Influence of the Sympathetic System on the Pacemaker Suppression Which Follows Overdrive

By Michael B. Pliam, M.D., Ph.D., Daniel J. Krellenstein, M.D., Ph.D., Mario Vassalle, M.D., and Chandler McC. Brooks, Ph.D.

SUMMARY

When ventricular pacemakers are electrically stimulated at a fast rate, the cessation of the drive is followed by a temporary suppression of automaticity ("overdrive suppression"). The role of the sympathetic system in the regulation of this overdrive suppression was studied and the following results obtained: 1) Hypotension induced during overdrive by amyl nitrite inhalation caused a shortening of the pause which follows the drive. 2) Bilateral resection of the stellate ganglia led to the opposite effect. 3) Maximal stellate ganglion stimulation halved the pause duration. 4) Norepinephrine infusion accelerated the idioventricular rate and shortened the pause. 5) Beta adrenergic blockade decreased the idioventricular rate and prolonged the pause.

It is concluded that the tonic sympathetic discharge not only controls the basal idioventricular rate but also plays a regulatory role in the suppression of idioventricular automaticity which follows overdrive. This regulatory role can be dissociated from changes in idioventricular rate prior to overdrive.

Additional Indexing Words:
Overdrive suppression  Norepinephrine  Ventricular asystole  Propranolol
Stellate ganglion stimulation  Reflex sympathetic stimulation  Dog

SUBSIDIARY pacemakers are normally inhibited by the fact that they are driven by the sinus node at a rate faster than their own intrinsic rate ("overdrive suppression"). In the ventricle, this type of inhibition can be readily demonstrated by overdriving the ventricles in the presence of complete atrioventricular block: the end of the overdrive period is followed by a long pause before resumption of spontaneous idioventricular activity. The phenomenon can also be shown to occur in Purkinje fibers perfused in vitro. The mechanisms by which overdrive suppresses spontaneous activity have been attributed to the release of acetylcholine in the atrium and to the activation of an electrogenic sodium pump in the ventricles.

If these two mechanisms account for the overdrive suppression, there must also be factors which influence the suppression, reinstating ventricular automaticity following overdrive. One of these factors must be changes in sympathetic discharge. When the ventricles are overdriven, the mean arterial blood pressure increased; this, in turn, should lead to a withdrawal of sympathetic discharge, which may affect the ensuing pause. With the ventricles inactive during the pause, the blood pressure falls and a reflexly-enhanced sympathetic discharge could accelerate the resumption of intrinsic automaticity. There is little doubt that the sympathetic system affects ventricular pacemakers and there are indications that it can also antagonize the inhibitory action of overdrive.

The aim of the present investigation was to analyze qualitatively and quantitatively the role of the neural and humoral influences in overdrive suppression of ventricular pacemakers.

Methods

Mongrel male dogs weighing 15-20 kg were pre-treated with morphine sulfate (5 mg/kg, intramuscularly) and anesthetized with alpha chloralose (75 mg/kg, intravenously). The animals were ventilated (40% O2 and room air) with a Bird Mark 8 respirator through a brass cannula placed in the trachea. The temperature of the animal was monitored and maintained at about...
38°C with the use of heat lamps as needed. The aortic blood pressure was recorded with a Statham pressure transducer (P23AA). Drugs and fluids were administered through a venous catheter. A lead II electrocardiogram was recorded on a Sanborn 4-channel (Model 964) recorder. In some experiments, both vagi were transected in the neck. The chest was opened through a midline sternotomy and the heart was supported on a pericardial cradle. One bipolar electrode was sutured to the epicardial surface of the right atrium and two to the surface of the ventricles. The electrode placed on the right ventricular outflow tract was employed for electrically driving the ventricles; the other electrodes were used to record bipolar electrograms. In some experiments, the ventricular rate was recorded by means of a cardiotachometer (Sanborn Cardio Tach Preamplifier 350-3400A). The stimuli for ventricular driving were provided by two sets of Tektronix waveform generators (Type 162) and pulse generators (Type 161). These stimuli were delivered through two Grass Stimulus Isolation Units (Model SIU 4678) and were monitored on an oscilloscope (Tektronix Type 561); they were 1 msec in duration, 4–8 volts in magnitude and delivered at rate of 30–300 pulses/min.

Determinations of blood pH, P02 and P02 were made at intervals during the experiment with a Radiometer Gas Monitor and pH Meter. Any degree of acidosis was corrected by adjusting the respirator and/or by administration of sodium bicarbonate.

Acute atrioventricular block was produced by placing a suture-ligation around the His bundle during inflow occlusion. Blood was replaced as needed with fresh, heparinized blood from another dog. The ventricles were driven at 60 beats/min between experimental procedures. Before a procedure was carried out, the ventricular drive was discontinued and sufficient time allowed for the intrinsic ventricular rate to stabilize. The ventricles were overdriven for a period of one minute at 4 or 5 different frequencies. To enhance sympathetic reflex discharge, hypotension was induced by placing a capsule of amyl nitrite,* anchored by a string, in the respiratory inflow tubing and fracturing the capsule at the beginning of an inspiratory cycle. Since it requires 15–30 sec for the maximal hypotensive effect of the nitrite, the capsule was crushed during the middle of the overdrive period. The “isolation” of both stellate ganglia was accomplished by severing all the branches of the ganglia with the exception of the cardiac nerves. The stimulation of one stellate ganglion (stimulus of 5 msec and 2–8 volts at a frequency of 20 pulses/sec) was initiated 30 sec after the beginning of the overdrive and was continued throughout the recovery period. Norepinephrine bitartrate† (5 µg/cc saline) was infused intravenously either by a continuous drip or by a constant speed infusion pump. The rate of infusion was usually between 0.5 and 1.5 µg/min/kg. Beta adrenergic blockade was carried out by intravenous administration of propranolol‡ (usually 50 µg/kg). The duration of overdrive suppression was fairly constant for periods of 3 to 6 hr. Reproducibility was generally within 1 sec for short pauses following low drive rates and did not exceed 3 sec for longer pauses.

Suppression of ventricular pacemaker automaticity by overdrive. LII = lead II of the ECG, RA = right atrial electrogram. BP = aortic blood pressure tracing; the vertical bar at the left of the blood pressure trace shows the calibration for the blood pressure in mm Hg. The period of drive which lasted one minute is indicated by the arrows.

*Vaporole, Borroughs Wellcome
†Levophed, Winthrop
‡Inderal, Ayerst

Figure 1
VENTRICULAR OVERDRIVE SUPPRESSION

Results

Idioventricular Rate in Dogs with Acute A-V Block

The average idioventricular rate following acute A-V block was 37.6 ± se 2.5 beats/min (range 20 to 56 beats/min, table 1).

Overdrive Suppression in Dogs with Acute A-V Block

The inhibitory effect of a one minute ventricular drive at a rate of 200 beats/min is shown in figure 1. The post-drive pause was followed by a progressive increase in idioventricular rate toward the control value. Table 1 compares the effect of overdrive at two different rates in 15 dogs. The average pause duration after 120 beats/min drive was 8.2 and after 240 beats/min drive was 17.3 sec. Thus, doubling the driving rate doubled the pause duration. The difference in the pause duration at the two rates was statistically significant (P < 0.005).

Reflex Sympathetic Enhancement

In 7 dogs the overdrive procedure was repeated during hypotension induced by amyl nitrite inhalation. In figure 2, the control procedure is shown in the upper panel. In the lower panel, amyl nitrite was inhaled at the arrow and there was an obvious fall in blood pressure during the second half of the drive. The ensuing pause was much shorter than in the control period, and the shortening was even

<table>
<thead>
<tr>
<th>Expt.</th>
<th>IVR Drive 120</th>
<th>Drive 240</th>
<th>ΔPause between 120 and 240</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beats/min</td>
<td>Pause, sec</td>
<td>Pause, sec</td>
</tr>
<tr>
<td>1</td>
<td>40</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>16</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>36</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>38</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>14</td>
<td>44</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>38</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Avg.</td>
<td>37.6</td>
<td>8.2</td>
<td>17.3</td>
</tr>
<tr>
<td>se</td>
<td>± 2.3</td>
<td>± 1.3</td>
<td>± 3.2</td>
</tr>
</tbody>
</table>

Expt. = identifying number, IVR = idioventricular rate. Pause values given in seconds. All hearts driven for one minute at 120 and 240 beats/min. Δ pause = difference in pause duration between two drive rates. Avg. ± se = average values ± standard error.

Figure 2

Effect of amyl nitrite induced hypotension on overdrive suppression. Upper record: control. Lower record: amyl nitrite capsule crushed at the arrow. Only blood pressure tracing shown. Other explanations as in figure 1.

Circulation, Volume XLVIII, August 1973
more pronounced following higher rates of overdrive. In table 2, the average pause following 120 beats/min drive decreased by 3.8 sec during nitrite hypotension (P < 0.025); in the same experiments the blood pressure at the end of the drive decreased by 41/43 mm Hg after nitrite. The average pause following 240 beats/min drive decreased by 9.3 sec during nitrite hypotension (P < 0.025); in the same experiments the blood pressure at the end of the drive decreased by 27/31 mm Hg after nitrite. The duration of the pause following overdrive decreased 36% with the 120 beats/min drive and 49.2% with the 240 beats/min drive following amyl nitrite administration.

**Stellate Ganglia “Isolation”**

In 16 dogs with acute A-V block, the idioventricular rate was 38.1 ± 2.6 before and 29.0 ± 1.2 beats/min after the isolation of the stellate ganglia. In two of these dogs the rate remained unaltered; in the other 14, the decrease ranged from 6 to 24 beats/min. The average decrease was 23.9% (P < 0.0025).

The overdrive procedure was carried out before and after stellate ganglia isolation. Figure 3 shows that the isolation of the ganglia resulted in an upward shift of the drive-suppression relationship. The pause duration increased at each drive rate,

![Figure 3](http://circ.ahajournals.org/doi/fig/10.1161/01.CIR.69.3.261)

**Figure 3**

Effects of bilateral stellate ganglion isolation on the duration of the pause at several drive rates in one dog.
but the effect was generally more pronounced at higher drive rates.

In 11 dogs, the average pause following ventricular drive at 120 beats/min increased by 4.7 ± 1.4 sec after bilateral stellate isolation (+79%, P < 0.025). Of interest is the fact that the blood pressure increased in some experiments and decreased in others just prior to the termination of the drive. Yet, such changes in blood pressure seemed to be unrelated to the duration of the subsequent pause, unlike the results before the stellate ganglia were isolated.

The average pause following ventricular drive at 240 beats/min was 15.5 ± 2.5 sec and was about the same (−0.2 sec) after bilateral stellate ganglion isolation (P > 0.4). This reflects the fact that the pause increased in 6 dogs and decreased or remained unaltered in 5 dogs.

**Stellate Ganglion Stimulation**

In 9 dogs, stimulation of the isolated stellate ganglion (usually the left) caused an increase in ventricular rate of 22.2 ± 6.7 beats/min from a control rate of 30.9 ± 2.0 beats/min (P < 0.01). In two dogs, not included in the results reported above, such stimulation caused ventricular tachycardia, which disappeared when the ganglion stimulation was discontinued.

Stellate stimulation was begun during the overdrive procedure and continued throughout the run (fig. 4). Sympathetic stimulation substantially increased the blood pressure and shortened the duration of the pause. The results obtained with 120 and 240 beats/min drives are plotted in figure 5. With the 120/min drive, the average control pause was 13.1 ± 2.7 and decreased by 9.0 ± 2.6 sec with stellate ganglion stimulation (P < 0.01). It should be noted that in some instances sympathetic stimulation abolished the pause altogether: the duration of the pause was approximately equal to the cycle length of the pre-drive idioventricular rate. With the 240 beats/min drive, the average control pause was 14.3 ± 3.3 and decreased by 8.7 ± 2.9 sec with stellate ganglion stimulation (P < 0.01).

**Figure 4**

*Effects of stellate ganglion stimulation on overdrive suppression. Upper record: control. Lower record: stellate ganglion stimulation started at the arrow. Only blood pressure tracing shown. Other explanations as in figure 1.*
Norepinephrine Infusion

The effect of a background increase in the sympathetic neurotransmitter on overdrive suppression was analyzed by intravenous infusion of norepinephrine in 9 dogs following bilateral stellate ganglion isolation. The average control idioventricular rate was 32.1 ± 3.1 and increased by 20.7 ± 6.2 beats/min during norepinephrine infusion ($P < 0.005$). The ventricles were overdriven before and during norepinephrine infusion and the pause duration compared. The results obtained in one experiment at three driving rates are illustrated in figure 6. Typically, norepinephrine shortened the pause at all frequencies. However, the effect was more pronounced at more rapid driving rates in agreement with the results obtained with reflex and direct sympathetic stimulation. With a drive of 120 beats/min, the control pause was 12.1 ± 1.9 and decreased by 5.0 ± 2.1 sec with norepinephrine infusion (8 dogs, $P < 0.025$). In one of the 8 dogs, the pause increased instead of decreasing during norepinephrine infusion. With a drive rate of 240 beats/min, the control pause was 14.3 ± 2.1 and decreased by 7.6 ± 1.3 sec during norepinephrine administration ($P < 0.0005$).

Beta Adrenergic Blockade

The beta receptors were blocked with propranolol to eliminate adrenergic influences which remained after acute isolation of stellate ganglia (table 3). The average idioventricular rate was 36

Table 3

Effect of Beta Adrenergic Blockade on Ventricular Automaticity and Overdrive Suppression

<table>
<thead>
<tr>
<th>Expt.</th>
<th>IVR</th>
<th>Pause</th>
<th>Control IVR</th>
<th>Pause</th>
<th>Propranolol IVR</th>
<th>Pause</th>
<th>ΔIVR</th>
<th>%ΔIVR</th>
<th>ΔPause</th>
<th>%ΔPause</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Drive 120/min</td>
<td>7 40 11 20 25</td>
<td>-20 -50</td>
<td>17 +283</td>
<td>13 40 9 40 13</td>
<td>0 0</td>
<td>4 + 44</td>
<td>16 29 16 20 22</td>
<td>-31 -31</td>
<td>6 + 38</td>
<td>36 Avg. 10.3 27 19.3</td>
</tr>
<tr>
<td>B. Drive 240/min</td>
<td>7 40 11 20 25</td>
<td>-20 -50</td>
<td>14 + 127</td>
<td>13 34 16 40 18</td>
<td>+ 6 +18</td>
<td>2 + 13</td>
<td>16 30 20 29</td>
<td>-10 -33</td>
<td>9 + 45</td>
<td>36 Avg. 15.7 27 24</td>
</tr>
</tbody>
</table>

Expt. = identifying number. Control, Propranolol = results obtained during the control period and following the administration of propranolol, respectively. IVR = idioventricular rate in beats/min. Pause = duration of the pause in seconds. ΔIVR, %ΔIVR = change in the idioventricular rate following propranolol administration, with respect to control, in beats/min and in percent, respectively. ΔPause, %ΔPause = change in the pause duration following propranolol administration, with respect to control, in seconds and in percent, respectively. Plus and minus signs signify an increase or decrease with respect to control, respectively. Avg. ± se = average values ± standard error.
beats/min before and 27 beats/min after the administration of propranolol. At 120 beats/min drive, the pause duration was 10 sec before and 19 sec after propranolol. At 240 beats/min overdrive, the average duration of the pause was 16 sec before and 24 sec after propranolol administration. In all three experiments, after the administration of propranolol norepinephrine failed to accelerate the idioventricular rate; and stellate ganglion stimulation was also ineffective when it was tested on two occasions.

Discussion

The plan of the discussion is to consider the role of the sympathetic system first on the regulation of idioventricular automaticity and then on the duration of overdrive suppression.

Regulation of Idioventricular Automaticity

The average idioventricular rate found in the present experiments (37.6 beats/min) is similar to that reported for dogs with chronic A-V block. Erlanger and Blackman15 found a rate of 41.8, Roberts and Modell16 46 ± 3.6, and Vassalle, Levine and Stuckey17 44.8 beats/min. The dogs of the latter study were anesthetized in the same manner as in the present experiments and the similarity of the average rates suggests that the acute experimental procedure employed here did not unduly influence the basal idioventricular rate. This impression is strengthened by the effects of bilateral stellate ganglion isolation. As a result of this procedure, the idioventricular rate fell by 9.1 beats/min; with isolation of only the left stellate ganglion the idioventricular rate fell by 4.7 beats/min.17 This suggests that the tonic sympathetic discharge through the two ganglia summates. In another study,16 the mean idioventricular rate fell by some 5 beats/min in 4 animals following adrenalectomy, and in 3 of the 4 animals subsequent bilateral thoracic sympathectomy decreased the rate by an additional 21 beats/min.

The present results are consistent with the view first expressed by Hunt18 that the heart is under control by a tonic sympathetic discharge. In particular, they suggest that sympathetic nerve discharge through the stellate ganglia accounts for about 9 beats/min of the idioventricular rate. In the absence of this factor the idioventricular rate would be reduced by about one-fourth. Also, the increase in idioventricular rate with stimulation of the left stellate ganglion (from 30.9 to 53.1 beats/min) is similar to that of dogs with chronic A-V block (from 44 to 61 beats/min),19 considering that in the present experiments both stellate ganglia were isolated and the control rate was lower. The response indicates an unimpaired ability to react to this stimulus.

It is not surprising that ventricular tachyarrhythmias should be encountered in some instances during stellate stimulation since it is generally appreciated that ventricular arrhythmias can be induced by catecholamines.19 A feature which helps distinguish ventricular tachycardias from the normal acceleration induced by sympathetic stimulation or catecholamine administration is that their rate is usually above some 120 beats/min and their onset and cessation are abrupt.14

The maximal acceleration during norepinephrine infusion was comparable to that obtained with maximal sympathetic stimulation. This suggests that the maximal ventricular response to high frequency sympathetic stimulation may be limited by the flat part of the dose-response curve of norepinephrine rather than by the inability of the sympathetic nerves to release more norepinephrine as the frequency of discharge is increased.

The fall in idioventricular rate induced by propranolol may be due to its ability to block beta receptors. After bilateral stellate isolation, Purkinje fibers still can be affected by catecholamines originating from residual sympathetic nerves, from the adrenal medulla or from local stores. By blocking the beta receptor, propranolol should give some quantitative indication of the influence exerted by these factors. A complicating factor in the evaluation of the results is that a direct action of the drug cannot be entirely ruled out.

Duration of Overdrive Suppression

Overdrive suppression persists after the elimination or marked reductions of sympathetic influences in vivo. This confirms the conclusion that the suppression is not due solely to sympathetic withdrawal. However, the present experiments make it clear that the sympathetic system affects overdrive suppression consistently and in a substantial way. Thus, increasing reflexly the sympathetic discharge by lowering the blood pressure during overdrive shortened the duration of the pause (fig. 2). This shortening presumably resulted from the abolition of reflex sympathetic withdrawal and/or from reflex enhancement of sympathetic discharge. With this maneuver, the control rate was not affected by the nitrite-induced hypotension and,
therefore, the shortening of the pause was certainly not related to a change in control idioventricular rate. A direct action of the nitrite on the ventricular pacemakers is rather unlikely for nitroglycerin fails to accelerate the sinus node after the elimination of the sympathetic innervation. In the absence of overdrive, nitrates accelerate the sinus as well as the idioventricular rate through a reflex enhancement of the sympathetic discharge. The lengthening of the pause after bilateral stellate ganglion isolation provides a confirmation for a role of the sympathetic nerve on the duration of the overdrive suppression. It should be noted that, if this happened in most of the runs at 120 beats/min, there were several exceptions with the drive at 240 beats/min. In those animals in which the pause was found to decrease following ganglionectomy, the blood pressure at the end of the drive was generally lower than control. Driving the heart at 200 beats/min or above can result in a lower blood pressure because of a decrease in the time available for ventricular filling. Furthermore, the elimination of the sympathetic outflow from the stellate ganglia may be responsible for the more frequent occurrence of lower blood pressure on fast drive. This effect might be further accentuated by the decrease in venous return following a decrease of venomotor tone after the interruption of the thoracic sympathetic trunks. Since bilateral stellate ganglion isolation does not eliminate entirely the sympathetic nerve pathways to the heart, the activation of the residual sympathetic innervation by the lower blood pressure may be responsible for the shortening of the pause in some instances of fast drive.

The stimulation of the left stellate ganglion at 20/sec permits the conclusion that with maximal sympathetic stimulation it is possible to halve the duration of the pause after both the 120 and the 240 beats/min drives. This sets the upper limit of the range of control of sympathetic nerves on overdrive suppression.

The results with norepinephrine infusion are similar to those obtained with the stimulation of the stellate ganglion, both qualitatively and quantitatively. Thus, norepinephrine shortened the pause somewhat following overdrive and more so when the drive was faster or the control pause longer. However, there was one important difference between nerve stimulation and norepinephrine administration, namely that the nerve stimulation was begun during the drive (therefore without any change of the spontaneous pre-drive rate) and norepinephrine infusion was begun before the drive (therefore causing an increase in the spontaneous pre-drive rate). The difference is important in that for the same driving rate the percent increment of the rate imposed is less when the control rate is higher (unpublished observations).

In keeping with the results so far discussed, the elimination of the residual sympathetic influences by administration of propranolol led to a marked increase in the pause duration, suggesting that other sources of catecholamines (besides neural stores) participate in regulating overdrive suppression.

Some general considerations are suggested by the present results. There are two situations in which idioventricular pacemakers are overdriven and therefore kept under inhibition. One of these situations is physiological: the overdrive imposed by the sinus node on the slower ventricular Purkinje fibers. If a sudden idioventricular block is provoked either by damage of the His bundle or by stimulating the vagus, the overdrive suppression of the sinus node becomes evident with a temporary ventricular arrest. The second situation obtains with the implantation of electric pacemakers in case of chronic A-V block: a sudden failure of the electric pacemaker results in a temporary ventricular arrest quite similar to that caused by cessation or block of the sinus impulses. The present experiments point out that duration of the overdrive suppression which follows the sudden cessation of pacemaker action is also a function of the sympathetic neural and humoral discharge. A number of investigators have demonstrated directly or indirectly that the initiation of ventricular escape during vagal stimulation or after overdrive is hastened by catecholamine administration. The present results indicate that not only the administration of catecholamines but also the reflex and direct activation of the sympathetic nerves during overdrive play a role in the regulation of the relationship between rate of drive and subsequent inhibition.

References


Circulation, Volume XLVIII, August 1973


23. Nonidez JF: The structure and innervation of the conducting system of the heart of the dog and the Rhesus monkey as seen with a silver impregnation technique. Am Heart J 26: 577, 1943


Influence of the Sympathetic System on the Pacemaker Suppression Which Follows Overdrive
MICHAEL B. PLIAM, DANIEL J. KRELENSTEIN, MARIO VASSALLE and CHANDLER McC. BROOKS

Circulation. 1973;48:313-321
doi: 10.1161/01.CIR.48.2.313
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 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/48/2/313

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/