Thermal Dilution Curves in the Intact Animal

By Allan V. N. Goodyer, M.D., Andrew Huvos, M.D., William F. Eckhardt, M.D., and Robert H. Ostberg, B.S.

The acceptance of thermal dilution curves for the estimation of cardiac output has been discouraged by unconvincing comparisons with the Fick method and by the possibility of the loss of "indicator" to the tissues of the central circulation. The present studies were undertaken to examine the technical and physiologic factors affecting thermal curves, with particular reference to tissue heat exchanges, and to provide adequate data for estimating the usefulness of the thermal curves for simultaneous measurements of right and left ventricular outputs.

Present methods for obtaining indicator-dilution curves in intact animals are beset by many problems which make difficult or uncertain the repeated, accurate quantification of the cardiac output from such curves. Indicators such as Evans blue dye or radioiodinated albumin have serious dosage limitations in human subjects, whereas agents such as K\textsuperscript{38} or saline may be lost to some extent in the lungs. Adequate detection of the time-concentration curves of these indicators in arterial blood requires the cumbersome technique associated with drawing blood steadily and quickly through a cuvette using tubing of suitable maximal dimensions.\textsuperscript{1} When dyes are used, the calibration of colorimetric cuvettes presents additional problems involving the linearity of photocell or phototube responses with increasing background dye concentrations, and the peculiar optical properties of flowing blood. The calibration difficulty is augmented when indirect detectors are used, and, with baseline instability, is a major disadvantage in the use of a conductivity cell.\textsuperscript{2} Most of these problems were avoided in the method first applied by Fegler\textsuperscript{3} in which changes of the temperature of flowing blood induced by injections of cold fluid were sensed by intravascular thermocouples. A small number of simultaneous determinations of cardiac output by this and the Fick methods were astonishingly similar. However, Fegler's results were not widely accepted for several reasons: some of the published thermal curve-baselines were unsteady; it seemed dubious that complete mixing of cold fluid injection at the entrance of the right atrium would occur regularly by the time of its detection by a thermocouple in the right ventricle; the problem of the loss of "indicator" by transfer of heat from tissues was only partly answered by the demonstration of negligible exchange of heat with alveolar air.

The present study was therefore undertaken to explore further the technical and physiologic factors affecting thermal dilution curves, and to determine fully their usefulness for estimating the simultaneous right and left ventricular outputs.

**METHODS**

Dilution curves (161 thermal, 72 dye), and 58 determinations of cardiac output by the Fick procedure were obtained in 22 dogs anesthetized with Dial-Urethane (6 mg./Kg., i.v.) and breathing 100 percent oxygen. The injectate consisted of a standard bolus of iced, dyed saline introduced rapidly from a marked syringe via a radio-opaque catheter directly into the right atrium at its junction with the inferior vena cava. Great care was taken to avoid, or to correct for, heat exchange with this bolus before its deposition in the right atrium. In particular,
THERMAL DILUTION CURVES

blood (at body temperature) was drawn through the catheter immediately before each injection, so as to avoid "contamination" of the bolus by fluid or blood within the catheter cooled to a temperature below that of the body by previous injections, or by exposure of part of the catheter to room temperature. A very important correction was found necessary for the transfer of heat from the catheter itself. This was ascertained by simple calorimetry, using a thermos flask and sensitive thermometer. The standard bolus of iced saline was injected from a marked syringe, via the same stopcock and catheter used in the dog studies, into a known volume of saline at 37 C. within the thermos. The catheter, dry on the inside, was immersed for about one half of its length in water at 37 C., the other half being exposed to room temperature, to simulate the conditions of the animal experiments. The loss of heat from the catheter into the bolus was then calculated as follows:

\[ K = (V_s S_t) \frac{(\Delta S_t)}{C} - (V_w S_w) \frac{(\Delta S_w)}{C} \]  

where \( K \) = heat transfer from catheter; \( V_s \) and \( V_w \) are the volumes of injectate (3.7 ml. with the catheter used) and of the water in the thermos, respectively; \( S_t \) and \( S_w \) are the calories required to raise by one degree the temperature of 1 ml. of the injectate or of 1 ml. of the thermos water. These values were equal to 1.00 in the present formula, since water was used. \( C \) = thermal equivalent of the calorimeter, itself, determined by direct injection of iced saline into the thermos. \( \Delta S_t \) = temperature change of injectate; \( \Delta S_w \) = temperature change of thermos water.

The injection catheter used in these experiments (a no. 8 Courmand) was found to contribute 21 calories to the standard cold bolus (constituting about a 15 per cent correction of the calculated calories required for warming the bolus to 37 C.). Several determinations of the specific heat of blood, employing this same calorimetric technic (using direct injection of blood into the thermos) gave values averaging 0.85, a figure very close to that obtained by Mendlowitz (0.87)\(^1\) using a more sophisticated calorimeter. The correction for catheter heat exchange obtained in this same way is therefore probably quite accurate.

In addition to the heat exchange between the catheter and the cold injectate, the possibility of continued cooling of blood flowing around the catheter by the residual cold saline left within the catheter after expulsion of the injectate had to be considered. This possibility was excluded in several experiments by rapid withdrawal of blood through the catheter following each injection. Consecutive thermal curves from the pulmonary artery and aorta were unchanged by alternate use and disregard of this post-injection maneuver, and it was, therefore, not used in the experiments of this report.

Intravascular temperature changes were measured continuously with thermistors (Veco,\(^ 1\) types 32A11 and 32A12 mounted at the ends of radio-opaque plastic catheters, and attached by enameled wires led through the catheters to Wheatstone bridge circuits incorporated in the input networks of chopper or carrier amplifiers.\(^1\) The voltage supplied to each thermistor was attenuated sufficiently to prevent appreciable electrical heating of the thermistor itself. An oscillograph was used to record several curves simultaneously with other appropriate measurements, such as blood pressure or the electrocardiogram. In order to minimize thermal drift due to gradual changes of the body temperature of each dog, a reference thermistor was paired in each Wheatstone bridge circuit with the sensing thermistor, the former being placed deeply subcutaneously in the flank, the latter in the thoracic aorta, main pulmonary artery or other selected intravascular site\(^ 4\) via appropriate peripheral vessels, and under fluoroscopic control. It was shown in several experiments, using a single thermistor, that there was no significant acute change of subcutaneous temperature in the region of the reference thermistor following intravascular injection of iced saline. The sensing thermistor was usually the type 32A11, which has a small but distinct thermal lag, being encased in a small glass probe. Its adequacy for faithful recording of thermal curves is indicated in figure 1 by its response to a "square wave"* of temperature change produced by its rapid alternate immersion in two containers of saline at different temperatures. In addition, sharp thermal curves obtained with this type of thermistor were identical with those obtained from the same intravascular location using the faster type 32A12, the "square wave"* response of which is also shown in figure 1.

The 32A11 was preferred because it was more easily mounted protruding from a water-tight seal at the end of a catheter, thereby avoiding the thermal insulation which would be introduced by enclosure within the catheter itself. The thermal sensitivity of each thermistor used was exactly determined during each experiment by recording the galvanometer deflection produced by removing the thermistor from its intravascular site and replacing it with a reference thermistor. The latter was always first placed in the thoracic aorta, main pulmonary artery or other selected intravascular site and properly disposed of before the experiment, and was then repositioned in the chest wall on the flank, to be used as a reference thermistor during each experiment.

\(^1\) Victory Engineering Corp., Union, N.J.
\(^4\) Sanborn Company, Waltham, Mass.
\(^\dagger\) Hathaway Instrument Division, Hamilton Watch Co., Denver, Colo.
\(^\dagger\) Correct position of each thermistor inserted into the coronary sinus was verified by postmortem examination.

\(*\) Correct position of each thermistor inserted into the coronary sinus was verified by postmortem examination.
FIG. 1. Responses of types 32A11 and 32A12 thermistors to sudden changes of temperature caused by quickly transferring the thermistor from one container of water to another and back again. Artefact due to cooling by air in transit from one container to the other. Times for full deflection, and for fall to 37 per cent of initial value (time constant) are indicated.

plunging it into the same container of iced saline used for the thermal injectate. The body (intra-rectal) temperature of each dog and the temperature of the iced saline were repeatedly measured by means of a sensitive thermometer.

Dye-concentrations in arterial blood were measured continuously by means of an oximeter-cuvette* attached either to a short carotid arterial cannula introduced to the level of the aortic arch or to a no. 8 catheter, the tip of which lay in the pulmonary artery. Blood was withdrawn through this cuvette at a constant rate (0.7 ml./sec.) by means of a syringe-driver† which also marked on the oscillograph the beginning and the end of sampling-syringe movement, the first mark being synchronous also with the time of dye injection. The carotid cannula was of 2.5 mm. internal diameter, the distance from carotid cannulation to cuvette-midpoint being about 20 cm. The electrical output of the cuvette was amplified by means of an oximeter amplifier* and recorded simultaneously on the oscillograph along with the thermistor curves. The cuvette was calibrated during each experiment by withdrawing blood with the syringe-driver alternately from the carotid artery and from a syringe attached to the same 3-way stopcock that also linked the cuvette-tubing with the carotid cannula. The blood in this syringe was withdrawn from the carotid cannula just prior to the calibration, was dyed uniformly by a few drops of Evans-blue already contained in the syringe, and was constantly agitated so as to eliminate the unsteady baseline encountered when blood was allowed to settle, even for a few moments, before withdrawal through the cuvette. This technic also provided repeated evaluation of the response of the entire system to a "square-wave" of changed dye concentration, as indicated in figure 2. Dye curves from the pulmonary artery were obtained in a few experiments by continuous withdrawal of blood via a no. 8 Cournand catheter and the same cuvette system as described above. The dye content of the blood samples was measured by standard spectrophotometric methods.

The Fick procedure was used as an independent measure of cardiac output. Oxygen consumption was measured using a 1,500 ml. bell-type spirometer† which delivered 100 per cent oxygen, through one arm of a circulating system containing a fan and CO₂ absorber, to a balloon-sealed intratracheal cannula. Mixed venous blood was obtained during one of two or three consecutive measure-
ments of oxygen consumption through a catheter placed under fluoroscopic guidance in the pulmonary artery. Arterial blood was obtained simultaneously. Analyses for blood oxygen were made by the Standard Roughton-Scholander technic.\textsuperscript{5} Cardiac output was varied acutely by brief (5 to 10 min.) occlusion of the inferior vena cava below the hepatic veins by a balloon at the end of a radio-opaque catheter.

Calculations of cardiac output. Cardiac output was calculated from the thermal curves according to a modified Stewart formula:

\[
\text{Cardiac output} = \frac{90 \left[ \left( \frac{V_s \Delta t}{A} \right) - K \right]}{0.84 A S_t}
\]

where \(V_s\), \(S_t\), \(\Delta t\), and \(K\) have the same meanings as given in formula (1); \(0.84 = 0.87 \div 1.04\).

Specific heat of blood \(c_s\); \(\Delta t\) = change of temperature per mm. of galvanometer deflection by the thermistor and its amplifier; \(A = \) area of the thermal curve in mm.-secs. excluding any recirculation by extending the downslope by semi-log plot.

Cardiac output was calculated from the dye curves according to the formula:

\[
\text{Cardiac output} = \frac{60 I}{A S_t}
\]

where \(I = \) amount of dye injected, expressed in optical density units and determined by injection of the same bolus of iced, dyed saline through the same catheter and stopcock as was used for this purpose in the dog, into a liter of saline, the optical density of which was then determined spectrophotometrically. \(A = \) area in mm.-secs. of the dye curve, excluding recirculation by semi-log plot. \(S_t = \) change of dye concentration (expressed in optical density units) in whole blood per mm. of galvanometer deflection by the cuvette and its amplifier, determined by the calibration method described above.

Heat exchange between the cold injectate and the tissues was studied in accordance with the following considerations:

If the tissues of the vascular walls of the central circulation were cooled by exchange of heat with the cold bolus, they would be re-warmed both by blood flowing in the tissue capillaries, and by blood flowing within the vascular lumina immediately following the cold bolus.

Cooling of capillary blood might remove some cold indicator from its initial circulatory pathway and might further its early and increased recirculation. Special studies were therefore made of the timing and extent of thermal recirculation by sensitive thermistor recordings of temperature changes within various venous channels, including the vena cavae and coronary sinus, after injection of iced saline into different regions of the heart and aorta. These studies also defined the character of recirculation, via arterial channels, of the primary mass of cold indicator, itself. Additional observations were made of the local exchange of heat between the cold bolus and the cardiac tissues by positioning the sensing thermistor so that it was contiguous to tissues opposite the end of the injection catheter, but in a different chamber of the heart from that containing the injection catheter.

Cooling of blood following the cold bolus, by tissues previously cooled by this bolus, would lead to "trailing" of the cold indicator as if its injection time had been prolonged. The effect of this process on the thermal curve in the aorta would be to lower the peak and prolong the downslope. The area of the curve, discounting early or late recirculation, would be the same as if the iced saline had been injected instantaneously\textsuperscript{6} and had remained entirely intravascular. On the basis of experience with dye-curves,\textsuperscript{7} if complete rewarming of the tissues occurred before the beginning of the primary thermal curve (i.e., if "prolongation of the injection" did not exceed the appearance time), the downslope would be truly defined before the recirculatory wave began. If, on the other hand, rewarming of the tissues took place slowly, a large portion of the injectate might be delayed in transit, and the downslope of the primary curve might be ill-defined before the recirculatory wave. Furthermore, if a large and variable fraction of the cold indicator arrived at the aortic thermistor during either the downslope or the recirculatory wave of the aortic thermal curve, any otherwise reliable method for predicting the total primary curve area from the build-up triangle\textsuperscript{8} might be expected to give quite variable results.

With these points in mind, the thermal curves were analyzed for:

The slopes of the downslopes of their semi-logarithmic plots, as compared with the simultaneous dye-curves corrected by superimposing to the same peak deflection. An index of the differences of these corrected downslopes was provided by calculation of the ratio

\[
\frac{Z_t \times P_t}{Z_o \times P_o}
\]

where \(Z_t\) and \(Z_o\) are the slopes of the downslopes of the semi-log plots of the thermal and dye curves respectively. \(P_t\) and \(P_o\) are the peak deflections of the thermal and dye curves respectively.

The timing and extent of the wave of recirculation of the thermal curves, as indicated in their semi-logarithmic plots.

The relative variability of \(H\), the "constant" in Hetzel's\textsuperscript{8} formula for predicting the curve area.
FIG. 3. Representative thermal curves from pulmonary artery and aorta with simultaneously recorded dye-curve from the carotid artery. Cold, dyed saline injected into right atrium. Changes of temperature (negative) from baselines to peaks of thermal curves are indicated. A, at cardiac output of 3.6 L./min.; B, at 2.9 L./min.; C, at 2.5 L./min.; and D, at 1.5 L./min., during partial obstruction of inferior vena cava.

\[ H = \frac{BT \times P}{2A} \]

Where \( BT \) = build-up time, secs.; \( P \) = peak deflection, mm.; \( A \) = area, mm.-secs., excluding recirculation, obtained by direct measurement of semi-logarithmic plots.

**Results**

Representative simultaneously recorded curves of changing blood temperatures in the pulmonary artery and aorta, and of changing blood-dye-concentrations in the aorta are presented in figure 3a-c. The aortic thermal curves were similar to the dye curves but had
earlier appearance times (due to the dead space of the cuvette and its cannula), and more gradual downstrokes, the slopes of which averaged 0.32 ± 0.12 (S.D.) of the slopes of the simultaneous dye curves. The downstrokes remained exponential down to a very low fraction of the peak concentrations, with only minimal indications of recirculation, as compared to dye curves (fig. 3c). The pulmonary artery thermal curves, though characterized by very abrupt contours, were slightly slurried and occasionally showed gross deformations such as displayed in the example of figure 3d obtained during temporary (10 min.) occlusion of the inferior vena cava. These irregularities, which could not be reproduced by catheter movement and which have not been observed in aortic thermal curves, were most probably caused by imperfect mixing of the injected bolus by the time of its passage into the pulmonary artery. This phenomenon may explain the less consistently accurate measurement of cardiac output provided by pulmonary arterial vs. aortic curves. More distal injections of the iced saline in the inferior vena cava might have minimized such irregularities.

Cardiac output determinations from the aortic thermal curves were very close to those from simultaneous carotid-dye curves and Fick values (fig. 4a-b). Flow determinations from the pulmonary arterial thermal curves...
FIG. 5. A. Thermal curves from the pulmonary artery and aorta recorded along with dye-curve from the pulmonary artery after injection of cold dyed saline into the right atrium. The pulmonary arterial thermal curves were recorded at very high sensitivity in order to bring out the recirculatory phase, hence, the peak was far off the top of the paper, and small (otherwise almost invisible) variations of baseline, mostly at respiratory frequency, were grossly exaggerated. Percentages and arrows refer to the heights of simultaneous portions of the dye and thermal curves (corrected for lag in the dye-cuvette system), in terms of the respective peak concentrations. The peak concentration of the pulmonary arterial thermal curve was estimated from a curve obtained by the same technic immediately prior to that of this figure, using greater recording attenuation. B-D. Thermal curves in various locations following cold saline injections into the aorta at several levels. Ratios of peak venous to peak arterial temperature changes indicate the high sensitivity (1.5-6 X 10^-4 degrees per mm.) at which the venous curves were recorded. Injection sites and positions of sensing thermistors also indicated. Injection for curves of D made at aortic valve, while recording from the lower aorta and coronary sinus.

Also compare well with values obtained by the Fick procedure or from simultaneous dye or aortic thermal curves, but there were scattered major discrepancies (fig. 4c) which detract from the over-all accuracy of the values derived from the pulmonary arterial curves. The reliability of the dye method as used in these experiments for estimating cardiac output is indicated in figure 4d, showing comparisons with the Fick method.
**THERMAL DILUTION CURVES**

*Special Studies of Recirculation and Tissue Cooling.* The small extent of recirculation of the cold bolus was indicated in thermal curves obtained at high amplification from the pulmonary artery, coronary sinus, right atrium and inferior vena cava after injections of iced saline into the right atrium, or into the aorta at various levels (fig. 5a–d). The pulmonary arterial thermal curve of figure 5a, recorded at twice the sensitivity of the aortic curve, showed no recirculatory peak during the period when dye recirculation was prominent in the simultaneous pulmonary arterial dye curve. This was directly explained by the primary venous curves of figure 5a–c. In spite of very marked temperature changes in the lower thoracic aorta, after cold injections in the ascending aorta, the peaks of these venous curves were only 1/15-1/19 of those in the aorta, and their downslopes were greatly prolonged. Even the rapid primary circulation of cold indicator via the coronary circulation (fig. 5e) was characterized by a curve with a markedly prolonged downslope and low peak. Since heat production in the tissues probably remained constant during the periods of these thermal curves, it was likely that all the cold indicator entering the arterial bed appeared ultimately in the venous drainage of the tissue concerned. Therefore, the low peak values and very prolonged downslopes of the venous thermal curves were probably due to exaggerations of the same process of cooling and rewarming of tissues by which the distortion of arterial thermal curves may best be explained. Recirculation of such small venous temperature changes could affect only the lowest and most delayed segments of the primary aortic thermal curves. Further justification is therefore provided for the thesis that recirculation contributes very little to the prolonged downslopes of those aortic thermal curves produced by cold injections into the right atrium.

The possible extent and time-characteristics of heat exchange between cardiac tissues near the tip of the injection catheter and the cold bolus are indicated in figures 6a and b. One sensing thermistor, passed deeply into the main coronary venous channels, lay near the root of the aorta within a few millimeters of the tip of the injection catheter positioned in the ascending aorta with its tip just above the aortic valve. An immediate brief temperature change was detected by the coronary venous thermistor upon injection of the iced saline, followed shortly, in one case (fig. 6a), by a curve of cooling from the coronary arterial circulation. Rewarming of the immediately cooled tissues at the root of the aorta in this experiment took place rapidly, and was accomplished by heat exchange with flowing aortic or coronary blood because when the
same experiment was immediately repeated following cardiac arrest induced by barbiturate, the temperature change in the region of the coronary sinus thermistor was extremely exaggerated and persistent over a period of several minutes. The total heat exchange with coronary blood in the experiments in the intact animal must have been very small, since only the curve of cooling from coronary arterial flow was detectable when the coronary venous thermistor was pulled back about 2 cm. closer to the sinus ostium (fig. 5d). It was, therefore, not unexpected that no early cold peaks were evident in the coronary sinus, even when recording at higher sensitivity, after cold injections into the upper inferior vena cava or right atrium.

An estimate of the proportion of the cold injectate delayed by heat exchange with the vascular tissues during passage through the central circulation was given by calculations of the $H$ constants for 73 dye and 119 aortic thermal curves. Values for $H$ of $0.31 \pm 0.06$ (S.D.) and $0.23 \pm 0.02$ were derived, the former comparing closely with the value of $0.37 \pm 0.01$ obtained by Hetzel from his own dye curves. The lower value for the thermal curves means that about 8 per cent more of the injectate arrives in the aorta following the peak of a thermal curve than following the peak of a simultaneous dye curve, due probably to delay of some of the cold indicator by exchange of heat with tissues, as described above. The small variation in this delay of cold indicator from one curve to another is indicated by the low standard deviation of $H$ for the thermal curves.

**Discussion**

The chief intuitive objection to the use of thermal dilution curves for the estimation of cardiac output concerns the obvious probability of heat exchange between the cold injectate and the warm tissues of the central circulation. The present experiments show, indeed, that brief cooling of tissues, particularly in the region of the injection itself, does occur. Furthermore, the fact that thermal curves have uniformly more prolonged downstrokes than do simultaneous dye curves is best explained by delayed exchange of heat between tissues cooled by the leading portion of the injectate, and circulating blood which follows. Certainly, the experiments with venous thermal curves indicate that recirculation of cold indicator can contribute very little to the downslope of an aortic thermal curve. In the present experiments the transient exchange of heat between the injectate and the tissues did not appreciably affect the estimations of cardiac output from the thermal curves, which agreed very closely with those derived from simultaneous dye curves or Fick determinations (fig. 4a and b). It must be concluded that heat exchange between the cold bolus and the tissues was essentially completely reversible and sufficiently transient to allow the full calor ic equivalent of the injectate (corrected for catheter exchange) to be represented in that area of the dilution curve bordered by its well-defined exponential downslope.

For the determination of cardiac output, the thermal dilution method has the great advantage over the dye-dilution technic of simple, continuous detection of the dilution curve, the calibration of which is extremely accurate. It is well suited to the simultaneous determination of right and left ventricular output, allowing for the slightly increased error inherent in using dilution curves from the pulmonary artery.

**Summary**

One hundred and sixty-one dilution curves, 72 simultaneous dye dilution curves, and 58 concomitant determinations of cardiac output by the Fick procedure were obtained in 22 lightly anesthetized dogs. Technical factors affecting the thermal curves were elucidated with particular reference to the proper measurement of the calor ic equivalent of the injectate. Physiologic factors affecting the thermal curves were examined by comparisons with the simultaneous dye curves, and by special studies of the recirculation of cold indicator. The prolonged curve downslopes, attributable to heat exchanges between the
cold injectate and the tissues, were barely affected by recirculation, and would not, therefore, be expected to invalidate cardiac output determinations from these curves. Cardiac output determinations from aortic thermal curves agreed very closely with determinations from simultaneous dye curves or by the Fick procedure. Values obtained from pulmonary arterial curves compared well, but less favorably, with the dye and Fick values.

Acknowledgment

The authors are indebted to Miss Francis Korb, Miss Janice Pongonis, Mrs. Helen Ujlaky, and Mr. Arnen Negri for their expert technical assistance in this project.

Summario in Interlingua

Cento sexanta-un curvas de dilution thermica, 72 simultaneae curvas de dilution de colorante, e 58 concomitante determinaciones del rendimento cardiac super le base de aortic curvas thermica concordava benissimo con determinationes super le base de simultaneae curvas de colorante e con determinationes secundo le metodo de Fick. Valores obtenite ab curvas pulmono-arterial concordava ben, sed minus stremente, con le valores a colorante e le valores de Fick.

References

Thermal Dilution Curves in the Intact Animal

ALLAN V. N. GOODYER, ANDREW HUVOS, WILLIAM F. ECKHARDT and ROBERT H. OSTBERG

Circ Res. 1959;7:432-441
doi: 10.1161/01.RES.7.3.432

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1959 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/7/3/432

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research 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 Research is online at:
http://circres.ahajournals.org/subscriptions/