Vasopressin and the Mature Coronary Collateral Circulation

Kevin G. Peters, MD, Melvin L. Marcus, MD, and David G. Harrison, MD

In isolated vascular rings, we have shown that mature coronary collateral vessels are highly responsive to the vasoconstrictor effects of vasopressin. The purpose of the present study was to determine the effect of concentrations of vasopressin encountered in pathophysiologic states on the collateral circulation in vivo. We studied eight open-chest anesthetized dogs with mature coronary collateral vessels 3–6 months after placement of an ameroid constrictor on the left circumflex coronary artery. The left anterior descending coronary artery was perfused at constant pressure, and peripheral coronary pressure was monitored continuously throughout each experiment. At baseline and during intracoronary infusion of vasopressin, which resulted in concentrations ranging from 8±3 to 1,340±327 μM/ml, we measured regional myocardial perfusion with radiolabeled microspheres. At baseline, regional myocardial perfusion to the collateral-dependent myocardium and to the normally perfused myocardium was similar; however, during vasopressin infusion, collateral-dependent zone flow decreased by 49±14% whereas normal zone flow decreased by only 9±9% (p<0.0005, normal zone perfusion vs. collateral perfusion). Vasopressin increased transcollateral resistance by 242±95% above baseline but produced a more modest increase in normal zone resistance (15±10%). The subendocardial to subepicardial perfusion ratio increased by 28±12% in the normal zone in response to vasopressin but decreased by 18±11% in the collateral-dependent zone. These data show that mature coronary collateral vessels are responsive to the vasoconstrictor effects of vasopressin at concentrations encountered in various pathophysiologic states. Moreover, these data suggest that endogenous vasopressin may modulate collateral resistance and have disparate effects on transmural perfusion to collateral-dependent and normal myocardium. (Circulation 1989;79:1324–1331)

Vasopressin is an endogenous vasoactive peptide secreted by the posterior pituitary in response to a variety of stimuli. Normally, plasma vasopressin levels are less than 10 μU/ml. However, in pathophysiologic states such as hemorrhage, surgery, cigarette smoking, and nausea, plasma levels of vasopressin may be greatly elevated (100–800 μU/ml).1-7

The antidiuretic activity of vasopressin has been considered its predominant endocrine role; however, recent studies demonstrate that vasopressin may importantly regulate systemic vascular resistance.8 Moreover, the vasomotor effects of vasopressin seem to be heterogeneous. In the peripheral circulation, renal flow is preserved whereas perfusion to the mesentery and to skeletal muscle decreases during vasopressin infusion.8 In the coronary circulation, vasopressin is a potent constrictor of resistance vessels.9-12 In contrast with this constricting action on the coronary resistance vessels, vasopressin has recently been shown to produce in large epicardial vessels dilatation that is in part mediated by the endothelium.13-14

In several species, including dogs, horses, and humans, coronary collateral vessels enlarge in response to gradual coronary occlusion. In the dog, native epicardial collateral vessels increase in diameter from about 40–100 μm to 1 mm or more.15 As these vessels enlarge, they also develop a muscular media composed of several layers of new smooth muscle that is capable of responding to a variety of neurohumoral and pharmacologic stimuli.16-21

In vitro experiments performed in our laboratory have shown that mature collateral vessels are hyper-responsive to the vasoconstrictor effects of vaso-
pressin.21 In isolated vascular rings, vasopressin produced pronounced constriction of collateral vessels but had minimal or no effect on proximal coronary arteries or normal vessels immediately adjacent to the collateral vessels. Moreover, in adenosine-vasodilated isolated hearts with mature collateral vessels, pharmacologic concentrations of vasopressin produced marked collateral constriction. This in vitro study illustrated the sensitivity of collateral vessels to pharmacologic concentrations of vasopressin but did not clarify the effect of vasopressin on perfusion to potentially ischemic collateral-dependent myocardium. The purpose of the present study was to examine the effects of vasopressin in concentrations encountered in pathophysiologic states on the mature coronary collateral vessels in vivo and to understand the net effect of vasopressin on perfusion to collateral-dependent myocardium.

Methods

Production of Mature Coronary Collateral Vessels

Sterile techniques were used in eight healthy mongrel dogs that underwent left thoracotomy through the fifth intercostal space during sodium pentobarbital anesthesia and mechanical ventilation. The pericardium was opened, and an ameroid occluder (Three Point Products, Montreal, Canada) 2.77–3.0 mm in diameter was placed around the proximal left circumflex coronary artery. The pericardium was then loosely closed, the thoracotomy was repaired, and the animals were allowed to recover. Experiments were performed 3–6 months after ameroid occluder placement.

Experimental Preparation

On the day of the study, the dogs were anesthetized with fentanyl (0.4 mg), droperidol (20 mg), and chloralose (15–20 mg/kg), intubated, and mechanically ventilated. Arterial blood gases were maintained within physiologic limits by varying the ventilation rate or tidal volume. The right femoral artery was catheterized to supply a coronary perfusion apparatus (see Figure 1). The left carotid artery was cannulated for arterial pressure monitoring. A left thoracotomy was then performed through the fourth intercostal space, the pericardium was opened, and a pericardial cradle was created. The left circumflex coronary artery was catheterized distal to the ameroid occluder and proximal to any major marginal branches for measurement of peripheral coronary pressure. The animals were heparinized (10,000 units i.v.), and a perfusion reservoir was primed with blood from the femoral arterial catheter. The left anterior descending coronary artery (LAD) was then ligated proximally. Immediately thereafter, a 13 gauge metal cannula was inserted into the LAD distal to the ligature, and this vessel was perfused with blood from the perfusion reservoir. LAD perfusion pressure was monitored through a side port of the metal cannula. Air pressure in the perfusion reservoir was controlled to maintain constant LAD pressure at 80 mm Hg. A snare was placed around the right coronary artery to exclude collateral flow from this vessel during measurements of myocardial perfusion.

Determination of Regional Myocardial Perfusion

For each determination of myocardial perfusion, approximately $5 \times 10^3$ $15 \mu m$ radioactive micro-
spheres (approximately 2 mCi) were injected as a bolus into the LAD perfusion tubing just proximal to a magnetic mixing chamber (see Figure 1). Reference samples were withdrawn from the perfusion tubing distal to the mixing chamber at a withdrawal rate of 4.94 ml/min starting 20 seconds before and for 90 seconds after microsphere injection. Myocardial samples were divided into endocardial, midwall, and epicardial layers. These pieces were further divided into samples weighing about 0.30–0.60 grams. Reference samples and tissue samples were placed in scintillation tubes and counted in a well-type gamma counter for 5 minutes. Myocardial blood flow was then calculated from the following formula: MBF = Cm × WR × 100/Cr, where MBF is myocardial blood flow (ml/min×100 g), Cm is counts/g of myocardium, Cr is counts/reference sample, and WR is reference sample withdrawal rate (ml/min).

**Measurement of Vasopressin Levels**

Vasopressin was infused proximal to a mixing chamber in the LAD perfusion tubing, and blood samples for vasopressin levels were withdrawn distal to the chamber (Figure 1). After each study the samples were centrifuged, and the plasma was removed and frozen. Vasopressin levels were then measured by radioimmunoassay according to Matsuguchi et al. This assay could detect 0.31 μU arginine vasopressin and had an intra-assay coefficient of variation of 4.7% and interassay coefficient of variation of 12.2%. Procedural recovery from plasma was 83%.

**Experimental Protocol**

Heart rate, aortic pressure, and peripheral coronary pressure were measured continuously. Constant LAD perfusion pressure was maintained throughout the experiments by the regulator attached to the pressurized perfusion reservoir (Figure 1). In the first experiment, aortic pressure was maintained at 100 mm Hg and in the subsequent studies at 80 mm Hg. We measured the vasopressin concentration in the LAD perfusate and determined myocardial perfusion at baseline and during intracoronary infusion of vasopressin at rates of 0.001, 0.005, 0.01, and 0.05 units/min. Vasopressin was always administered in increasing concentrations. During measurements of myocardial perfusion, the right coronary artery was occluded to prevent collateral blood flow from this vessel. In two experiments, flow measurements were not obtained at all infusion rates.

**Identification of Collateral-Dependent Myocardium**

After completion of each study, the hearts were perfused with a barium sulfate gelatin mixture for 5 minutes at a pressure of 100 mm Hg through catheters in the proximal LAD and left circumflex coronary arteries. After fixation in 6% formaldehyde for at least 2 days, the atria and right ventricles were removed, and the left ventricles were sectioned into five to seven transmural slices of approximately equal thickness (0.8–1.1 cm) parallel to the atrioventricular groove and perpendicular to the long axis of the left ventricle. Radiographs of these sections were done without magnification with 20 electron volts and 2 mA for 5 minutes on x-ray film (Kodak X2L2). By following the course of each vessel from one slice to the next on the barium angiogram, the perfusion field of each vessel was identified and traced on a sheet of transparent Plexiglas. The myocardial slices were then placed on the Plexiglas, and samples were obtained from the center of each perfusion field.

**Data Analysis and Statistics**

Normal zone resistance was calculated as the quotient of LAD perfusion pressure divided by the flow in the LAD perfusion field (normal zone flow). The transcollateral resistance was calculated as LAD pressure minus peripheral coronary pressure (the transcollateral pressure gradient) divided by flow in the circumflex perfusion field (collateral dependent zone). Total collateral resistance was calculated as LAD pressure divided by flow in the circumflex perfusion field. Normal zone flow, collateral dependent zone flow, normal zone resistance, transcollateral resistance, and total collateral resistance are expressed as absolute values and as percent change from baseline. The effect of the vasopressin infusion rate on the percent changes in hemodynamics, pressures, and flows within groups was analyzed with one-way repeated-measures analysis of variance, and, where applicable, multiple comparisons were made with a Fisher’s least significant difference test. To compare the relative effect of vasopressin on collateral-dependent and normal myocardium, percent change in flow and percent change in resistance in these regions were plotted as function of the log of the vasopressin concentration using linear regression analysis. The slopes of these relations were compared between the normal and collateral-dependent regions with paired Student’s t tests. All values are reported as the mean±SEM.

**Results**

At the time of the study, all hearts had large collateral vessels visible on the epicardial surface of the heart. Baseline peripheral coronary pressure averaged about one half of the LAD perfusion pressure (Table 1). This pressure is approximately four times that of peripheral coronary pressure in hearts with unstimulated collateral vessels. Collateral flow from the LAD to the circumflex artery perfusion field was quite variable but averaged 99±32 ml/min/100 g. Transcollateral resistance and total collateral resistance were 1.1±0.5 and 1.9±0.6, respectively. These values are approximately one third to one fourth of values encountered in hearts with unstimulated collaterals. Thus, ameroid constrictor placement resulted in substantial collateral growth.
Hemodynamic Effects of Vasopressin Infusion

Intracoronary vasopressin infusion increased plasma vasopressin concentrations from a baseline value of 8±3 µU/ml to a peak value of 1,340±327 (Table 2). These local concentrations of vasopressin had no effect on heart rate or aortic pressure. Constant LAD perfusion pressure was maintained throughout the experiment. Peripheral coronary pressure tended to decrease during vasopressin infusion (Table 2).

Effect of Vasopressin on Collateral Perfusion and Resistance

Increasing vasopressin concentrations resulted in a stepwise decrease in collateral flow from the LAD to the circumflex artery (Figure 2). Similarly, vasopressin increased transcollateral resistance by an average of about 2.5 times over baseline values (Figure 3).

Comparison of Vasopressin Effect on Normal Zone and Total Collateral Resistance

The effects of vasopressin on normal zone and collateral-dependent zone perfusion and resistances are illustrated in Figure 4. To compare the relative effect of vasopressin on normal zone flow and collateral flow, the percent decrease in each flow was expressed as a function of the log of the vasopressin concentration. The slopes of these relations could be used to determine the dependence of regional myocardial perfusion on vasopressin concentration with a slope of zero indicating no relation between perfusion and vasopressin concentration. The slope of this relation for the normal zone was not different from zero (0.07±0.07) whereas that of the collateral-dependent myocardium was significantly less than zero (−0.30±0.05, p<0.025 compared with the normal zone). Similarly, the slope of the relation between normal zone resistance and the log of the vasopressin concentration was 10.8±5.2 (not different from zero) and for the collateral dependent region was 114±37 (p<0.025 compared with normal zone).

By dividing peripheral coronary pressure by collateral blood flow, it was possible to estimate arteriolar resistance within the ischemic region. This value was similar to arteriolar resistance within the normally perfused region under baseline conditions (0.78±0.12 vs. 0.75±0.19 mm Hg/ml/min/100 g, respectively). During vasopressin perfusion, arteriolar resistance within the collateral-dependent zone increased by more than 150% whereas normal zone arteriolar resistance increased by only 15–20%. Thus, the decrease in collateral flow and the increase in total collateral resistance during vasopressin infusion were due to pronounced increases in both transcollateral resistance (collateral constriction) and accentuated increases in arteriolar resistance within the collateral-dependent region.

Table 1. Baseline Collateral Flow and Resistances

<table>
<thead>
<tr>
<th>Experiment number</th>
<th>LAD pressure (mm Hg)</th>
<th>Peripheral coronary artery pressure (mm Hg)</th>
<th>Collateral flow (ml/min/100 g)</th>
<th>Transcollateral resistance (mm Hg/ml/min/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>27</td>
<td>18</td>
<td>4.01</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>57</td>
<td>294</td>
<td>0.09</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>54</td>
<td>148</td>
<td>0.19</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>40</td>
<td>27</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>46</td>
<td>110</td>
<td>0.34</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>26</td>
<td>101</td>
<td>0.55</td>
</tr>
<tr>
<td>7</td>
<td>82</td>
<td>44</td>
<td>61</td>
<td>0.62</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>30</td>
<td>29</td>
<td>1.72</td>
</tr>
<tr>
<td>Mean</td>
<td>84</td>
<td>40</td>
<td>99</td>
<td>1.13</td>
</tr>
<tr>
<td>SEM</td>
<td>2</td>
<td>4</td>
<td>32</td>
<td>0.46</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery.

Table 2. Hemodynamics During Control State Vasopressin Infusion

<table>
<thead>
<tr>
<th>Vasopressin dose (U/min)</th>
<th>Vasopressin concentration (µU/ml)</th>
<th>Heart rate (beats/min)</th>
<th>LAD pressure (mm Hg)</th>
<th>Peripheral coronary artery pressure (mm Hg)</th>
<th>Mean aortic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8±3</td>
<td>159±11</td>
<td>84±2</td>
<td>40±4</td>
<td>77±6</td>
</tr>
<tr>
<td>0.001</td>
<td>36±18</td>
<td>160±9</td>
<td>85±3</td>
<td>38±4</td>
<td>73±7</td>
</tr>
<tr>
<td>0.005</td>
<td>98±18</td>
<td>162±8</td>
<td>83±4</td>
<td>34±3</td>
<td>63±7</td>
</tr>
<tr>
<td>0.01</td>
<td>268±94</td>
<td>172±7</td>
<td>81±1</td>
<td>41±6</td>
<td>75±8</td>
</tr>
<tr>
<td>0.05</td>
<td>1,340±327</td>
<td>167±6</td>
<td>83±4</td>
<td>35±4</td>
<td>68±7</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

LAD, left anterior descending coronary artery.
Effect of Vasopressin on Transmural Myocardial Perfusion

Under control conditions, the endocardial to epicardial ratios of perfusion were similar in the normally perfused and collateral-dependent regions of myocardium (1.05±0.4 and 0.80±0.22, respectively). Vasopressin infusion, however, produced disparate effects on the endocardial to epicardial perfusion ratio (Figure 5). Vasopressin increased the endocardial to epicardial ratio of perfusion in the normally perfused region and decreased this ratio in the collateral-dependent region of myocardium.

Discussion

In the present study, we found that mature coronary collateral vessels are responsive to the vasoconstrictor effects of vasopressin at concentrations encountered in a variety of common pathophysiologic states. Although the vasculature perfusing normal myocardium is relatively insensitive to these levels of vasopressin, vasopressin caused a pronounced increase in transcollateral and total collateral resistance. Consequently, collateral-dependent zone flow fell sharply with vasopressin infusion, but normal zone flow fell only modestly. Moreover, the transmural distribution of blood flow in the collateral-dependent zone was adversely affected by vasopressin infusion. Thus, in certain clinical settings such as major surgery, hemorrhage, or cigarette smoking, endogenous vasopressin may decrease flow to collateral-dependent myocardium.

Comparison With Previous Studies

Intracoronary or systemic administration of pharmacologic concentrations of vasopressin have been shown to greatly decrease coronary blood flow; this decrease is presumably due to constriction of resistance vessels.8-12 In contrast with this effect, vasopressin has recently been found to dilate large epicardial coronary arteries, a response that is in part dependent on the endothelium.13,14 Using isolated vascular rings in our laboratory, we observed that vasopressin had minimal effect on either large coronary vessels or smaller vessels adjacent to the collateral vessels but produced marked constriction of collateral vessels.21 In separate experiments, pharmacologic concentrations of vasopressin produced increases in transcollateral resistance in hearts with mature collateral vessels studied in a Langendorf type preparation during adenosine vasodilation. The present study confirms and extends these in vitro findings to an in vivo finding. Taken together, these findings show that the response to vasopressin in the canine coronary circulation is heteroge-

**FIGURE 2.** Plot of percent changes from baseline in collateral flow during vasopressin infusion. Collateral flow from the left anterior descending coronary artery to the circumflex coronary artery region of myocardium was measured with microspheres under baseline conditions and during infusion of increasing concentrations of vasopressin. Data are presented for each individual experiment.

**FIGURE 3.** Plot of percent changes from baseline in transcollateral resistance during vasopressin infusion. Transcollateral resistance was calculated as the quotient of aortic pressure minus peripheral coronary pressure divided by collateral flow and measured with radioactive microspheres. Data are presented for each individual experiment.
neous and that compared with other epicardial vessels, collaterals are more responsive to the constrictor effects of vasopressin.

Mechanisms of Collateral Hypersensitivity

The present study does not provide insight into the mechanism of collateral constriction to vasopressin. However, several mechanisms may contribute. If endothelium of the collateral vessel, unlike other epicardial vessels, lacked vasopressin receptors or had a diminished capacity to manufacture or secrete endothelium-dependent relaxation factors, vasopressin receptors on the vascular smooth muscle would function unopposed to cause vasoconstriction. A second possibility is that vasopressin receptors on collateral endothelial cells cause release of a constricting substance. Finally, vasopressin receptors may be more numerous or have a higher affinity for vasopressin on the newly formed smooth muscle of the mature collaterals.

Mechanisms of Resistance Vessel Constriction in Collateral-Dependent Myocardium

In the present study, vasopressin produced marked constriction of the arterioles within the collateral-dependent myocardium but had little effect on arteriolar resistance in normal myocardium. One explanation for this finding relates to differences in resting vascular tone. Because the driving pressure distal to the collateral vessels is substantially lower than aortic pressure, the resistance vessels supplying the collateral-dependent myocardium are more dilated than the vessels supplying the normally perfused myocardium. Vasopressin may produce greater constriction of the dilated resistance vessels in the collateral-dependent zone than of the already partially constricted vessels in the normal zone. This concept is supported by recent observation in the porcine cerebral circulation. A second possibility is that during collateral development the resistance vessels in the collateral-dependent myocardium develop an enhanced sensitivity to vasopressin. Nevertheless, constriction of collateral vessels and augmented constriction of arterioles both seem to be important components of the decrease in flow to the collateral-dependent region in response to vasopressin.

Strengths and Limitations of the Present Study

To calculate collateral resistance, we assumed that pressure at the origin of the collateral vessels was similar to the LAD perfusion pressure. This assumption is based on anatomic studies showing that mature collateral vessels largely arise and insert in proximal coronary arteries and physiologic studies showing that, under conditions of intact vaso-motor tone, the pressure at the origin of the collateral vessels is not substantially different than aortic pressure. LAD perfusion pressure and peripheral coronary pressure were used to calculate the transcollarial pressure gradient and subsequently the transcollarial resistance. Transcollateral resistance provides a more accurate assessment of the effect of a vasoactive agent on the collateral vasculature than does flow in the collateral-dependent zone because it excludes the effect of the vasoactive agent on the resistance vessels within the collateral-dependent myocardium.
The perfusion fields of the large coronary arteries interdigitate so that peninsulas of tissue perfused by one coronary artery commonly overlap into the perfusion field of another coronary artery.\(^{25,26}\) To avoid inclusion of overlap flow we identified each perfusion field from the barium angiogram and then selected samples from the center of each field. Since collateral flow is homogeneously distributed throughout the ischemic region, measurements of flow to the center of this region should represent perfusion to the entire collateral-dependent region.\(^{27}\)

In this study we examined collateral blood flow from the perfused LAD to the collateral-dependent myocardium of the circumflex perfusion field. The right coronary artery may provide substantial collateral flow to the ischemic circumflex perfusion field.\(^{28,29}\) To exclude flow from the right coronary artery, we occluded this vessel during measurements of myocardial perfusion. In addition, collateral perfusion from the septal coronary artery was not measured because the cannula in the left anterior descending coronary artery was always placed distal to the origin of this vessel. These measures were necessary because a pressurized perfusion system was used to maintain a constant collateral driving pressure. This also permitted intracoronary administration of vasopressin and avoided systemic effects of this agent.

Collateral flow from the LAD to the circumflex artery varied markedly between dogs. This reflects the tremendous variability in the capacity for mongrel dogs to develop collateral flow and is consistent with previous observations.\(^{21,28}\)

**Clinical Implications**

The effect of vasopressin on the coronary collateral circulation in patients has not been directly examined. However, therapeutic infusion of vasopressin has been associated with myocardial ischemia, myocardial injury, cardiac dysrhythmias, and sudden death in patients with and without known coronary artery disease.\(^{30-33}\) Moreover, in two patients who died suddenly after intramuscular administration of vasopressin, autopsy revealed chronic total occlusion of at least one coronary artery and no evidence of previous myocardial infarction.\(^{34}\) These findings strongly suggest that these patients had collateral-dependent myocardium that may have been rendered ischemic by vasopressin-induced collateral constriction.

Vasopressin levels are elevated in various pathophysiologic states such as surgery, hemorrhage, and cigarette smoking. The present study demonstrates that the levels of vasopressin encountered in these states are sufficient to cause constriction of collateral vessels and ischemia of collateral-dependent myocardium. This phenomenon may help explain the excess mortality and morbidity of noncardiac surgery in patients with severe coronary artery disease and the strong association of cigarette smoking with ischemic events.\(^{35-36}\) Interpreted conservatively, these data suggest that endogenous vasopressin or vasopressin infusion may exacerbate myocardial ischemia in patients with occlusive coronary artery disease.

**References**

15. Schaper W, Vandesteene R: The rate of growth of interar
21. Harrison DG, Chilian WM, Marcus ML: Absence of function-
33. Slotnik KL, Teigland JD: Cardiac accidents following vaso-
pressin injection (pitressin). JAMA 1951;146:1126-1129
34. Mills MD, Burchell HB, Parker RL, Kirklin BR: Myocardial infarction and sudden deaths following the administration of pitressin; additional electrocardiographic study of 100 patients given pitressin for cholestrography. Staff Meetings of the Mayo Clinic, Rochester, Minnesota, 1949, pp 254-258

KEY WORDS • collateral vessels • coronary perfusion •
vasopressin
Vasopressin and the mature coronary collateral circulation.
K G Peters, M L Marcus and D G Harrison

_Circulation._ 1989;79:1324-1331
doi: 10.1161/01.CIR.79.6.1324
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 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/79/6/1324

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/