 5.1%; p < .001).

**RPiz.** Although values of RPiz could be obtained during both atrial and ventricular stimulation, the effects of metoprolol and sotalol on the atrioventricular node prevented the achievement of sufficiently high ventricular rates or short V1V2 intervals during atrial

---

**FIGURE 1.** Effects of sotalol and metoprolol on sustained VT. Control tracing shows a sustained VT provoked by a single ventricular premature stimulus. The ECG pattern is regular, as is the pattern of interectopic electrical activity in the two areas of the infarct zone (IZ1 and IZ2). After metoprolol the tachycardia was still inducible and was of unchanged morphology. Repeat control stimulation on the following day resulted in a tachycardia that was identical to the control tracing shown. Sotalol prevented the induction of a sustained monomorphic tachycardia despite the use of a stimulation protocol identical to control.
stimulation to allow measurement of the drug effects on RP<sub>1Z</sub>. The effect of sotalol on refractoriness in the infarct zone is illustrated in figure 3. During control stimulation at a cycle length of 350 msec, the infarct zone electrogram ended with a small voltage spike inscribed early after the end of the QRS complex of the ECG. The spike remained intact after a premature ventricular beat at a coupling interval of 240 msec, but an early extrasystole at 220 msec caused widening of the terminal part of the main ventricular depolarization and fractionation extending as far as the T wave. After sotalol, fractionation was already present at a cycle length of 350 msec, and was present even after slowing to 400 msec. Thus, the RP<sub>1Z</sub> was lengthened from 220 to over 400 msec, but for the purposes of calculating percentage change, the postdrug value was taken to be 400 msec.

Comparative measurements made with single premature ventricular stimuli at a pacing cycle length of 350 msec (RP<sub>1Z</sub>) and during the ventricular pacing frequency series are listed in table 1. In some dogs fragmentation was not observed except with dual premature stimuli or after the induction of ventricular reentry, so that the numbers given are less than the total number of studies in each group. Sotalol significantly prolonged RP<sub>1Z</sub>, while metoprolol was ineffective. The percentage increase in RP<sub>1Z</sub> after sotalol was 41 ± 45% when measured after single ventricular stimuli, and 49 ± 49% when determined during the ventricular pacing frequency series. These values differ significantly (p < .01) from the insignificant increases in the metoprolol group (1.7 ± 4.9% and 5.6 ± 14.2%, respectively).

**Comparison of drug effects on normal and ischemic myocardium.** The percentage increases in RP<sub>1Z</sub> produced by sotalol, whether measured with extrastimuli (41 ± 45%) or during the frequency series (49 ± 49%), were significantly greater than the increase in ERP<sub>V</sub> (14 ± 5.5%; p < .05). Linear regression analysis showed no significant correlation between individual percentage changes in ERP<sub>V</sub> and RP<sub>1Z</sub> (r = .25).

**Effect on ECG variables.** The effects of sotalol and metoprolol on sinus cycle length, QRS duration, and QT interval were listed in table 2. The latter two measurements were made during constant atrial pacing (cycle length 350 msec) to eliminate the effect of heart rate. However, the QT interval measured during sinus rhythm and corrected by the Bazett formula<sup>16</sup> is given for completeness.

Although both drugs slowed heart rate significantly, the 34 ± 15% increase in sinus cycle length after sotalol was significantly greater than that after metoprolol (21 ± 16%; p < .05). Neither drug prolonged QRS duration significantly. Sotalol produced an increase of 12.6 ± 7.8% in QT interval during constant atrial pacing, compared with 3.9 ± 4.3% after metoprolol (p < .01). The clear prolongation of QT at constant heart rate by sotalol is in contrast to the non-significant change in the QTc interval. Metoprolol caused shortening of the QTc interval. Problems in the correction of QT interval for heart rate after β-blockade have been discussed elsewhere.<sup>17</sup>

![FIGURE 2. Comparison of effects of sotalol and metoprolol on sustained and nonsustained VT. Sotalol was completely effective in five of eight sustained and one of 11 nonsustained VTs, and partially effective in another five of 11 episodes of nonsustained VT. Metoprolol was effective in only one episode of sustained VT.](image)

**TABLE 1**

<table>
<thead>
<tr>
<th>Effect of sotalol and metoprolol on refractoriness in normal and ischemic myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Sotalol</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Metoprolol</td>
</tr>
</tbody>
</table>

Values are in msec, mean ± SD.

RP<sub>1Z</sub> freq series = longest cycle length of continuous ventricular pacing at which fragmentation or block of late potential occurred.

<sup>a</sup>By paired t test; control vs drug.
Despite the similar percentage increases in ERP, and QT interval produced by sotalol, data from individual dogs did not show a significant correlation between the percentage increase in QT and ERP (r = .39) nor between QT and RPIZ changes (r = .02).

Comparison of sotalol responders and nonresponders. There were no significant differences between control values for ERP, sinus cycle length, QRS duration, QT interval (paced), QTc (sinus rhythm), or plasma sotalol levels in the group of dogs that responded completely or partially to sotalol and the group of those that did not. Of the variables above, only the percentage increase in QT interval was significantly greater in the sotalol responders (14.8 ± 10.3%) than in the nonresponders (5.2 ± 4.5%; p < .05).

Discussion

Critique of the experimental model. The rate-dependent characteristics of conduction in the infarct zone, mode of initiation and termination of reentry, and consistency of interectopic patterns during stable ventricular tachycardia we observed were similar to those previously reported.8, 9, 10 We also found that stable continuous VT produced a consistent epicardial interectopic pattern in one or more leads of the infarct-zone electrogram (figure 1), while nonsustained repetitive ventricular activity had a pleomorphic infarct-zone electrographic pattern. Although stable VT is readily induced in the open-chest dog 4 days after infarction,9 there has been debate as to whether stable VT can be produced in a closed-chest conscious dog. Karagueuzian et al.18 elicited stable VT in only 20% of dogs after complete occlusion of the left anterior descending coronary artery, although the success rate was higher in an occlusion/reperfusion preparation. Echt et al.19 were unable to produce stable VT, and found a high incidence of ventricular fibrillation. We gave 30 mg/kg methylprednisolone before coronary ligation.

![TABLE 2](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effect of sotalol and metoprolol on ECG variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCL</td>
</tr>
<tr>
<td>Control</td>
<td>390 ± 13</td>
</tr>
<tr>
<td>Sotalol</td>
<td>510 ± 12</td>
</tr>
<tr>
<td>Control</td>
<td>398 ± 60</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>478 ± 50</td>
</tr>
</tbody>
</table>

Values are in msec, mean ± SD.
SCL = sinus cycle length; QRS AP 350 = QRS duration; atrial pacing at cycle length 350 msec; QT AP 350 = QT interval, atrial pacing at cycle length 350 msec; QT<sub>s</sub> SR = corrected QT interval in sinus rhythm.

<sup>a</sup>By paired t test; control vs drug.
which has been shown to produce stable VT in 58% of dogs in which open-chest stimulation is used.\textsuperscript{9} We obtained stable VT after 13 of 33 (39%) stimulations. The difference between open- and closed-chest stimulation may be mediated by the increased levels of endogenous sympathetic activity in the former, with effects on the conduction properties of the infarct zone.\textsuperscript{20}

The use of composite electrographic recordings is subject to limitations, and may fail to provide as accurate an estimate of overall duration of activation as can be obtained with large numbers of bipolar electrodes.\textsuperscript{21} Although continuous interectopic electrical activity recorded by the composite electrode was thought to be highly suggestive of reentry activity, El-Sherif et al.\textsuperscript{8} recognized that gross fractionation of the infarct zone potential was not invariably associated with ectopic formation,\textsuperscript{8} a finding that is confirmed here (figures 1 and 3). Epicardial isochronal mapping has shown that nonsustained wavelets of delayed activation not responsible for the maintenance of an epicardial reentry circuit may nevertheless occur throughout the interectopic interval\textsuperscript{22} and appear as “continuous electrical activity” in a composite electrode recording.\textsuperscript{23} If these wavelets were uniformly present on a beat-to-beat basis in a sustained tachycardia, they would be misinterpreted in a composite electrogram as indicating the presence of a reentry circuit. However, an excellent correlation has been found between the demonstration of local continuous electrical activity with the composite electrode in sustained VT and the ability to terminate the tachycardia by localized cooling at that site.\textsuperscript{24} These data suggest that the composite electrogram does record potential or actual reentrant electrical activity in most cases.

Comparison of studies on the electrophysiologic effects of lidocaine on refractoriness in infarcted myocardium with composite electrode recordings and epicardial isochronal mapping have shown that results are consistent.\textsuperscript{25,26} This suggests that observations on changes in cycle length–dependent fractionation and block of infarct-zone late potentials, as recorded by the composite electrogram,\textsuperscript{25} are likely to correspond to the demonstrable slow conduction, unidirectional block, or inexcitability that can be recorded directly by epicardial isochronal mapping.\textsuperscript{26} Nevertheless, the problems of determining the refractoriness of areas of delayed depolarization in ischemic myocardium by the composite electrode technique are considerable and the results obtained in this study should be interpreted with caution and verified by isochronal mapping studies.

**Actions of sotalol.** Sotalol was found to be more effective than metoprolol against ventricular tachyarrhythmias in this preparation. Although there was a significant difference between sotalol and metoprolol with respect to prolongation of ventricular ERP, the most striking difference was in their effects on refractoriness in the infarct zone. The percentage increase in refractoriness in the infarct zone produced by sotalol was significantly greater than the effect of the drug on normal myocardium. This observation suggests that sotalol may act by selectively increasing refractoriness in depressed myocardial areas.

A “selectivity hypothesis” has been proposed to explain the antiarrhythmic effects of lidocaine and diphenylhydantoin in the canine postinfarction preparation.\textsuperscript{14,15,25} Similar hypotheses have also been advanced for other class I antiarrhythmic drugs that act by inhibition of the rapid sodium channel.\textsuperscript{27,28} Sotalol has very little effect on upstroke velocity of the action potential, being 300 times less potent than propranolol.\textsuperscript{1} We cannot exclude on the basis of our data the possibility that a gross enhancement of the weak class I activity of sotalol occurs in ischemic myocardium, but this seems unlikely in view of the finding that propranolol had very little effect on infarct-zone refractoriness in a similar canine preparation.\textsuperscript{29}

A more likely explanation for our results is that the class III effect of sotalol was responsible for its antiarrhythmic activity. Although we did not measure action potential duration in this study, we did demonstrate a significant increase of 12.5% in QT interval and of 14% in ventricular ERP after sotalol, both values being significantly greater than the changes produced by metoprolol. Recent studies in man have shown that intravenous sotalol increased right ventricular monophasic action potential duration, ventricular ERP, and QT interval by approximately 10%.\textsuperscript{2} Previous in vitro studies have also shown that sotalol produced a parallel increase in action potential duration and ERP.\textsuperscript{2} It seems likely, therefore, that there was an increase of approximately 10% to 15% in action potential duration in the nonischemic myocardium in these experiments, but this does not explain the 40% increase in refractoriness in the infarct zone.

It is of interest that we did not demonstrate any paradoxical arrhythmogenic effects of sotalol, despite the fact that we used doses up to 4.5 mg/kg that produced clear prolongation of the QT interval. Isolated case reports have suggested that high plasma levels of sotalol are associated with torsade de pointes and other ventricular tachyarrhythmias,\textsuperscript{30,31} but the association has been challenged by others.\textsuperscript{32} It is also noteworthy that sotalol was much less effective in preventing non-
sustained VT (1/11 experiments) than sustained VT (5/8). The mechanisms responsible for the two types of tachycardia appear different, and the effect of an antiarrhythmic drug may also differ. In these experiments and in others, monomorphic sustained VT has been associated with an interectopic pattern that is highly reproducible on a beat-to-beat basis, while polymorphic nonsustained VT demonstrates beat-by-beat variation in the pattern of epicardial activation, whether demonstrated directly by isochronal mapping, or indirectly with the composite electrode. The mean cycle length of the nonsustained tachycardias (140 ± 19 msec) was less than of the sustained tachycardias (185 ± 40 msec). The effect of sotalol on action potential duration and ERP is diminished at higher heart rates in vitro, and this might account for the differences in effect shown here.

In conclusion, we have found that intravenous sotalol at least partly protected against ventricular tachyarrhythmias in 58% of studies. Sotalol produced modest increases in ventricular ERP and QT interval, but induced a major increase in the refractoriness of potential reentrant circuits in ischemic myocardium. These results are consistent with the hypothesis that sotalol possesses significant class III antiarrhythmic properties in addition to its β-adrenergic blocking actions.

References
5. Echt DS, Berte LE, Clusion WT, Samuelsson RG, Harrison DC, Mason JW: Prolongation of the human cardiac monophasic action potential by sotalol. Am J Cardiol 50: 1082, 1982
29. El-Sherif N, Lazzara R: Re-entrant ventricular arrhythmias in the late myocardial infarction period. 7. Effect of verapamil and D-600 and the role of the "slow-channel." Circulation 60: 605, 1979
Action of sotalol on potential reentrant pathways and ventricular tachyarrhythmias in conscious dogs in the late postmyocardial infarction phase.

S M Cobbe, E Hoffman, A Ritzenhoff, J Brachmann, W Kübler and J Senges

_Circulation_. 1983;68:865-871
doi: 10.1161/01.CIR.68.4.865

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
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/68/4/865

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/