Determination of Fraction of Left Ventricular Volume Ejected per Beat and of Ventricular End-Diastolic and Residual Volumes

Experimental and Clinical Observations with a Precordial Dilution Technic

By Roland Folse, M.D., and Eugene Braunwald, M.D.

The determination of the fraction of left ventricular end-diastolic volume ejected per beat and of the ventricle's end-diastolic and residual systolic volumes has been of interest to investigators for many years. Despite the continued efforts that have been directed toward the development of techniques suitable for such determinations, these methods have not been entirely acceptable theoretically and, at the same time, easily applicable to intact human subjects. The purpose of this report is to describe a method utilizing a radioisotope indicator-dilution technique with precordial detection that permits estimation of the fraction of the left ventricular end-diastolic volume ejected per beat. The theoretical basis of the method, its validation in a circulatory model and in open-chest dogs, as well as its clinical applications, are presented.

If an indicator is rapidly injected into a ventricular cavity and is completely mixed therein, the relative decline of the concentration of indicator in the ventricle or in the artery immediately beyond it during each cardiac cycle represents the fraction of blood in the ventricular cavity at the end of diastole that is ejected per beat. If the ventricular stroke volume is known, and the fraction of the end-diastolic volume constituted by the stroke volume has been determined, the ventricular end-diastolic volume can be calculated. The residual volume represents the difference between end-diastolic volume. Thus:

\[ \frac{F.S.V.}{E.D.V.} = \frac{C_n - C_{n+1}}{C_n} \]

\[ E.D.V. = F.S.V. = F.S.V. \left[ \frac{C_n - C_{n+1}}{C_n} \right] F.S.V./E.D.V. \]

\[ R.V. = E.D.V. - S.V. \]

where F.S.V. = effective forward stroke volume.

E.D.V. = ventricular end-diastolic volume.

R.V. = ventricular end-systolic (residual) volume.

C_n = concentration of indicator at onset of a cardiac cycle.

C_{n+1} = concentration of indicator at onset of the subsequent cycle.

Methods

Detection and Recording Technic

The radiation detector employed was a 3 inch diameter activated thallium-sodium iodide crystal.* This was surrounded by a collar of lead, 1 inch in thickness; collimation was provided by a tapered lead shield extending 5 inches beyond the surface of the crystal with an aperture having a diameter of 1.5 inches. The efficiency characteristics of the collimator are illustrated in figure 1, in which the detector field lines represent the percentage of radioactivity detected as a point source was moved away from the aperture. Utilization of the large crystal resulted in a high sensitivity of the detector, and the shielding and collimation largely eliminated the radioactivity emanating from anatomic areas not directly in the axis of the crystal and collimator. The detector and lead shielding weighed 120 lbs. and they were mounted on a por-

_________

*From the Clinic of Surgery and the Cardiology Branch, National Heart Institute, Bethesda, Maryland.

*Model DSSR-1, Nuclear Chicago Corporation.
table stand which permitted a wide range of motion. The photomultiplier of the scintillation detector was led into a count rate meter* which was modified to permit a response time of 0.05 second, with a full-scale deflection of 100,000 counts per minute; in the observations described below a response time of 0.05 or 0.20 second was employed. The output of the rate meter was directly proportional to the radioactivity detected and was led to the D.C. preamplifier of a multichannel oscillographic photographic recorder (fig. 2).

Circulatory Model

The theoretical validity of the technic employed was examined in a simple model, consisting of a cylinder and piston with inflow and outflow valves, to represent the left ventricle. A glass chamber proximal to the inflow valve simulated the left atrium, and “mitral” regurgitant volume and end-diastolic volume could be controlled and measured. The indicator, I131-labeled Diodrast, was injected into the center of the cylinder, and the detector was placed immediately above and scanned the entire cylinder.

Dog Experiments

These were undertaken to determine whether the isotope-dilution technic would correctly indicate directional changes in the E.D.V. when the latter was varied. A recording rotameter3 was inserted into the aorta of five open-chest dogs, weighing 16 to 25 Kg., in the manner described by Sarnoff and Berglund4 so that it metered total systemic blood flow, i.e., left ventricular output minus coronary blood flow. The latter was assumed, on the basis of the experiments of Eckenhoff et al. to equal 5 per cent of the systemic flow,5 and thus forward stroke volume (F.S.V.) could be calculated. Catheters were placed into the left atrium and central aorta for measurement of pressure; a multiholed catheter was inserted into the left ventricle via the left atrium for injection of the isotope. A Whitney mercury-in-rubber gage6 was sewn to the surface of the left ventricle between its base and apex, thus measuring the longitudinal dimension of the left ventricle. The characteristics of this instrument have been described in detail by Lawton and Collins7 and it has been utilized extensively to provide measurements of changes in the end-diastolic dimensions of the ventricle.8 9 The detector was placed directly over the exposed left ventricle and changes in the left ventricular end-diastolic volume were induced by means of transfusion and hemorrhage. Mitral regurgitation was produced toward the end of each experiment by sectioning several chordae tendineae.

*Model 1620B, Nuclear Chicago Corporation.

Clinical Observations

Isotope dilution curves were recorded at the time of transseptal left heart catheterization in
47 patients.10 The catheter, which was employed for the measurement of left ventricular pressure and for the injection of the indoxyline dye and the 131I Diodrast was a large, multitholed radiopaque polyethylene catheter. The radiation detector was positioned so that the aperture was at the apex of the left ventricle; its direction was in the axis of the left ventricular cavity, estimated fluoroscopically (fig. 2). Following placement of the detector the cardiac output was determined by the indicator-dilution technic, with the use of indoxyline dye and a cuvette densitometer, as described in detail elsewhere.11 Immediately thereafter, 25 to 50 μc of 131I labeled Diodrast in a volume of 1 to 2 ml were injected into the left ventricle in less than 1 second and the precordial dilution curve was recorded. In most of the patients these curves were obtained in duplicate, the catheter having been moved within the left ventricular cavity between injections.

Seven of the patients studied were not considered to have any abnormalities involving the left ventricle. These included three patients without detectable cardiovascular disease, two patients with congenital isolated pulmonic stenosis, one patient with atrial septal defect, and one patient with a right atrial myxoma. Fourteen patients with pure mitral stenosis were studied; this diagnosis was confirmed subsequently at operation in six patients; five patients were studied following mitral valvulotomy. There were five patients with pure aortic stenosis (two congenital and three acquired), in whom this diagnosis was established by hemodynamic and clinical study. These patients had not experienced congestive heart failure and only one had roentgenographic evidence of cardiac enlargement. The diagnosis was confirmed at operation in three of these patients. There were eight patients with predominant aortic regurgitation, and in six of them the clinical and hemodynamic findings of this lesion were confirmed at open operation. Of the 12 patients with the clinical and hemodynamic features of predominant mitral regurgitation, this diagnosis was confirmed at operation in six, at postmortem examination in one, and by means of left ventricular angiocardiography in another. One patient was considered to have left ventricular failure secondary to arteriosclerotic heart disease.

When the radioactivity occurring at the end of each successive diastole was plotted on semilogarithmic paper, there was little or no deviation from a straight line for 4 or 5 cardiac cycles. All calculations were made on these beats, prior to the interruption of the descending limb.

Results

Circulatory Model

A total of 13 determinations of F.S.V./E.D.V. and of E.D.V. were carried out. The "mitral" valve in the circulatory model was regurgitant in five of these trials. In these experiments the F.S.V. and the "mitral" regurgitant volume were varied over a wide range. The mean difference between the calculated and the actual F.S.V./E.D.V. and between the calculated and actual E.D.V. was 3.6 per cent of the actual values; one
standard deviation of the difference between the calculated and the actual F.S.V./E.D.V. was 3.1 per cent of the actual values. A representative dilution curve obtained from the circulatory model is reproduced in figure 3.

**Dog Experiments**

A total of 45 separate determinations of E.D.V. were carried out in five dogs. The results were similar in all dogs studied and a representative experiment is plotted in figure 4. It was observed that with serial blood transfusions both the left atrial pressure and the left ventricular end-diastolic segment length (E.D.S.L.) increased (fig. 4A). As the total blood volume was augmented and the left atrial pressure and the E.D.S.L. increased step-wise, the forward stroke volume also increased progressively (figs. 4B and 4C). It was observed that the fraction of E.D.V. ejected per beat, i.e., the F.S.V./E.D.V., was relatively low both when the dog was hypovolemic, i.e., when the left atrial pressure and stroke volume were depressed, as well as when the dog was grossly hypervolemic, as reflected in an abnormally elevated mean left atrial pressure (fig. 4D). E.D.V. was calculated from the isotope dilution curve and from the S.V. which had been determined by the flowmeter. It was observed that E.D.V. varied in the same direction as did the E.D.S.L. (fig. 4E) and the mean left atrial pressure (fig. 4F). The relatively low values of F.S.V./E.D.V. observed are believed to be related to the tachycardia (rate 162-178 per minute) which was present.

In all five experiments, when the animal was transfused and the mean left atrial pressure, the E.D.S.L. and F.S.V. increased, the E.D.V. also rose, i.e., under conditions in which an increase in the actual E.D.V. would be anticipated, the calculated E.D.V. also increased (fig. 5). The acute production of mitral regurgitation consistently decreased F.S.V./E.D.V. and increased E.D.V.
Clinical Observations

Duplicate isotope dilution curves were obtained in rapid succession in 25 patients; the catheter was moved within the left ventricular cavity between injections. In any given patient the curves were quite similar and one standard deviation of the differences between the F.S.V./E.D.V. calculated from the paired curves and expressed as a percentage was 1.3 per cent (fig. 6). The curves obtained from patients without hemodynamic abnormalities involving the left ventricle exhibited a rapid ascending limb and a relatively less rapid descending limb (fig. 7). In the patients with aortic or mitral regurgitation the ascending limb was rapid, but the descending limb was prolonged. Individual cardiac cycles could be distinguished more easily in patients with regurgitation than in those without. During ventricular systole, as the isotope was ejected from the left ventricle, the curve fell abruptly; during diastole, as isotope returned to the left ventricle the curve rose (fig. 8).

The F.S.D./E.D.V. ratio, expressed as a percentage, ranged from 25 per cent to 50 per cent and averaged 37±8 per cent, in the patients without a hemodynamic abnormality involving the left ventricle, including the patients with mitral stenosis (fig. 9).

In contrast, the patients with mitral regurgitation, aortic regurgitation, and left ventricular failure exhibited lower values for F.S.V./E.D.V. In this group of patients the values ranged from 6 per cent to 23 per cent, with a mean value of 16±5 per cent. The five patients with aortic stenosis who were studied did not have elevation of left ventricular end-diastolic pressure, cardiac enlargement, or a history of left ventricular failure. In these patients the F.S.V./E.D.V. was in the same range as that observed in patients without left ventricular disease and averaged 36 per cent (fig. 9).

Calculation of the E.D.V. per M.²B.S.A. in the patients without a hemodynamic abnormality involving the left ventricle ranged from 43 ml. to 145 ml./M.²B.S.A. and the mean value was 89±26 ml./M.²B.S.A. In the patients with valvular regurgitation and left ventricular failure the E.D.V./M.²B.S.A. was generally much higher and ranged from 116 ml. to 368 ml./M.²B.S.A. and averaged 209±75 ml./M.²B.S.A. In the patients with aortic stenosis the values for E.D.V./M.²B.S.A were in the range of the higher values observed in patients without a hemodynamic abnormality involving the left ven-
LEFT VENTRICULAR STROKE VOLUME

In general, F.S.V./E.D.V. was found to be inversely related to E.D.V. (fig. 10). When the left ventricular end-diastolic pressure was related to the E.D.V., it was observed that the E.D.V. exceeded 150 ml./M.²B.S.A. (the highest value observed in patients without left ventricular abnormalities) in all but one patient in whom the end-diastolic pressure was above the upper limits of normal (12 mm. Hg). However, the converse was not always the case; several patients whose E.D.V. exceeded the highest value observed in patients without left ventricular disease (150 ml./M.²B.S.A.) did not exhibit abnormal elevations of left ventricular end-diastolic pressure (fig. 11).

Discussion

The principle of the indicator-dilution technic employed in the present investiga-
tion was first utilized by Bing and collaborators¹ for the estimation of the residual volume of the right ventricle. These investigators, and more recently Freis et al.¹³ injected an indicator dye into the right ventricle and recorded dilution curves after sampling through a cardiac catheter, the tip of which was positioned in the pulmonary artery. Holt applied and extended this approach by studying the volumes of each ventricle individually, during a variety of experimental situations.¹⁴, ¹⁵ Both dye-dilution and electrical conductivity technics were employed in these studies, and the indicators were injected into the ventricle and their concentration was determined either in the pulmonary artery or aorta. Rapaport and associates¹⁶ have employed a thermal indicator-dilution technic for the estimation of the left ventricular volume of the dog by the same basic principle.

Two major difficulties appear to limit the potential applicability of these technics to the study of left ventricular end-diastolic volume in intact human subjects. First of all there is now abundant evidence that an indicator injected into a ventricle is not completely mixed therein,¹⁷-¹⁹ and that different concentrations of indicator can be

---

Figure 7

Precordial isotope dilution curve obtained from a patient who was studied 6 months after mitral commissurotomy, who had no aortic valve disease or mitral regurgitation.

Figure 8

Isotope dilution curve in a patient with aortic regurgitation; the presence of this lesion was subsequently confirmed at open operation.
recorded simultaneously from several sampling sites in the ventricle or the ascending aorta. In the present study, a radioactive isotope served as the indicator. Instead of determining the concentration of indicator at a single, perhaps nonrepresentative, sampling point in the left ventricle or aorta, the total quantity of isotope in the left ventricular cavity was estimated by means of a scintillation detector placed on the precordial area. This made it possible to determine the rate of washout of all of the indicator particles that had been injected into the left ventricle, regardless of how well these particles had been mixed within that chamber.

Angiocardiographic studies in the dog have indicated that blood which enters the left ventricle from the left atrium may not mix completely in the ventricular cavity prior to its ejection into the aorta. The extent to which this also occurs in human subjects would influence the F.S.V./E.D.V. and the E.D.V. calculated by the method described herein. This technic employed for the estimation of E.D.V. is therefore considered to provide a measurement of the volume of that portion of the left ventricular cavity into which the indicator had penetrated. Similarly, the F.S.V./E.D.V. represents the rate of washout of indicator from the volume under consideration.

The heart rate which is slower in human subjects than in dogs provides a significantly longer diastolic period for blood to pass from the left atrium into the ventricle and to become widely distributed in that chamber. Support for the view that the indicator was in fact distributed within the entire left ventricular cavity is provided by the reproducibility of the technic (fig. 6). Since the catheter was passed into the ventricle by the transeptal route, it was always possible to position its tip near the apex, and the multiple openings near the tip facilitated dispersion of the injected isotope. The position of the catheter within the ventricle was moved between these "paired" determinations. Under these circumstances it would seem improbable that the rate of wash-
Graph depicting the relationship between the E.D.V., corrected for body surface area, and the F.S.V./E.D.V.

A second limitation of the nonisotopic dilution technics is that they require the introduction of two catheters into the left heart or aorta. One catheter is necessary for the injection of the indicator and the second is required for sampling blood or detecting the indicator in the blood directly. While the introduction of one catheter into the left ventricle is relatively simple, the use of two catheters is technically more complex.

A number of workers have utilized radioactive isotopes for the determination of left ventricular volumes. In all these previous studies the indicator was not injected into the left ventricle itself, but rather at a point proximal in the circulation. When the isotope is inhaled and is thus introduced by way of the pulmonary capillary bed or when it is injected into the pulmonary artery it does not reach the left ventricle as a single bolus, but rather over a variable period of several seconds. Under these circumstances some of the indicator particles leave the ventricle simultaneously with the arrival of others. The resultant precordial dilution curve, therefore, represents not a simple washout of isotope from the ventricle, but rather indicates the differences between the rate of entry into the rate of exit of the isotope out of this chamber.

One of the difficulties encountered in the evaluation of any indirect technic for the measurement of ventricular volumes is that no absolute or standard method is available to serve as a basis for comparison with the technic under investigation. However, the validity of the technic described in this report could be assessed indirectly by two approaches. The demonstration that the F.S.V./E.D.V. and E.D.V. could be measured...
accurately in the circulatory model provided assurance of the theoretical validity of the approach that was employed. The experiments on the open-chest dogs showed that a sudden transfusion augmented the mean left atrial pressure, the left ventricular end-diastolic segment length, and the stroke volume, all measured by independent methods. Under these circumstances, a concomitant increase in E.D.V. is certainly to be expected, and it was again reassuring that the E.D.V. determined by the radioisotope dilution technic increased pari passu with the atrial pressure, the end-diastolic segment length and the stroke volume. Furthermore, it was shown that bleeding had the opposite effect. When mitral valvular regurgitation was suddenly induced and atrial pressure and the ventricular end-diastolic segment length rose, the F.S.V./E.D.V. decreased and the E.D.V. rose, again as expected.

It is evident that the precordial dilution technic introduced a number of errors resulting from the detection of radioactive emanations from areas other than the left ventricle. An attempt was made to minimize the contributions of radioactivity from the aorta and from the left atrium by aligning the detector with the axis of the left ventricle. Similarly, by analyzing only the first portion of each dilution curve, i.e., the segment resulting from the first four or five cycles following injection, the contribution of isotope particles in the blood perfusing the chest wall and the coronary vascular bed was kept at a minimum. Furthermore, the effects of motion of the ventricle on the resultant curves must also be considered. Only the radioactivity recorded at the end of diastole was employed in this analysis. It would seem reasonable that at the end of each diastole the heart would return to the same position within the thorax and that it would therefore assume the same relationship to the external detector which it held during the previous end-diastole. The effects of cardiac movement during the respiratory cycle could be obviated by asking the patient

**Figure 11**

Graph depicting the relationship between left ventricular end-diastolic pressure and E.D.V. corrected for body surface area.
to suspend respiration in the end-expiratory position for the five cardiac cycles following injection of the isotope.

In the present study, a relatively large variation of the calculated F.S.V./E.D.V. as well as of the E.D.V. was observed among the patients without any abnormality of left ventricular function. It must be emphasized that these patients formed a diverse group. There were wide variations in age, physical condition, and exercise tolerance. Although left ventricular function was considered to have been normal in all of these patients, organic heart disease was present in the majority and several of the patients with mitral stenosis, in particular, suffered considerable cardiac disability. It would appear likely that in ambulatory subjects without any cardiovascular disease, the F.S.V./E.D.V. would fall in the upper range of the values observed in our patients without apparent abnormalities of left ventricular function.

The values for F.S.V./E.D.V. in these patients (37±8 per cent) are greater than those observed by Thode et al.,21 who introduced the indicator into the circulation by inhalation and found average values of 17.5 per cent and 20.5 per cent in normal males and females respectively. This discrepancy is perhaps not surprising, since the site and method of introduction of the indicator would tend to slow the rate at which the isotope disappeared from the left ventricle. Our values are not too dissimilar from those reported by Courand and associates22 for trained subjects at rest (F.S.V./E.D.V. = 45 per cent average). Angiocardiographic estimations of F.S.V./E.D.V. have, in general, yielded higher values than those reported herein; Bruce and Chapman23 noted values of 76.5 per cent in normal males studied in the sitting position, while Bunnell et al.24 reported an average of 71 per cent in a group of children with coarctation of the aorta. It is probable that these wide discrepancies are related not only to differences in the technics employed but also to the wide variations in the age and condition of the patients who were studied.

The radioisotope method described in the present report would seem to offer a number of distinct advantages over other methods utilized for the estimation of left ventricular volumes. The procedure is technically quite simple to perform in the course of left ventricular catheterization. It requires little time and no additional risk to the patient beyond that of transseptal left heart catheterization. The total amount of radioactivity injected is minimal. The procedure can conveniently be added to the left heart catheterization and the additional information may be of clinical as well as of physiologic importance. In patients with either mitral or aortic valve regurgitation a significant portion of the blood ejected during systole returns to the left ventricle during diastole. It would be anticipated that in such patients the F.S.V./E.D.V. would be reduced and the E.D.V. elevated. In actual practice this indeed was the case (fig. 9). In several of the patients with mitral regurgitation in whom the F.S.V./E.D.V. was distinctly lower than that observed in any of the patients without evidence of left ventricular disease, the presence of valvular regurgitation could not be detected by the analysis of left atrial pressure pulse, but was subsequently confirmed at operation.

Determination of the F.S.V./E.D.V. may be particularly helpful in the preoperative study of patients with mitral or aortic stenosis. The finding of a value for F.S.V./E.D.V. which is lower than that usually observed would suggest the presence of associated valvular regurgitation or left ventricular failure or both. As might be anticipated from theoretical considerations,25 the descending limb of the isotope dilution curve in the patients with mitral regurgitation sometimes deviated slightly from a straight line on a semilogarithmic plot. The beat-to-beat variations in F.S.V./E.D.V., however, were small and the average values for four beats were recorded in the present study.

From a theoretical as well as from a simple empiric point of view, determination of the F.S.V./E.D.V. appears to be helpful in
the recognition of valvular regurgitation. It must, however, be recognized that reduction of F.S.V./E.D.V. occurs not only in patients with valvular regurgitation, but also in patients with left ventricular failure unassociated with valvular disease; in such patients the F.S.V. is often reduced and the E.D.V. elevated, resulting in an abnormally low ratio.

It was of interest that in contrast to the patients with valvular regurgitation, the patients with aortic stenosis had values of F.S.V./E.D.V. and of E.D.V. which were in the range observed in the patients without left ventricular abnormalities. It should be noted that although these patients with aortic stenosis had large pressure gradients across their aortic valves, there was little evidence of left ventricular enlargement on roentgenographic examination and no elevation of their ventricular end-diastolic pressures. It is well recognized that in such patients there may be little, if any, enlargement of the left ventricular cavity.

The estimations of the fraction of the left ventricular end-diastolic volume that is ejected into the aorta during each cardiac cycle, as well as of the ventricular end-diastolic and residual volumes, provide information that is fundamental to a hemodynamic analysis of left ventricular function. These studies are not difficult to carry out and when combined with measurements of ventricular systolic and diastolic pressures and of stroke volume, they should permit a more complete understanding of the activity of the left ventricle in normal subjects and in patients with a variety of cardiovascular abnormalities.

Summary

A technic has been developed for determining the fraction of left ventricular end-diastolic volume that is ejected during each cardiac cycle. Radioiodinated Diodrast was rapidly injected into the left ventricle at the time of transseptal left heart catheterization and the fraction of isotope discharged from this chamber per beat was determined with a well-shielded scintillation probe placed on the chest wall over the left ventricle. Left ventricular end-diastolic volume was estimated from the stroke volume, determined by the dye-dilution method, and the fraction of isotope discharged per beat. Difficulties resulting from inadequate mixing of isotope in the left ventricle were minimized by this technic, since the probe detected indicator in the entire left ventricular cavity. The accuracy of this technic was first demonstrated in a circulatory model and then in open-chest dogs in which ventricular dimensions were continuously monitored by means of mercury-in-rubber gages. In 21 patients without detectable abnormalities of left ventricular function the fraction of left ventricular volume discharged averaged 37±8 per cent per beat and the end-diastolic volumes averaged 89±26 ml./M.²B.S.A. In 21 patients with heart failure or valvular regurgitation, or both, in whom left ventricular function was compromised, the fraction of left ventricular volume discharged into the aorta averaged 16±5 per cent per beat and the end-diastolic volumes averaged 209±75 ml./M.²B.S.A. This technic has been found to be sensitive to changes in left ventricular function and practical to apply routinely in the course of left heart catheterization.

References

2. HOLT, J. P.: Estimation of left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) in the dog. Am. J. Physiol. 179: 645, 1954.

Circulation, Volume XXV, April 1962
LEFT VENTRICULAR STROKE VOLUME


Common-sense nerve fibers are seldom medullated before forty—they are never seen even with a microscope before twenty.—Sir William Osler. Aphorisms From His bedside Teachings and Writings. Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 130.
Determination of Fraction of Left Ventricular Volume Ejected per Beat and of Ventricular End-Diastolic and Residual Volumes: Experimental and Clinical Observations with a Precordial Dilution Technic
ROLAND FOLSE and EUGENE BRAUNWALD

_Circulation_. 1962;25:674-685
doi: 10.1161/01.CIR.25.4.674

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 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/25/4/674

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/