Left Ventricular Pressure-Volume Characteristics in Congenital Heart Disease

By M. M. Jarmakani, M.D., Sam B. Edwards, B.S., Madison S. Spach, M.D., Ramon V. Canent, Jr., M.D., M. Paul Capp, M.D., Mary J. Hagan, B.S., Roger C. Barr, B.S., and Vishnu Jain, M.D.

SUMMARY
The continuous pressure-volume relationships throughout the cardiac cycle were evaluated in children with tetralogy of Fallot, isolated ventricular septal defect, and patent ductus arteriosus. Biplane cineangiocardiology and simultaneous left ventricular pressures were utilized for data acquisition. Normal pressure-volume loops demonstrated only small changes in left ventricular volume during the isovolumic periods. In tetralogy of Fallot, there was a decrease in left ventricular volume during the interval of the "isovolumic" contraction with 12 to 43% of the total stroke volume being ejected during this phase. A decrease in left ventricular volume during this time was also found in large ventricular septal defects; however, volume changes during this interval were minimal in those patients judged to have small defects.

With large left-to-right shunts of comparable magnitude, the relative area of the pressure-volume loop was greater in patent ductus arteriosus as compared with ventricular defects. Both conditions demonstrated marked increase in stroke volume, with peak systolic pressures rising higher in those patients with patent ductus arteriosus as compared to those with ventricular septal defect.

Additional Indexing Words:
Tetralogy of Fallot
Patent ductus arteriosus
Biplane cineangiocardiology

The need for quantitative description of the functional status of the left ventricle in a variety of congenital cardiac defects is well appreciated by cardiologists. The ability to determine the changing volume characteristics of the left ventricle by means of biplane cineangiocardiology while measuring the ventricular pressure provides a method for detailed study of changing events throughout the cardiac cycle. Additionally, the use of digital computers to perform complex and time-consuming calculations has become an important adjunct in humans for the detailed study of ventricular muscle mechanics, which previously could be evaluated only in laboratory animals.

The left ventricular pressure-volume relationships should vary throughout the cardiac cycle in a variety of congenital cardiac anomalies, depending upon the integrity of the ventricular septum and the competence of the mitral and aortic valves. Because of the marked variation in left ventricular dynamics produced by different congenital cardiac defects, a logical initial step in the study of quantitative left ventricular function in cardiac anomalies would be the general characterization of the left ventricular pressure-volume relationship throughout the cardiac cycle. This report describes the characteristic patterns
Data acquisition and processing methods. All patients were studied in the supine position with biplane cineangiocardiography after injection of contrast medium into the pulmonary artery while simultaneously monitoring left ventricular pressure. Special photocell devices in the x-ray beams of the AP and lateral tubes were used to record the timing of individual cine frames (A, B). All data were tape recorded for later playback at rapid paper speeds. The individual cine frames were projected with a calibrated optical system for drawing the LV chamber silhouette (C). The longest length of the LV cavity in each projection was divided into ten equal parts where perpendicular lines were constructed to the border of the silhouette. The values of the length and width dimensions were transcribed to punch cards (D). All data were analyzed by a digital computer (E), which calculated the instantaneous volumes by the longest length-area method. The instantaneous volumes, first time derivative of volume (net flow), mid (hoop) circumference and its velocity of change, and pressure values were outputted in numerical form (F). Additionally, automated time plots of selected variables were displayed in graphic form with a Calcomp plotter (G).

found in three types of commonly encountered cardiac anomalies: tetralogy of Fallot, isolated ventricular septal defect, and patent ductus with and without mitral insufficiency.

Methods

Patient Population

A total of 52 patients were studied during cardiac catheterization. The number of patients in each diagnostic category is indicated in table 1. All patients were studied under light nitrous oxide anesthesia in the supine position. Systemic and pulmonary shunts were calculated from blood-oxygen saturation data (Fick method). Simultaneous left ventricular pressure and biplane cineangiocardiograms were recorded 50 to 90 minutes after the onset of anesthesia. During
the filming sequence, heart rates varied from 90 to 120 beats per minute.

**Data Acquisition Methods**

The over-all procedure of data acquisition is illustrated in figure 1, A and B. Biplane cineangiograms were filmed at a sampling rate of 60 frames per second in the anteroposterior (AP) and lateral views after injection of 75% Hypaque (1 cc/kg of body weight) into the pulmonary artery. During the filming sequence of the levogram, left ventricular pressure was monitored via a retrograde arterial catheter. During the initial portion of the study, left ventricular pressures were monitored with either a no. 6 or 7 catheter and a Statham P23Gb pressure transducer. Calibration of this system showed that the impulse transmission time varied from 8 to 15 msec; the response of the system was found to be over-damped and flat to 9 cps.1 During the latter portion of the study, 21 patients had left ventricular pressures recorded with a transducer-tip catheter.*

Special photocell devices3 were placed in the AP and lateral x-ray beams to record the individual x-ray pulses. The outputs of the photocells were recorded on magnetic tape simultaneously with the electrocardiogram and left ventricular pressure. Playback of the tape-recorded data at rapid paper speeds allowed identification of the individual x-ray pulses corresponding to their respective cine frames; these in turn could be related to the corresponding instantaneous left ventricular (LV) pressure (fig. 1 B). A careful review was made of the electrocardiogram, left ventricular pressure tracing, and levogram phase of the bpline cine to ensure that only those patients who have technically good data were utilized for detailed analysis. Any filming sequence that involved movement of the patient, coughing, or premature ventricular beats was excluded from analysis.

The bpline cineangiographic unit consisted of 9-inch image intensifiers with 16-mm film recording at 60 frames per second. The bpline housing was mechanically linked so that the lateral focal spot, object, and film distance remained constant while the geometry for the AP system could be varied over a distance of 3 cm. The measurement of these distances was utilized in correcting for nonparallel x-ray magnification by the method of Dodge and associates.4This magnification was checked in each patient at the conclusion of the study by filming a 3- by 1-inch metallic cylinder. The degree of distortion produced in the peripheral regions of the image amplifier tube was checked with a series of coins placed throughout the image field. The area distortion remained less than 5% in the inner two-thirds area of the field; in the outer one-third area, distortion produced 7 to 14% overestimation of area. In most of the children studied, the left ventricular silhouette occupied the inner 70% of the total area of the field. No adjustment was made for this inherent image tube distortion. A comparison of calculated and measured volumes was made from contrast media-filled balloons. The results of 15 experiments of 7 to 100 cc balloons showed the calculated values to underestimate the measured volume by 2 to 7%.

**Data Processing and Display Methods**

The individual AP and lateral cine frames were analyzed to determine the dimensions of the left ventricle on the levogram for 2 to 5 consecutive beats. The individual frames were aligned to their corresponding pressure. Pressures recorded with fluid-filled catheters were shifted 16.6 msec to their corresponding cine frame to correct for the pressure transmission delay. No time shift was introduced for pressures recorded with the transducer-tipped catheter. Each frame was numbered for identification and projected at fixed distances. The outline of the left ventricle for each projection was traced by hand. The longest length was drawn for each projection, and the image was divided into 10 equal parts with perpendicular lines to the longest length. These length and width dimensions were used to calculate the area for each projection by a

---

**Table 1**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. &quot;Normal&quot; left ventricle</td>
<td></td>
</tr>
<tr>
<td>(Vascular ring, mild valvular</td>
<td></td>
</tr>
<tr>
<td>pulmonic stenosis, peripheral pulmonary</td>
<td></td>
</tr>
<tr>
<td>artery stenosis)</td>
<td></td>
</tr>
<tr>
<td>B. Tetralogy of Fallot</td>
<td></td>
</tr>
<tr>
<td>(R-L shunt: 20-43% of systemic flow)</td>
<td>9</td>
</tr>
<tr>
<td>C. Isolated VSD</td>
<td></td>
</tr>
<tr>
<td>Low to moderate elevation of RV</td>
<td>12</td>
</tr>
<tr>
<td>systolic pressure (12)</td>
<td></td>
</tr>
<tr>
<td>RV = LV systolic pressure (10)</td>
<td></td>
</tr>
<tr>
<td>D. Patent ductus arteriosus</td>
<td></td>
</tr>
<tr>
<td>Without mitral regurgitation (9)</td>
<td></td>
</tr>
<tr>
<td>With associated mitral regurgitation (3)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
</tr>
</tbody>
</table>

---

*Statham Laboratories, Inc., Hato Rey, Puerto Rico.
Sequential pressure-volume loops. The loops shown above represent the automatic Calcomp plots of pressure-volume loops for three sequential beats obtained during the levogram in two children with "normal" left ventricles (vascular ring and peripheral stenosis of the pulmonary artery). Note the very slight beat-to-beat variation and the stable volume during the intervals of isovolumic contraction and relaxation.

The final values were displayed in numerical form for each 16.6-msec interval (fig. 1 F). Additionally, the pressure-volume loops and the time graphs of the various parameters were plotted automatically by a Calcomp plotter (fig. 1 G). The automatically plotted pressure-volume loops of two "normal" patients are shown in figure 2. Note that these loops show only slight beat-to-beat variations in both end-systolic and end-diastolic volumes as well as the LV pressure throughout each cardiac cycle during filming of the levogram.

**Results**

**Normal Left Ventricle**

The normal pressure-volume loops (32 beats) were characterized by their relatively stable volume during the periods of isovolumic contraction and relaxation* (figs. 2 and 3). Many of these loops showed a very slight decrease in the calculated volume (0.2 to 0.8 ml) during isovolumic contraction. During the isovolumic relaxation phase this tendency was not found.

**Tetralogy of Fallot**

All these patients demonstrated clinical cyanosis, and the right-to-left shunts comprised 20 to 43% of systemic blood flow. The major abnormality was the consistent finding of a decreasing left ventricular volume during the "isovolumic" contraction phase (fig. 3). By estimating the time of the beginning of ejection into the aorta from the relationship of the left ventricular and aortic root pressures, the left ventricular volume had decreased 12 to 43% of the total stroke volume prior to opening of the aortic valve. The period of isovolumic relaxation demonstrated variable results. Of the 30 beats analyzed,

\[
\frac{\Delta \text{Vol}}{\Delta T} = \frac{\text{Vol}_2 \text{ (volume 16.6 msec after)}}{T_2 \text{ (16.6 msec after)}} - \frac{\text{Vol}_1 \text{ (volume 16.6 msec before)}}{T_1 \text{ (16.6 msec before)}}
\]

*The period of isovolumic contraction was approximated and identified as that interval between the onset of LV pressure rise to the time LV pressure exceeded aortic root pressure (measured prior to and after angiocardiology). The interval of isovolumic relaxation was identified as the time during the rapid fall of LV pressure beginning at the pressure level of aortic incisura to the time LV pressure fell to a level of 10 to 15 mm Hg.

_Circulation, Volume XXXVII, June 1968_
Comparison of normal and tetralogy left ventricular pressure-volume loops. Note the minimal change in volume during the interval of pressure rise (isovolumic contraction) for the normal. All patients with tetralogy (below) demonstrated a decrease in volume during this interval as shown for two sequential beats in a tetralogy patient whose right-to-left shunt comprised 28% of systemic blood flow.

one half showed slight increases (0.5 to 3.0 ml) in the calculated LV volume during this interval. The changing LV volume during the “isovolumic” periods could be correlated with the timing of intracardiac shunting across the ventricular defect. The nine patients with tetralogy in this study demonstrated similar intracardiac pressure-flow patterns as pre-
Figure 4

Pattern of intracardiac shunting in tetralogy of Fallot. The changes in left ventricular volume could be correlated with the timing of intracardiac shunting across the ventricular defect. The timing and direction of flow across the defect are shown in relationship to the simultaneously recorded right and left ventricular pressures (above). Below is shown the continuous pressure difference across the defect. The pattern indicated for the tetralogy patients in this study was also consistently found in similar patients whose right-to-left shunt comprised 20 to 40% of systemic blood flow as previously reported. At the end of diastole (A) minimal left-to-right pressure gradients and flow are present. During isovolumic contraction (B) the development of a left-to-right pressure gradient is associated with flow from the left ventricle across the defect into the right ventricle and into the pulmonary artery. Both ventricles eject blood into the aorta during the systemic ejection phase (C). During isovolumic relaxation (D), a significant right-to-left gradient develops with an earlier fall in the LV pressures as compared with that of the right ventricle. During this interval LV volume changes in the pressure-volume loop indicated no change or a slight increase in LV volume. These findings suggest that right-to-left flow across the defect during isovolumic relaxation is small in magnitude or occurs late, during early filling of the left ventricle while the RV pressure is still elevated.

Previously reported for such patients who comprise a moderately severe hemodynamic group (R-L shunt 20 to 40% of systemic flow). At this point it is pertinent to review the pattern of intraventricular shunting (fig. 4) as related to the LV pressure-volume changes in this homogeneous group of patients.

During late diastole the ventricular pressures are nearly equal, with slight predominance of the left ventricle (fig. 4 A). During isovolumic contraction the left ventricular pressure rise precedes that of the right and is associated with flow across the defect from the left ventricle into the body of the right ventricle, with some of this shunted blood being ejected into the pulmonary artery prior to aortic valve opening (fig. 4 B). As noted above, an estimated 12 to 43% of the total LV stroke volume occurred during this interval. During systemic ventricular ejection both chambers ejected blood into the aorta, without interventricular flow being demonstrable across the defect (fig. 4 C). The period of "isovolumic" relaxation in this hemodynamic group of tetralogy patients was characterized by the left ventricular pressure falling earlier than that of the right, with the development of a prominent right-to-left pressure gradient (fig. 4 D). Since the continuous volume curves indicated either no or slight increase in left ventricular volume during this interval, the right-to-left shunting that can be seen during this interval on cine-angiograms may occur at a time when the LV pressure has fallen to low values, allowing opening of the mitral valve with development of a brief interval during early LV diastole when right ventricular pressure remains elevated (25 to 35 mm Hg) and is accompanied by right-to-left shunting. Thus, in this group, mitral valve opening should occur before that of the tricuspid, this interval being characterized by the left ventricle receiving a slight amount of blood from the right ventricle in addition to the left atrial contribution.

The effect of the intracardiac left-to-right shunt during "isovolumic" contraction was especially apparent when LV "net flow"-pressure curves were compared with normal ones. Figure 5 A illustrates that in the normal left ventricle, the onset and peak rate of flow occur at high pressures. However, in tetralogy of Fallot there is a rapid increase in flow.
Normal and tetralogy left ventricular net flow-pressure curves during systole. The rate of change of volume (net flow) as plotted against LV pressure is shown during systole for a single beat in each patient. Note that in the normal left ventricle (A) with the onset of contraction the pressure becomes elevated to systemic levels, and following this, decrease in volume occurs with peak rate of flow occurring at high pressure. In the tetralogy patient with a 28% right-to-left shunt (B) note that there is commencement of flow during the early portion of the pressure rise and maximal rate of flow developed at low LV pressures prior to the opening of the aortic valve. The curve shown for tetralogy is illustrative of those plotted for the remaining patients in this group and showed a characteristic change from normal with two accentuated flow intervals during systole (isovolumic contraction and mid-systole).

during early “isovolumic” contraction. In some patients the peak rate of LV flow occurred at pressures below 45 mm Hg, and many beats demonstrated a tendency to have two intervals of accentuated flow; that is, during early isovolumic contraction and during mid-systole, as shown in figure 5 B. In “normal” and tetralogy patients, the graphs demonstrating the rate of change of the mid-circumference of the left ventricle plotted against left ventricular pressure yielded curves quite similar to those in figure 5.

Ventricular Septal Defect

Of the 22 patients in this group, 12 had normal to mildly elevated right ventricular systolic pressures, with small left-to-right shunts (less than 35% of pulmonary blood flow). The left-to-right shunt was visualized as commencing across the defect at the same time flow began in the aorta; these patients demonstrated a stable LV volume during isovolumic contraction. However, in those patients with low right ventricular pressure, whose shunts were greater than 35%, there was consistently left-to-right flow across the defect prior to the onset of flow into the aorta; this was associated with a decrease in LV volume during the isovolumic contraction interval. The comparison of the pressure-volume loops in a patient before and after closure of the ventricular septal defect is shown in figure 6 A. Note the postoperative marked drop in stroke volume and the absence of volume changes during the isovolumic periods.

Of the 10 patients with systemic right ventricular pressures in the presence of a ventricular defect (fig. 6 B), four had pulmonary-to-systemic vascular resistance ratios
Figure 6
Left ventricular pressure-volume loops in patients with varying hemodynamic states with isolated ventricular septal defects. Patients with normal right ventricular pressure and large left-to-right shunts demonstrated a broad loop with large end-diastolic volumes and large stroke volumes. In those patients with left-to-right shunts comprising greater than 35% of pulmonary blood flow, there was a perceptible decrease in LV volume during the isovolumic contraction period. The tracings shown in A were obtained in a patient with a ventricular septal defect whose left-to-right shunt was 68% of pulmonary blood flow preoperatively. His postoperative pressure-volume loop, which was obtained 2 years after surgery, appeared normal as shown above. In patients with systemic right ventricular pressures, there was consistently a decrease in volume during the isovolumic contraction interval (B). The area of the loop was large in those patients with high flow and normal in those patients with predominantly right-to-left or equal bidirectional shunting.

greater than 0.6. The remainder of the group were patients with moderate to large left-to-right shunts. All 10 of these patients demonstrated a decreasing left ventricular volume during the isovolumic contraction period. This decrease in volume could be related to left-to-right flow across the defect prior to the opening of the aortic valve. Those patients with high pulmonary resistance and predominant right-to-left shunting demonstrated narrow loops, which consistently revealed a decreasing LV volume during isovolumic contraction, and an increasing LV volume during the period of isovolumic relaxation (fig. 6 B).

Patent Ductus Arteriosus
Five of the 12 patients in this group had left-to-right shunts comprising more than 60% of pulmonary blood flow (ages 2½ to 7 years). The shape of the pressure-volume loop indicated a stable ventricular volume during the periods of isovolumic contraction and relaxation. The loops appeared normal in three patients with small left-to-right shunts; however, in the group with large left-to-right shunts, the area of the pressure-volume loop (stroke work) was much larger than normal. This increase in area could be attributed both to the abnormally large stroke volume and to the higher than normal systolic pressures developed in those patients with large shunts (fig. 7 A). In 3 patients with associated mitral insufficiency, a decreasing LV volume was found during the interval of isovolumic contraction (fig. 7 B).

Discussion
The design of the present study was limited
Left ventricular pressure-volume relationships in patient ductus arteriosus. These patients demonstrated minimal LV volume changes during the isovolumic contraction and relaxation periods (A). Those patients with shunts less than 30% of pulmonary flow demonstrated normal-appearing pressure-volume loops. However, in the presence of large left-to-right shunts the loops were broadened due to the increased stroke volume, and taller than normal due to elevated systolic pressure with large shunts (A). All patients with patent ductus arteriosus underwent direct left ventricular angiocardiography. Associated mitral regurgitation was found in three, and their LV pressure-volume loops showed a decrease in volume during the isovolumic contraction phase as illustrated in B.

Primarily to delineation of data that could be obtained directly from the pressure-volume relationships in several congenital cardiac defects. This approach was utilized first to clarify the changes in these variables during contraction and relaxation since the derivation of other variables (for example, tension and rate of fiber shortening) are dependent upon the accuracy of continuous pressure-volume measurements. Although this approach offers a method for detailed analysis of left ventricular geometry and function in the intact human, several problems should be noted. A major unresolved problem at present with this approach is the extent to which injection of contrast media may alter the naturally occurring phenomena. However, the "continuous" pressure-volume loops constructed by the methods of this study demonstrated only slight beat-to-beat variations over 2 to 5 consecutive beats (fig. 2).

The technique used in the early part of this study was to perform left ventricular pressure measurements followed by direct LV injection of contrast media; then, after each cine frame was analyzed, the volumes were aligned with the previously recorded pressures when the rate remained constant (minimal R-R interval change). The results of this analysis in "normals" demonstrated considerable variation with increasing or decreasing volume during both isovolumic contraction and relaxation phases. This inconsistency seemed to be due to improper instantaneous pressure-volume

Circulation, Volume XXXVII, June 1968
alignment. Therefore, the method was altered to monitor simultaneously left ventricular pressure after injection of contrast media into the pulmonary artery. The results of time alignment of the instantaneous volume and pressure measurements with this approach demonstrated stable LV volumes during the isovolumic periods in normal subjects.

Pressure gradient and cine studies have shown left-to-right flow across the ventricular defect in patients with moderately severe tetralogy of Fallot during the isovolumic contraction phase. The results of this investigation indicated a significant decrease in LV volume during this interval. All of these patients had associated direct left ventricular injections, which demonstrated the absence of mitral regurgitation; thus this decrease in volume was related to left-to-right shunting across the defect. These data therefore suggest that the time course of fiber shortening, as related to the development of tension, is considerably altered from normal in tetralogy patients because of volume changes during "isovolumic" contraction.

Patients with isolated ventricular septal defects which can be categorized as large in size (that is, left-to-right shunts greater than 50% of total pulmonary blood flow or with pulmonary-to-systemic resistance ratios greater than 0.6) all showed a detectable decrease in the LV volume during the isovolumic contraction phase. Such changes were absent or equivocal in those patients who were considered to have relatively small defects (normal pulmonary resistance with left-to-right shunts comprising less than 35% of total pulmonary blood flow). This suggests that the size of the defect, in addition to the left-to-right pressure gradient generated in the isovolumic phase, influences left ventricular volume changes (flow across the defect) during this interval.

In patients with patent ductus arteriosus the pressure-volume loops showed minimal volume changes during the isovolumic periods. The configuration of the pressure-volume loop was progressively taller and broader in those patients with increasing degrees of left-to-right shunting (fig. 7 A). The increased area of this pressure-volume loop was contributed to both by an increase in stroke volume and an elevated systolic pressure. This contrasts with the changes noted for the ventricular septal defect group with large left-to-right shunts where the increased area of the pressure-volume loop was due to the increase in stroke volume alone, without systolic pressure elevation. The results suggest that in patients with large left-to-right shunts of comparable degree, more work is required of the left ventricle in patent ductus arteriosus as compared to isolated ventricular defect. The presence of the ventricular defect was associated with (1) intracardiac flow and decreasing LV volume during the isovolumic contraction period at less than systemic pressures, and (2) ejection of a large quantity of blood at normal systemic pressure levels. In the patent ductus group with large left-to-right shunts, flow from the LV did not commence until systemic pressure (tension) was achieved and the large stroke volume was ejected at higher pressure levels than those encountered in the ventricular defect group. That there is a greater work load placed on the left ventricle in patent ductus arteriosus as compared to VSD with comparable left-to-right shunts is further indicated by recent studies of Mason (personal communication). He created ventricular defects and aortico-pulmonary connections in dogs and showed that with equally large left-to-right shunting, there was marked elevation of left ventricular end-diastolic pressure with aortico-pulmonary shunting, whereas this pressure remained near normal with ventricular defect shunting.

References


4. Dodge, H. T., Sandler, H., Ballew, D. W.,


50 Years Ago
Publication of Starling’s Linacre Lecture
The Law of the Heart

Within physiological limits the larger the volume of the heart, the greater the energy of its contraction and the amount of chemical change at each contraction.

An Epitomist’s Appraisal:
The objections that have developed to Starling’s views on intrinsic cardiac control stem largely from the Linacre Lecture. It was pointed out that with the onset of exercise, end-diastolic volume declines instead of increasing, and that there is poor correlation between venous pressure and ventricular performance in the intact human being. The great tendency has been to take Starling at his word in the Linacre Lecture and not to read the other relevant papers. But be this as it may, the Linacre Lecture on the Law of the Heart must be counted one of the most influential biomedical presentations in the twentieth century to date.—Starling on the Heart, edited by Carleton B. Chapman and Jere H. Mitchell. London, Dawsons of Pall Mall, 1965, p. 120.
Left Ventricular Pressure-Volume Characteristics in Congenital Heart Disease
M. M. JARMAKANI, SAM B. EDWARDS, MADISON S. SPACH, RAMON V. CANENT, JR., M. PAUL CAPP, MARY J. HAGAN, ROGER C. BARR and VISHNU JAIN

Circulation. 1968;37:879-889
doi: 10.1161/01.CIR.37.6.879

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 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/37/6/879

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/