Measurement of Heart Chamber Volumes by Analysis of Dilution Curves Simultaneously Recorded by Scintillation Camera

By Yasushi Ishii, M.D., and William J. MacIntyre, Ph.D.

SUMMARY

After a peripheral injection of Technetium-99m, an Anger scintillation camera placed over the precordium of nine patients without and three patients with hemodynamic abnormalities was used to record in rapid sequence the flow of the injected material through the central circulatory system. After the data were processed as sequential frames of digitized spatial matrices, the position of various chambers or compartments was identified and dilution curves from six sites were obtained, providing a series of input-output relations through the central circulatory system, i.e., superior vena cava, right atrium, right ventricle, lung, left atrium, and left ventricle. These relations were assumed to be cascaded as a series of first order lag systems, with or without time delay, on an analog computer, which allowed estimation of the time constant of the transfer function of each chamber or compartment (volume/flow) by reducing the problem to a consecutive, one-parametric manipulation. Measurement of the flow rate through the series (cardiac output) permitted the volume of each chamber to be estimated. Results correlated well with mean values established by other methods.

Additional Indexing Words:
Analog computer    Cardiac output    Pulmonary blood volume    Radiocardiogram
Data processing    Transfer function

The recent development of methods using scintillation cameras capable of recording sequential radioisotope images from the precordium has provided a means of visualization of both the anatomic and functional features of the heart and great vessels without the hazards of cardiac catheterization or rapid administration of a large volume of radiopaque dye into the circulation under high pressure, as necessitated by other methods. By use of this technic, scintiphotographic images produced by gamma-emitting radioisotopes can be recorded in rapid sequence as the isotope flows through the circulatory system. However, most applications of the camera to dynamic studies of the heart have been concerned only with the visual observation of the flow pattern of the isotope tracer or with the estimation of directly measured parameters, such as transit times.

What has been generally neglected is the ability of the scintillation camera to record simultaneously a series of input-output dilution processes representing the passage of the tracer through various segments of the central circulatory system. By means of an appropriate storage and playback system, distinct
indicator-dilution curves of these dilution processes have been recorded from the vascular compartment of the superior vena cava, right atrium, right ventricle, lung field, left atrium, and left ventricle. These dilution curves can then be operated upon by consecutive parametric manipulation of an analog computer\(^6,7\) by which means those parameters related to volume and flow values of each vascular compartment are determined.

**Methods**

A Nuclear Chicago Pho-Gamma II scintillation camera was used for these measurements. The field of view of the scintillation camera is large enough to encompass the heart and the major portion of both lung fields. The patient was placed in the sitting position. The collimator of the camera faced at a left anterior oblique view, approximating the plane of the interventricular septum, and hopefully separating the right side of the heart chamber from the left and the left atrium from the descending aorta.

Technetium-99m, as sodium pertechnetate, was used throughout this investigation. Approximately 5 mCi of \(^{99m}\text{Tc}\)-pertechnetate in about 3 cc was injected into a right antecubital vein, followed by 10 cc of saline flush solution. Gamma rays from the injected isotope strike the crystal, are converted to electronic signals, and are accumulated by an RIDL 1600 channel analyzer as a digitized 40 by 40 matrix in a pattern corresponding to the isotope location within the body. The diameter of the collimator is 10.5 inches, so that each element of the 40 by 40 matrix can be represented spatially as a square with sides approximately one-quarter inch in length.

As the isotope bolus flowed through the heart and great vessels, the rapidly changing sequence of images was recorded at 0.60-sec intervals, and was transferred to an Ampex TM-7291 digital tape recorder for processing by an IBM 360/40 digital computer. With respect to the 0.60-sec interval, the numerical data were collected during the first 0.36 sec, and the subsequent 0.24 sec was required for transfer of the data from the 1600 channel analyzer to the magnetic tape. Data were then printed out for digital computer processing in the form of 40 by 40 elements for each frame sequentially. Regions of interest were identified on these printouts by spatial and temporal analysis. The essential elements of the data retrieval system described are shown diagrammatically in figure 1.

In order that dilution curves that are derived from one chamber alone and, thus, represent a single concentration curve may be obtained from the sequential printouts, it is desirable to select the region of interest from that part of the compartment that does not superimpose on any other chamber. If this is not possible, it is desirable then to select a region where the

![Figure 1](image-url)

*Figure 1*

Schema for recording time sequential distribution of change in radioactivity through the central circulatory system for derivation of a series of dilution curves following an injection of \(^{99m}\text{Tc}\) to a patient. The passage is monitored by a rate meter (lower left curve), and each square on the upper curve represents a matrix collected and transferred. Lower right curves show the dilution curve readout for the histograms after sites are selected.
Figure 2
Computer printout with contour lines showing areas of increased counting rate and shaded areas representing the regions of maximum counting rate which are flagged for derivation of dilution curves from specific compartments. When regions superimpose, as with the right atrium (RA) and right ventricle (RV) in this example, it is desirable to select areas most widely separated in space and time. In this case, selection was made of the region of outflow of the right ventricle to the pulmonary artery for best separation of RV from RA.

superposition of counting rate is most widely separated in time so that contamination from each compartment can be more easily identified and separated. For utilization of the camera for a dynamic process, both spatial and temporal superposition must be considered, and identification of specific compartments must be attempted by obtaining optimal resolution in both domains. An example of the selection of regions of interest from the matrix printouts is shown in figure 2.

After the identification of the best resolved region of interest, time-activity curves from the sequential matrices are read out from areas representing the superior vena cava, right atrium, right ventricle, lung field, left atrium, and left ventricle. These curves are read out in the form of an incremental histogram, as illustrated in figure 1. These dilution curves represent the raw data that are to be analyzed by the analog computer fitting analysis, as shown in figure 3. Each compartmental unit may be represented as an input-output relationship, and may thus be used to construct an analog computer model, expressed simply in terms of the Laplace transform and transfer function. By searching iteratively for the optimal parameters, \( T_1 \) or \( \tau_0 \), for the closest fit of the model curve to the data curve, the property of each compartment can be determined in terms of flow/volume (\( T_1 \)) or transport delay (\( \tau_0 \)) on the computer controls. This fitting procedure is performed step by step in the order of the course of the tracer by cascading the determined output onto the next compartment as an input.

When adjusted for best fit, the computer parameters yield the time constants, \( T_{ERV} \) for
ANALOG FITTING ANALYSIS

ANALOG COMPUTER MODEL

\[ x_{i-1} \xrightarrow{1 - \tau_i \cdot s} \frac{1}{T_i \cdot s + 1} \xrightarrow{\alpha_i} x_i \]

INPUT DATA

RIGHT VENTRICLE

GEOMETRIC FACTOR

PARAMETER ESTIMATION

RIGHT VENTRICLE

CURVE FITTING

\( (T_i, \tau_i) \)

Figure 3

Block diagram representing one compartmental unit that reconstructs a simulated dilution curve of the compartment. By fitting the simulation curve on the right to the input data on the left, we can estimate the parameters of the compartment. The block consists of a first order delay system and a simple time delay.

superior vena cava, \( T_{RA} \) for right atrium, \( T_{RV} \) for right ventricle, \( T_L \) for the mixing part of lung, \( T_{LA} \) for left atrium, and \( T_{LV} \) for left ventricle, and \( \tau_p \) for the time delay part of the lung. If the cardiac output or flow rate, \( F \), is determined, the distribution volume, \( V_i \), defined for each mixing chamber can be expressed as:

\[ V_i = T_i \times F \quad (1) \]

Since the lung has a delay component, \( \tau_p \), the pulmonary blood volume, \( PBV \), can be expressed as:

\[ PBV = V_p + F \times \tau_p \quad (2) \]

If a dilution curve is contaminated by a dilution curve from another compartment (as is usually the case for the curve for the left atrium, which is frequently obscured by activity from the outflow tract of the right ventricle), the analog fitting analysis requires that a single compartment curve be derived by subtraction of the undesired component from the composite curve. The theoretical foundation of the above analysis is discussed in the Appendix.

The analog computer used is the EAI-TR 20, with an x-y recorder; a square wave pulse generator is used to simulate the injection input. For calculation of the volume of a compartment from the time constant value, \( F/V \), read from the computer settings, and the cardiac output, \( F \), should be known. In these measurements, the determination of cardiac output was obtained by a standard method using RISA-131 by external single probe monitoring immediately preceding the injection of Technetium-99m.

An illustrated example of curves derived from the regions of interest selected from the sequential printout of each frame is shown in figure 4. The simulated curve is the dotted line superimposed over the recorded histogram. As a first step, the exponentially extrapolated area under each dilution curve was measured by a planimeter. This area ratio was set on the computer control as

\[ \text{Circulation, Volume XLIV, July 1971} \]
the geometric factor, α_, before the fitting procedure was started. The output from the computer for each dilution process was fit to the recorded dilution curve by iterative adjustment of the T_ values on the computer control in the order of the course by tracer bolus through the circulatory system. In the illustrated example, the injection input was approximated by a rectangular wave input with a time duration of 0.7 sec. Following this input, the time constant of each chamber was selected sequentially in this order. There is a time delay between right ventricle and lung, and lung and left atrium, which in this example amounts to 4.0 sec. For each fitting step for selection of T_ values, two or more iterations were required. On the average, all of these procedures required about 15 min for completion.

The first nine patients were randomly selected from a group with no evidence of hemodynamic abnormalities by clinical examination. The subsequent three patients have hemodynamic abnormalities, two with mitral regurgitation and one with congestive heart failure due to ischemic heart disease with ventricular aneurysm, as determined by clinical examination.

**Results**

The volume of each heart chamber of a series of vascular segments in the central circulatory system was calculated according to equation 1, and pulmonary blood volume was calculated according to equation 2, after determination of the chamber parameter by analog computer fitting analysis. Table 1 shows the values for the volumes of each compartment for the nine patients without and the three patients with hemodynamic abnormalities. In two cases of mitral regurgi-

---

**Figure 4**

Results of analog simulation of curves derived from regions designated in Figure 2. Dashed lines represent the simulated analog curves. Sequential procedure of fitting yields potentiometer reading from the computer as 1/T and α values.
Table 1
Heart Chamber Volumes of Patients With and Without Hemodynamic Abnormalities

<table>
<thead>
<tr>
<th>Patients</th>
<th>Diagnosis</th>
<th>CI (liters/min/m²)</th>
<th>SVC (ml/m²)</th>
<th>RA (ml/m²)</th>
<th>RV (ml/m²)</th>
<th>PBV (ml/m²)</th>
<th>LA (ml/m²)</th>
<th>LV (ml/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Hemodynamic Abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Dermatitis</td>
<td>4.13</td>
<td>—</td>
<td>139</td>
<td>135</td>
<td>270</td>
<td>112</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>Dermatitis</td>
<td>5.55</td>
<td>38</td>
<td>83</td>
<td>75</td>
<td>383</td>
<td>68</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>Hypertension</td>
<td>3.90</td>
<td>18</td>
<td>78</td>
<td>59</td>
<td>345</td>
<td>96</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>Hypertension</td>
<td>6.00</td>
<td>13</td>
<td>71</td>
<td>108</td>
<td>425</td>
<td>99</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>IHD</td>
<td>2.58</td>
<td>17</td>
<td>72</td>
<td>103</td>
<td>265</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>Pyelitis</td>
<td>3.80</td>
<td>18</td>
<td>85</td>
<td>59</td>
<td>290</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Pulmonary fibrosis</td>
<td>3.18</td>
<td>21</td>
<td>101</td>
<td>77</td>
<td>285</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>Pulmonary embolism</td>
<td>2.76</td>
<td>42</td>
<td>94</td>
<td>98</td>
<td>230</td>
<td>64</td>
<td>105</td>
</tr>
<tr>
<td>9</td>
<td>Hypertension</td>
<td>3.94</td>
<td>62</td>
<td>130</td>
<td>81</td>
<td>243</td>
<td>112</td>
<td>78</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>28.6</td>
<td>94.8</td>
<td>88.3</td>
<td>304.0</td>
<td>88.0</td>
<td>81.1</td>
<td></td>
</tr>
<tr>
<td>With Hemodynamic Abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>IHD; CHF</td>
<td>1.40</td>
<td>65</td>
<td>110</td>
<td>90</td>
<td>316</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>MI</td>
<td>1.38</td>
<td>6</td>
<td>41</td>
<td>79</td>
<td>185</td>
<td>263</td>
<td>56</td>
</tr>
<tr>
<td>12</td>
<td>MI; MS</td>
<td>2.41</td>
<td>—</td>
<td>55</td>
<td>70</td>
<td>220</td>
<td>200</td>
<td>57</td>
</tr>
</tbody>
</table>

Abbreviations: CI = cardiac index; SVC = superior vena cava; RA = right atrium; RV = right ventricle; PBV = pulmonary blood volume; LA = left atrium; LV = left ventricle; IHD = ischemic heart disease; CHF = congestive heart failure; MI = mitral insufficiency; MS = mitral stenosis.

Discussion
In general, the calculated volumes reported here revealed reasonable volume size as compared to anatomical volumes derived from previous determinations by other methods.

Reliable pulmonary blood volumes (PBV) have been reported by sampling of a single dilution curve from the left atrium after injection of dye indicator into the pulmonary artery. Using this method, Levinson et al. obtained a value of 311 ml/m² for normal average PBV. This compares well with the value of 304 ml/m² of the present study.

According to the thermodilution method, Rapaport et al. reported an average normal ventricular end-diastolic volume (EDV) of the RV of 103 ml/m², while the average we found was 88 ml/m². A normal left EDV by the same method was found to be 99 ml/m² by Bristow et al. and 96 ml/m² by Gorlin et al., while ours was 81 ml/m².

There is some criticism of the thermodilution data by Kennedy et al. They state that uneven mixing of indicators injected into the ventricle results in falsely high values for the calculated EDV in comparison with their results by quantitative angiocardiography. We believe we have avoided such an uneven
mixing due to direct indicator introduction, and, therefore, our data correlate well with their mean left EDV value of 70 ml/m².

Although there are few reliable data concerning the atrial volume, the mean LA value by the same angiocardiographic estimation was found to be 63 ml/m² by Murray et al.⁴ and 35 ml/m² by Sauter et al.,¹⁵ while ours was 88 ml/m². The plausible reason for this somewhat greater difference is that our atrial volume in terms of mixing volume probably includes the volume of the inflowing great vessels of the pulmonary veins. However, since there are no definite anatomical boundaries between the atrium and the pulmonary veins, it might be impossible to define the functional boundary separately. Although there are no comparable data by other methods, the same point can be made concerning the RA volume.

It must be kept in mind, however, that with the method used at present for determination of the dilution curves, our ventricular data calculations approximate the EDV, but are not really identical to it. If the dilution curves were measured by sampling data synchronized with heart pumping action the correlation would be expected to be closer. In addition, cardiac output was determined separately for these measurements. The use of albumin tagged with Technetium-99⁷ would eliminate the necessity for a separate determination and would also extend the present method to volume measurements under conditions of shunt flow, wherein the flow through the entire system is not necessarily a constant and the quantitative rate of shunt flow or regurgitant flow could also be determined at the same time. This procedure would have been desirable for patients 11 and 12 if this material had been available. The present analysis assumes that a perfusing flow through the entire system is common, whereby volume, V, of each compartment can be derived from the time constant value, T = V/F, by multiplication by the common flow rate, F. The availability of the tagged albumin tracer would enable us to estimate the flow rate, F, independently for each compartment, where-

by the value for the volume of each compartment can pertinently be calculated from its own flow rate whenever the flow rate is different from compartment to compartment (such as with shunt flow or regurgitant flow).

Since the isotope dilution data of the present method are necessarily liable to be contaminated by dilution data of other regions because of the limitation of the resolution ability, extensive analysis in terms of sophisticated mathematics does not seem to be justified. Our approach to the analysis is concerned primarily with finding a practical interpretation for clinical studies and not with the simulation refinement needed for a model of the circulatory system. Our model for the central circulatory system is considered to be a series of first order lag approximations with a time delay part through the lung, and this approximation allows cascading of elements of the analog computer as a successive one-parametric selection process. This simplification of the manipulation turns out to be, indeed, a practical convenience, especially in making the iterative fitting by visual observation for data for contaminated dilution. According to our model experiment,⁷ the values obtained by such a series of fitting procedures fall predominantly within a ±10% agreement.

The primary contribution of the present study is the demonstration that the scintillation camera can provide data for a complete functional description of the central circulatory system so that input-output relations can be established for each compartment. We realized that at this point the work must be considered preliminary. Further investigations should include a comparison of this method with other technics of chamber volume measurement as well as extension of the analog model to more complex configurations involving shunt flow.

Refinement of the present approach should lead, undoubtedly, to the most comprehensive innocuous tool for clinical evaluation of circulatory function, since this method has the potentiality to provide a complete description
of flow as well as volume simultaneously for any desired compartment of the circulatory system. So far this analysis has been applied only to the heart. It is expected that a similar approach will be made to other organs, such as kidney and brain.

Acknowledgments

We would like to thank Doctors Walter H. Pritchard, Robert E. Botti, Bruce Miller, and Scott R. Inkley for their assistance in patient determinations. The efforts of Miss Elaine Roth and Mr. George A. Dines, in the analog computer model design, and of Miss Roth, Mr. William P. Drescher, and Mr. S. Tucker Taft, in the digital data acquisition and processing, have been invaluable.

Appendix

Although the actual circulatory system is a more complicated dilution process, the central circulatory system is here assumed to be stationary and linear. When a radioactive tracer bolus is introduced into the input of this system, the dilution processes of each vascular compartment may be obtained by identification of each compartment or region by its spatial and temporal location in the scintillation camera field.

It is further assumed that the traveling distribution of the injected isotope is identical with that of the normal constituents of blood flow, and that the concentration, \( x_i(t) \), of the isotope is homogeneous within the \( i \)th vascular compartment in the system. The total amount of isotope in the compartment at the time \( t \) is simply expressed as the difference between the input flowing into the compartment up to the time \( t \) and the output that leaves the compartment until the time \( t \).

Thus:

\[ V_i x_i(t) = F \left[ \int_0^t x_{i-1}(t) \, dt - \int_0^t x_i(t) \, dt \right] \quad (3) \]

where \( V_i \) is the volume of distribution in the \( i \)th vascular compartment and \( F \) is the flow perusing the system. The term \( x_{i-1}(t) \) is the concentration of the preceding vascular compartment that feeds the input to the \( i \)th compartment and has the same characteristics of distribution as the \( i \)th compartment. In situations where there is a transport delay, \( \tau_i \), without any significant dispersion of the tracer between these compartments, \( i-1 \)th and \( i \)th, equation 3 can be rewritten as:

\[ V_i x_i(t) = F \left[ \int_0^t x_{i-1}(t - \tau_i) \, dt - \int_0^t x_i(t) \, dt \right] \quad (4) \]

Differentiation of both sides of equation 4 and rearrangement gives the expression:

\[ T_i \frac{dx_i(t)}{dt} + x_i(t) = x_{i-1}(t - \tau_i) \quad (5) \]

This is a familiar first order differential equation where \( T_i \) is defined as \( V_i \) and is equivalent to a time constant of a first order lag system and \( \tau_i \) is a simple time delay. Thus the central circulatory system can be treated here as a series of vascular compartments defined by equation 5, interconnected in a cascade fashion with or without time delay. In other words, this system is defined as a series of so-called mixing chambers consisting of the superior vena cava, right atrium, right ventricle, lung vasculature, left atrium, and left ventricle. In addition to the mixing part of lung vasculature, there is a time delay part for the passage of tracer through the lung vascular tree. Each component of the system has thus been assumed to be a rather simple model, with the simplification facilitating the following analytical manipulation of the analog computer.

Taking the Laplace transform of equation 5 and further rearrangement yields the expression:

\[ X_i(s) = \frac{e^{-\tau_i s}}{(T_i s + 1)} \cdot X_{i-1}(s) \quad (6) \]

The mathematical expression within the bracket of the right hand side of the equation is the transfer function of the \( i \)th compartment, which determines what output, \( X_i(s) \), would be obtained for any given input, \( X_{i-1}(s) \). Here, the system properties of the \( i \)th compartment are defined by the transfer function, which is characterized by the parameters \( T_i \) or \( \tau_i \). Thus, we are given the input, system law, and the output, and we can derive the system parameters \( T_i \) or \( \tau_i \) for each compartment. From these parameters, the physical properties, such as chamber volume, \( V_i \), can be obtained.

Each fitting analysis has been simplified as a one-parametric manipulation by the analog computer, provided that the gain-factor, \( a \), is known. It has been shown\(^5\) that the ratio of the area under the dilution curves from each compartment is proportional to the ratio of each corresponding geometric relation. This relationship, called effective volume by others,\(^6\) allows the data from each compartment to be treated in terms of the same unit of concentration, \( x_i(t) \). The term \( a_i \) is the geometric factor (fig. 2) and is assigned to each block of the analog computer as the gain factor. On analog fitting analysis, the geometric factor is set for each block on the computer control from the relationship of the area ratios of the data curves. Then the fitting procedures as described in Methods are started consecutively, following initiation of the injection input as a square wave approximation.

As previously stated, the validity of this approach, the application of the transfer function to the central circulatory system in order that flow or volume might
HEART CHAMBER VOLUMES

be calculated by the indicator-dilution method, is dependent upon the assumption that the system is linear and stationary. The linearity of the system has experimentally been substantiated by other investigators for the circulatory system through the lungs and heart of the dog. The possible violation of the stationarity by cardiac fluctuation in flow has been demonstrated to produce relatively little error. Since the variations due to cardiac cycle are of relatively high frequency, the effect would be similar to the introduction of small amplitude high frequency noise into the system.

The scintillation camera differs from the usual arterial sampling device in that it can collect the sampling data directly from the region of interest. Then, if each frame of the camera data were triggered by the ECG to gate the synchronized sampling data with the cardiac cycle, as has been attempted by other investigators, no assumption approximation of stationarity neglecting cardiac fluctuation would be required. Thus, the derived time constant value in the ventricle, for example, would exactly represent the ratio of stroke volume and end-diastolic volume in our data.

In spite of the recent criticism, there is good evidence that a ventricle can be approximated as a complete mixing chamber. It is uncertain, however, what kind of transfer function best represents the distribution process in the atria or lung vasculature. Recently, the lung vascular system has been considered to be a parallel pathway system. If so, we will need a number of elemental dilution processes passing through the lung in parallel fashion to determine quantitatively their regional pattern of gain and dispersion characteristics, which might merit the next step in our future refinements. At present, though it might be considered simple, our assumed model has been fit well to actual data and appears to be well within the range of clinical usefulness. Since any transfer function model that produces a correct result is a suitable model, it becomes appropriate to use one that is easily handled.

References

6. Ishii Y, MacIntyre WJ: Analytical approach to dynamic isotope data. Submitted for publication


Measurement of Heart Chamber Volumes by Analysis of Dilution Curves
Simultaneously Recorded by Scintillation Camera
YASUSHI ISHII and WILLIAM J. MACINTYRE

_Circulation._ 1971;44:37-46
doi: 10.1161/01.CIR.44.1.37
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1971 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/44/1/37

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/