Hemodynamic Effects of Vasodilator Agents in Dogs with Experimental Ventricular Septal Defects

DAVID P. SYNTHORST, M.D., RONALD M. LAUER, M.D., DONALD B. DOTY, M.D., AND MICHAEL J. BRODY, PH.D.

SUMMARY The ratio of pulmonary to systemic vascular resistance (Rp/Rs) largely determines the amount of left-to-right shunting and pulmonary to systemic flow ratio (Qp/Qs) in the presence of a large isolated ventricular septal defect. The possibility that pharmacologic reduction of systemic vascular resistance with α-adrenergic receptor blockade or β-adrenergic receptor stimulation would increase the ratio Rp/Rs, and therefore reduce the ratio Qp/Qs, was studied in dogs in which ventricular septal defects had been surgically created. Administration of phentolamine and phenoxybenzamine caused a 42% reduction in Rs and no reduction in Rp. Qs was unchanged and Qp declined by 24% and the ratio Qp/Qs fell by 32%. Infusion of the β-adrenergic receptor stimulant isoproterenol also reduced Qp/Qs. However, this was accomplished as a result of an increase in Qs and at the expense of an increase in heart rate. As a decline in the ratio Qp/Qs has been shown to be beneficial to patients with large left-to-right shunts, pharmacologic reduction of systemic vascular resistance may prove to be helpful in treating congestive heart failure in those patients with large left-to-right shunts at the ventricular level who are refractory to the usual decongestive measures.

THE AMOUNT OF INTERVENTRICULAR SHUNTING found in patients with ventricular septal defect is largely determined by the ratio of pulmonary to systemic vascular resistance and the size of the interventricular defect. Infants with large ventricular septal defects may develop high volume left-to-right shunts and symptoms of heart failure as their pulmonary vascular resistance falls during the first few weeks of life. If pharmacological treatment can control the heart failure and permit the child to grow normally, the defect may become smaller or spontaneously close or a low risk surgical repair can be done when the child is larger. Current drug therapy includes the use of digitalis to increase contractility of the heart and diuretics to decrease congestion, neither of which would be expected to alter significantly the resistances which determine shunt flow. Pharmacologic agents which can lower the systemic vascular resistance should reduce the amount of left-to-right shunting found in these patients and improve their cardiovascular status. This study was undertaken using an experimental model of ventricular septal defect to determine if a reduction in left-to-right shunting could be effected pharmacologically by vasodilator agents which lower systemic vascular resistance in excess of pulmonary vascular resistance.

Methods

Ventricular septal defects were produced in twenty adult mongrel dogs (11–21 kg) and hemodynamic data were gathered. After anesthesia with 30 mg/kg of intravenous sodium pentobarbital an endotracheal tube was placed and the dogs were ventilated 12 times per minute at 25 ml/kg tidal volume with a positive pressure respirator. Arterial oxygen saturations averaged 92 ± 4 (SD)%; and pH averaged 7.33 ± .09 at these ventilator settings. Aortic and pulmonary artery catheters were placed through the brachial artery and vein and mean pressures were recorded using Statham arterial and venous pressure transducers. A midline sternotomy was done, the pericardial sac opened and the great vessels dissected free. Flow probes of 12 mm diameter were placed around the ascending aorta and main pulmonary artery and flows were recorded using a Carolina Medical Electronics, Inc. electromagnetic flowmeter. The latter portion of diastole was used as zero flow. Probe interaction was not a significant problem and equal mean aortic and pulmonary flows were recorded in each instance prior to creation of the septal defect. Mean left atrial pressure was measured by passing a catheter through the left atrial appendage into the left atrium. All measurements were recorded using a Beckman RM Dynograph Recorder.

Ventricular septal defects were made using the device and technique shown in figure 1. The right atrial appendage was purse-stringed and lidocaine 2 mg/kg intravenously was given to prevent ventricular fibrillation at the time the defect was made. (In preliminary experiments performed without lidocaine ventricular fibrillation occurred frequently.) The right atrial appendage was then amputated and the 6 mm internal diameter prosthesis on the obturator was passed through the right atrium to the apex of the right ventricle. The heart was grasped for stability and the prosthesis was forced through the muscular interventricular septum. With the flange on the prosthesis holding it in place, the obturator was removed and the right atrial purse string tightened. The presence of a left-to-right shunt was confirmed by a palpable thrill over the right ventricle and elevation of the pulmonary artery flow and pressure. Over the next 20 minutes the dogs were given an infusion of blood volume equal to 20% of their estimated total (70 cc/kg body weight) blood volume. This was done to mimic the blood volume increase seen in animals with chronic ventricular septal defects. Following this infusion, any blood which accumulated in the chest cavity was reinforced at a constant rate in an attempt to keep blood volume constant.

The dogs were separated into four groups of five each. Group I animals served as controls and were monitored without pharmacologic intervention for 210 minutes following creation of the defect. In groups II, III and IV, a drug was administered to animals after they had exhibited stable

From the Department of Pediatrics, Division of Pediatric Cardiology, Department of Surgery, Division of Thoracic and Cardiovascular Surgery, and Department of Pharmacology, University of Iowa College of Medicine, Iowa City, Iowa.

Supported in part by USPHS Grants HLP-14388, HL-12964, HL-T01-5577 and HL-07121.

Address for reprints: Ronald M. Lauer, M.D., Department of Pediatrics, University Hospitals, Iowa City, Iowa 52242.

Received December 22, 1975; revision accepted April 30, 1976.

472
hemodynamic measurements for at least 45 minutes after creation of the defect. Dogs in group II were given phentolamine (1 mg/kg) intravenously and those in group III received phenoxybenzamine (1.5 mg/kg) intravenously over a 3 minute period. Dogs in groups II and III were monitored for one hour after drug administration. Each of the five dogs in group IV was given isoproterenol at three different infusion rates: 0.05, 0.125 and 0.25 μg/kg/min. After each infusion was completed, the hemodynamic measurements were allowed to return to preinfusion values before the next administration was begun.

Throughout the experiment, mean pressures in the aorta (Ao), pulmonary artery (PA) and left atrium (LA) were recorded as well as mean flow in the aorta (Qs) and pulmonary artery (Qp). Total systemic vascular resistance (Rs) and pulmonary vascular resistance (Rp) were calculated and the ratios PA/Ao, Qp/Qs and Rp/Rs were determined. Left ventricular external minute work was calculated by multiplying Qp by Ao, as the Qp is equal to the volume which the left ventricle is ejecting per minute (Qs plus the volume per minute of left-to-right shunt).

The hemodynamic stability of the animals in which ventricular septal defects had been created was evaluated by subjecting the above data to a one-way analysis of variance.6 In the control animals this was done on data taken at 15 minute intervals for the 210 minutes of the study period. In the drug treated groups (II, III, IV) the data collected for 45 minutes prior to drug administration were analyzed for variance.

Statistical evaluation of the changes in hemodynamic data following drug administration was done using a paired t-test. Data taken at ten minute intervals after the drug was given were compared to values obtained immediately prior to drug administration. Values of P < 0.05 were considered significant.

Results

Group I

The pressures, flows, resistances and pulmonary artery to aortic flow ratios found in the control animals before and after creation of the defects are shown in figure 2. Analysis of variance in Ao, PA, Qs, Qp, Rs, Rp, PA/Ao, Qp/Qs, Rp/Rs and left to right shunt flow showed no significant variation in any of these parameters during the 210 minutes after the ventricular septal defect was made. All measurements in the drug treated animals (groups II, III, IV) were completed prior to 210 minutes following creation of the septal defect.

Group II

The animals in this group were given the α-adrenergic receptor blocking agent phentolamine (1 mg/kg) when stable for at least 45 minutes after the defect was created.
The fall in total systemic vascular resistance was statistically significant and persisted for 35 minutes. Aortic pressure was also lowered for this time. Pulmonary flow was reduced and aortic flow did not change, resulting in an average fall in Qp/Qs from 2.8 to 1.9 during the period of significantly reduced total systemic vascular resistance. The mean pulmonary artery pressure was reduced throughout the study period.

Group III

Dogs in group III were given 1.5 mg/kg of the long acting α-adrenergic receptor blocker phenoxybenzamine. This second blocking agent was used because its long duration of action might be advantageous if this approach to treatment of left-to-right shunts was used clinically. The results at the time of maximal reduction of the systemic vascular resistance were not different from those seen with phentolamine. The effects persisted throughout the 65 minute study period, whereas the phentolamine effects began to decline after 35 minutes.

The effects of the decrease in total systemic vascular resistance produced by phentolamine and phenoxybenzamine are listed in the combined summary shown in table 1. Values obtained immediately prior to the administration of the drugs are compared with those at the time of maximal effect on the vascular resistance. Data are combined for the two agents because the changes seen with each at the time of maximal effect were not different. There was a 42% reduction in total systemic vascular resistance and no decline in pulmonary vascular resistance. The ratio Rp/Rs increased while pulmonary flow fell and aortic flow did not change significantly. Qp/Qs was reduced and left atrial pressure was unchanged. Pulmonary artery pressure and mean aortic pressure were both reduced. The net volume of blood shunted from left to right through the ventricular septal defect declined from 1.2 to 0.7 L/min.

Group IV

The effects of isoproterenol administration are shown in table 2. Values shown are for the highest of the three infusion rates, at which the effect on Rs was similar to that of the α-adrenergic receptor blockers. The effects of isoproterenol were dose-related but were qualitatively similar at all doses. There was a significant reduction of systemic vascular resistance and pulmonary vascular resistance did not change, resulting in an increase in Rp/Rs. Systemic flow increased dramatically and pulmonary flow did not change significantly, resulting in a decline of Qp/Qs. Aortic mean pressure declined and pulmonary artery and left atrial pressure did not change. The volume of left to right shunting across the ventricular septal defect did not change significantly with the administration of isoproterenol.

Discussion

The degree of left-to-right shunting in patients with ventricular septal defect is determined by the relative ease with which blood is ejected into the aorta or through the septal defect. The total systemic vascular resistance largely determines the ease of aortic escape. The size of the defect and the pulmonary vascular resistance determine resistance to flow through the defect. In patients with small defects little blood is shunted, irrespective of the pulmonary vascular resistance. In those with large defects the pulmonary vascular resistance is more important and, as this progressively declines after birth, more blood is shunted from the left to the right ventricle. In the presence of a defect large enough to permit equalization of systolic pressures in the two circuits, the shunt volume is determined almost entirely by the pulmonary to systemic resistance ratio. The size of the defect orifice in the animals used in this study provides some resistance to flow and prevents equalization of systolic pressures in the pulmonary and systemic circuits. We created a large left-to-right shunt (pulmonary flow 2.5 times

Figure 3. Response of animals with ventricular septal defect to administration of phentolamine (1 mg/kg) intravenously. The drug was given at 0 time and the open circles indicate significant change from pre-drug administration values.
Table 1. Response of Dogs with Ventricular Septal Defect to Phentolamine and Phenoxybenzamine

<table>
<thead>
<tr>
<th>Prior to drug administration</th>
<th>Rs</th>
<th>Rp</th>
<th>Rp/Rs</th>
<th>Ao</th>
<th>FA</th>
<th>FA/Ao</th>
<th>LA</th>
<th>QS</th>
<th>Qp</th>
<th>Qp/Qs</th>
<th>Q shunt</th>
<th>Heart rate</th>
<th>LVEMW</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
<td>6</td>
<td>.07</td>
<td>78</td>
<td>20</td>
<td>.26</td>
<td>8</td>
<td>.9</td>
<td>2.1</td>
<td>2.5</td>
<td>1.2</td>
<td>169</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>At time of maximal reduction of systemic vascular resistance</td>
<td>57</td>
<td>6</td>
<td>.11</td>
<td>52</td>
<td>16</td>
<td>.31</td>
<td>7</td>
<td>1.0</td>
<td>1.6</td>
<td>1.7</td>
<td>0.7</td>
<td>173</td>
<td></td>
</tr>
</tbody>
</table>

Percent change from pre-drug values and statistical significance

* = P < 0.05, ** = P < 0.01, *** = P < 0.001.

Table 2. Response of Dogs with Ventricular Septal Defect to Isoproterenol

<table>
<thead>
<tr>
<th>Prior to drug administration</th>
<th>Rs</th>
<th>Rp</th>
<th>Rp/Rs</th>
<th>Ao</th>
<th>FA</th>
<th>FA/Ao</th>
<th>LA</th>
<th>QS</th>
<th>Qp</th>
<th>Qp/Qs</th>
<th>Q shunt</th>
<th>Heart rate</th>
<th>LVEMW</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>6</td>
<td>.09</td>
<td>94</td>
<td>21</td>
<td>.23</td>
<td>5</td>
<td>1.3</td>
<td>2.6</td>
<td>2.0</td>
<td>1.3</td>
<td>165</td>
<td>244</td>
<td></td>
</tr>
</tbody>
</table>

During infusion of 0.25 μg/kg/min isoproterenol

<table>
<thead>
<tr>
<th>Mean difference and standard error of difference</th>
<th>Rp</th>
<th>Rp/Rs</th>
<th>Ao</th>
<th>FA</th>
<th>FA/Ao</th>
<th>LA</th>
<th>QS</th>
<th>Qp</th>
<th>Qp/Qs</th>
<th>Q shunt</th>
<th>Heart rate</th>
<th>LVEMW</th>
</tr>
</thead>
<tbody>
<tr>
<td>-.37 ± .05</td>
<td>-.37</td>
<td>-1</td>
<td>.05</td>
<td>-16</td>
<td>-1</td>
<td>-.3</td>
<td>.2</td>
<td>-.3</td>
<td>.4</td>
<td>-.4</td>
<td>+3</td>
<td>204</td>
</tr>
</tbody>
</table>

Percent change from preinfusion values and statistical significance

* = P < 0.05.

systemic flow) comparable to a medium-sized defect in children. This indicates the volume of left-to-right shunting in this model is determined by the ratio of pulmonary vascular and defect resistance to the systemic vascular resistance. Administration of vasodilator agents in this study caused no change in the pulmonary vascular resistance and, as the resistance of the defect is fixed, there was no alteration in the resistance to blood flow from the left to the right ventricle. The absence of change in the pulmonary vascular resistance suggests that if the defect were nonrestrictive, the resistance to flow across it would have been unchanged and the resultant alteration in the pulmonary to systemic flow ratio would have been of similar magnitude to what was found.

It should also be noted that mature animals would be expected to have less prominent pulmonary vascular muscle than is found early in life.

Ventricular septal defects have been shown to cause a volume overload to the left ventricle. With runoff through the septal defect into the pulmonary circuit, large volumes of blood return to and must be ejected by the left ventricle to maintain systemic output. The pulmonary to systemic flow ratio (Qp/Qs) describes the relation between the total volume which passes through the left ventricle to that which passes usefully into the systemic circulation. The volume per minute which is ejected during left ventricular systole can be estimated by measuring the pulmonary flow per minute, as pulmonary flow is equal to systemic flow plus the net left-to-right flow across the ventricular septal defect. This somewhat overestimates the volume of blood ejected during left ventricular systole as some left-to-right shunt has been shown to occur during diastole. Calculation of external left ventricular minute work by multiplying pulmonary flow by mean aortic pressure is subject to yet another error. Some blood is shunted from the left ventricle to the right during "isovolumic" contraction, and thus is not ejected when ventricular pressure is equal to aortic pressure. However, these errors in calculating the volume per minute ejected by the left ventricle and external minute work of the left ventricle are similar before and after the administration of drugs to the animals with ventricular septal defects. For this reason we have used these calculations in evaluating the hemodynamic changes effected by drug administration.

Current methods of treatment, short of repair of the defect in infancy, include the use of inotropic agents, diuretics and pulmonary artery banding. Digitalis preparations increase contractility and allow pumping of the same volume at lower filling pressures or of larger volumes at the same filling pressure. The reduction of volume with diuretics should reduce left atrial pressure and symptoms of pulmonary congestion. Neither of these interventions would be expected to alter Qp/Qs significantly. Surgical banding of the pulmonary artery increases resistance to right ventricular outflow and reduces the gradient across the ventricular septal defect. This lowers the Qp/Qs and diminishes the volume of blood the left ventricle must eject to maintain systemic flow. This reduction in Qp/Qs has been demonstrated to be beneficial to patients with large ventricular septal defects. Pulmonary artery banding has also proved useful in palliating the heart failure seen with other congenital heart defects in which left-to-right shunting is present. However, banding of the pulmonary artery is associated with significant mortality.

The use of the α-adrenergic receptor blockers phen-
tolamine and phenoxybenzamine could be expected to alter the hemodynamics of ventricular septal defect in two major ways. The reduction of peripheral vascular resistance lowers impedance to the ejection of blood into the aorta. This results in a decrease of the pulmonary to systemic flow ratio (Qp/Qs), and a decrease in left ventricular volume overload.

This effect was seen in the experimental animals in groups II and III. The resistance to systemic flow was reduced while the resistance of the defect remained fixed and the pulmonary resistance did not change. This resulted in a reduction of Qp/Qs by 32% and a decrease in the blood shunted from left to right by 42%. The systemic output was unchanged and the total volume ejected by the left ventricle per minute was reduced by 24%.

The second expected change in hemodynamics seen with administration of α-receptor blockers is also due to the reduction of systemic vascular resistance. Mean aortic pressure is a measure of afterload on the left ventricle and if this pressure is reduced, the ventricle can eject a larger volume of blood at the same filling pressure. Such increases in stroke volume have been demonstrated in newborn lambs in which the aortic pressure was reduced and filling pressure was maintained at a constant level. The fact that systemic flow did not increase in the presence of a significant decrease in aortic pressure (afterload) could be due to a significant decrease in preload (decreased filling volume), or depression in ventricular contractility.

Thus, both the volume of blood which the left ventricle must eject per minute to maintain systemic flow and the pressure against which it is ejected are reduced with the administration of α-adrenergic receptor blockers. Both these factors are considered in comparing the external work per minute of the left ventricle before and after the α-blocking agents were given. The work was reduced by 48% during the time of maximal α-adrenergic receptor blockade and systemic flow at this time was unchanged.

The effects of isoproterenol are those of β-adrenergic stimulation, which increases contractility of the heart and, through systemic vasodilation, lowers peripheral vascular resistance. It has been used as an emergency measure to increase contractility in infants with ventricular septal defect and severe heart failure. The reduction in systemic vascular resistance would be expected to reduce Qp/Qs, as with the α-adrenergic receptor blockers, and increase systemic flow with respect to the total volume pumped by the left ventricle. The reduction in systemic resistance and resultant alteration in Qp/Qs were seen in this study. The pulmonary flow did not change significantly but the systemic flow rose by as much as 77%, indicating that approximately the same volume per minute was ejected by the left ventricle but a larger percentage went into the systemic circulation. Interestingly, the calculated external minute work of the left ventricle did not change during the isoproterenol infusions, as the small increase in Qp was accompanied by a fall in mean aortic pressure. Catecholamines are known to increase myocardial oxygen consumption and thus the calculated external work may not reflect the increased demands imposed on the left ventricle by isoproterenol. The increase in heart rate produced by isoproterenol in these animals suggests that oxygen consumption was increased.

In this experimental preparation, phen tolamine, phenox ybenzamine and isoproterenol all altered the Qp/Qs favorably. The α-blockers achieved this by lowering Qp while maintaining Qs whereas isoproterenol did so by increasing Qs without significantly altering Qp. Calculated left ventricular work was markedly reduced with the α-blockers and was unchanged with isoproterenol.

The use of isoproterenol to increase contractility in critically ill infants with ventricular septal defect would appear to have the additional advantage of altering the Qp/Qs favorably. Use of sympathomimetics with prominent α-adrenergic stimulating effects would not be expected to have this advantage and might actually increase Qp/Qs by raising total peripheral vascular resistance.

Drugs which lower the systemic vascular resistance are being studied extensively in the treatment of heart failure following myocardial infarction or associated with mitral regurgitation or myocardial infarction. Findings of clinical improvement and increased urine flow in these patients suggest that the regional distribution of systemic blood flow is not unfavorably altered. Information concerning the regional distribution of systemic blood flow in patients with congenital heart disease treated with vasodilators is not available, and thus caution should be taken in the use of these agents.

The data presented in this study suggest that interventricular septal defects with large left-to-right shunts and resulting heart failure may benefit from pharmacologic reduction of systemic vascular resistance. Such vasodilator therapy has also been suggested for use in children who have low systemic output and high peripheral resistance following cardiac surgery. Lesions which cause low aortic diastolic pressures due to runoff from the aorta, such as patent ductus arteriosus, may not benefit from this form of therapy, as coronary artery flow may be compromised by further reduction of diastolic blood pressure.

References

13. Goldblatt A, Bernhard WF, Nadas AS, Gross RE: Pulmonary artery...
Impaired Forearm Oxygen Consumption during Static Exercise in Patients with Congestive Heart Failure

JOHN LONGHURST, M.D., PH.D., WILLIAM GIFFORD, M.D.,
AND ROBERT ZELIS, M.D.

SUMMARY In this study, the effects of forearm static exercise were determined on local blood flow and oxygen consumption in 15 normal individuals (NL) and their responses were compared with ten patients in congestive heart failure (CHF). Forearm blood flow was determined by a plethysmographic technique before and during 15% of maximum voluntary contraction of the forearm. Regional arterial and venous oxygen contents were sampled and forearm oxygen consumption calculated by the Fick principle. At rest, forearm blood flow was less in patients with heart failure than in normal individuals; however, this was compensated for by an increased oxygen extraction, thus maintaining forearm oxygen consumption at a normal level.

IT HAS RECENTLY BEEN DEMONSTRATED that during forearm dynamic exercise of graded intensity patients with congestive heart failure fail to increase their forearm blood flow to the same level as normal individuals.1 Despite an increased oxygen extraction, these patients failed to achieve the same level of forearm oxygen consumption as normal volunteers exercising at a comparable level. Two problems are encountered in the interpretation of this study. First, the level of exercise was not standardized for the patients’ capacities to perform work. Thus, patients with congestive heart failure, though exercising at an absolute level of severity comparable to that of normal individuals, may have been exercising at a greater percent of maximal exertion than their normal counterparts. Second, during dynamic exercise, forearm blood flow can only be approximated because of the marked fluctuations in blood flow noted during intermittent grip exercise.2 During muscular contraction, forearm blood flow falls and during the post-contraction relaxation phase, a hyperemia is seen. Although it has been determined that the plethysmographic blood flow measured during the postcontraction relaxation phase closely correlates with that measured by brachial artery electromagnetic flowmeter, flows obtained plethysmographically are still an estimate of true flow. Therefore, the calculations of forearm oxygen consumption derived from these flows were also an estimate.3

In contrast, during static exercise, forearm blood flow failed to rise normally with heart failure (NL 9.31; CHF 4.35 ml/min • 100 ml, P < 0.001) and the increased oxygen extraction was not sufficient to maintain a normal forearm oxygen consumption (NL .82; CHF .44 ml/min • 100 ml, P < 0.01). Therefore, patients with congestive heart failure demonstrate regional circulatory and metabolic abnormalities during static exercise that are comparable to those present during dynamic exercise. Because of a limited ability of their skeletal muscle resistance vessels to respond to dilator stimuli, they have an attenuation of their exercise hyperemia which leads to an earlier shift to anaerobic metabolism.

From the Laboratory of Clinical Physiology, University of California, Davis, School of Medicine, Davis, California and the Division of Cardiology, Pennsylvania State University College of Medicine and Hershey Medical Center, Hershey, Pennsylvania.

Supported in part by American Heart Association grant 71-888 and USPHS Grant HL-17853. Dr. Longhurst was supported by a Bank of America-Giannini Fellowship.

Dr. Longhurst’s present address is Cardiology Division, University of Texas Southwest School of Medicine, Dallas, Texas.

Address for reprints: Robert Zelis, M.D., Chief, Division of Cardiology, Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033.

Received March 8, 1976; revision accepted May 3, 1976.
Hemodynamic effects of vasodilator agents in dogs with experimental ventricular septal defects.
D P Synhorst, R M Lauer, D B Doty and M J Brody

Circulation. 1976;54:472-477
doi: 10.1161/01.CIR.54.3.472

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 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/54/3/472

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/