A Method Using Induced Waves to Study Pressure Propagation in Human Arteries

By MILTON LANDOWNE, M.D.

This report describes a method for utilizing externally induced impacts as a means of studying the propagation of pressure waves in intact human arteries. Because it is a new method its description is prefaced by a brief presentation of several factors relevant to wave propagation in living vessels; the description is followed by a critical evaluation.

The observation that small pressure disturbances could be induced in the brachial artery and readily detected on radial arterial pressure records prompted the study of induced waves of two general types, impact transients and forced sinusoidal waves. This report describes the method we have used to study "impact" waves and indicates the general nature of our findings.

The interpretation of pulse wave transmission has been based upon the concepts of wave propagation in an ideal elastic thin walled tube. These principles were first developed and applied to the arterial pulse by Thomas Young and have been further formulated by many others. While the qualitative nature of such an interpretation seems to be acceptable, the quantitative aspects of pulse wave propagation remain open to question. Some of the limitations to quantitative interpretation of conventional pulse wave velocity are imposed by the methods of measurement, while additional difficulty arises from the fact that a living artery resembles a thin walled ideal elastic cylindrical tube only as a first approximation.

Previous methods for the study of arterial wave propagation in living human subjects have utilized the wave produced by cardiac systole. Direct, i.e., intra-arterial pressure records, have been obtained in only a few instances. In all cases the pulse wave transmission time is calculated from the delay in the inscription of "corresponding" points on the pulse contour. The fact that the pulse form becomes modified in its transmission may make it difficult to establish "corresponding" points. The change in pulse form certainly indicates some nonuniformity in the propagation of wave components. Under these circumstances, corresponding geometric configurations (inflections, equal ordinates, equal or maximal slopes), may not indicate correspondence in phase of any component.

In principle, the waves used to determine the elastic behavior of the vessel wall should be of relatively small amplitude, so that they do not appreciably alter the conditions under observation. This is additionally important if the elastic properties might vary with the degree of arterial distension. The marked pressure dependence of wave velocity observed in isolated arteries by Bramwell, Downing and Hill, and the anomalous thermoelastic properties observed by Roy attest to the striking deviations of these tissues from ideal elastic behavior and demonstrate that distensibility and elastic modulus both vary with the applied stress. Remington, Hamilton and Dow have sought to retain the relative simplification of Hookian behavior by considering the artery substantially as 3 systems of differing orders of elasticity. Alternatively it may be recognized that the dominant rheologic behavior of the arterial wall is non-Hookian. The long

---

* Distensibility (of a cylindrical tube) may be defined as the relative increment in volume contained per unit increase in pressure, or \( \frac{dV}{dP} \).

† Elastic modulus (of wall material) may be defined as the ratio of the increase in component of force per unit cross sectional area of wall to the relative increase in the corresponding component of length per unit length, or \( \frac{dF/a}{dL/L} \) or \( \frac{\text{stress}}{\text{strain}} \).

---

From Gerontology Branch, National Heart Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, and the Baltimore City Hospitals, Baltimore, Md.

Received for publication May 8, 1957.
range reversible extensibilities, the anomalous thermoelastic behavior and the relatively low stretch moduli of these tissues are better explained by considering that a considerable part of the restoring force in stretched fibrous proteins may be associated with varying entropy of the material rather than with changing internal energy.\textsuperscript{7,8} Under these circumstances elastic deformation may be thought of as due to a large extent to uncoiling of molecular chains, stretching of secondary valence forces\textsuperscript{9} of the material rather than with changing in-ternal energy.\textsuperscript{7,8} Under these circumstances elastic deformation may be thought of as due to a large extent to uncoiling of molecular chains, stretching of secondary valence forces\textsuperscript{9} of the material rather than with changing in-ternal energy.\textsuperscript{7,8} Under these circumstances elastic deformation may be thought of as due to a large extent to uncoiling of molecular chains, stretching of secondary valence forces\textsuperscript{9} of the material rather than with changing in-

METHODS

Impact waves can be set up in an artery or vein by brisk tapping of the overlying skin. Repetitive transients of reproducible form were created with the mechanical impactor diagrammed in figure 1.

Although no dimensions are critical, the impactor used in these studies has the following characteristics:

- A coil (A) composed of approximately 200 turns of no. 24 copper wire with a total resistance of 4 ohms serves as a solenoid. The core (B) is a $\frac{3}{8}$ inch carriage bolt, the threads of which have been turned down to slightly over $\frac{3}{8}$ inch diameter. When magnetized, this core drives the impacting probe (C), which is a 2$\frac{1}{4}$ inch length of $\frac{3}{8}$ inch brass rod weighing 20 G.

- An outer lucite sleeve and foot plate (D) are used to depress and fix the overlying tissues and the artery, enabling a more effective impact. The apparatus may be held by hand or conveniently mounted and positioned on a camera tripod. Proper positioning is essential. Advancement and withdrawal along the thrust axis was made easier by a screw driven sliding mount for which we are indebted to Dr. Robert L. Bowman.\textsuperscript{*} Independent angular positioning of the

\textsuperscript{*} Technical Developments Section, National Heart Institute.

---

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Schematic diagram of arterial impactor, approximately to scale. \(A\) = 4 ohm solenoid, \(B\) = iron core, \(C\) = brass impactor, \(D\) = lucite foot plate, \(S\) = repositioning spring, \(k\) = contact points.}
\end{figure}
FIG. 2. Schema of accessories to pressure measuring apparatus. Upper diagram, arrangement of impactor for inducing waves and of pressure transducers coupled by 3-way metal stopcocks to intra-arterial needles and to hydrostatic reference level for calibration. Lower diagram, manifold and regulating valves for obtaining various air pressures. Tubing connections to pressure transducers P1, P2 provide a constant small differential flow of heparin-saline; S1, S2 communicate with back of transducer diaphragm to permit differential application of atmospheric or other standardization pressure by rotating stopcock D. Connection CAL provides selected constant calibrating pressure.

Simultaneous recording from two sites, a pair of Lilly Technitrol (capacitance) manometers model 115-1 were used, each connected through a 3-way stopcock to 19 gauge thin wall 1/8 inch needles (i.d. = .035 inch). These records were photographed from the face of a dual beam cathode ray oscilloscope on moving 35 mm. film, and projected for reading at scales of 1 to 2 mm./mm. Hg and 33 to 100 cm./sec. Each system had a natural frequency of over 200 c.p.s., the dual systems were matched to within 10 per cent in amplitude and less than 1 msec. phase to over 200 c.p.s. Independent time scales and baseline were registered simultaneously, careful attention was paid to possible errors of parallax.

To keep the recording system patent (and to enable frequent calibration and sensitivity checks, the ingenious procedure of Petersen[1] was modified (fig. 2), using a pressurized inverted latex balloon instead of a pressurized syringe as a source of purging heparinized saline. This has been further improved by using a plastic bag to contain the saline, which is placed alongside a rubber sphygmomanometer bag in a closely fitting box. Manostats were provided to enable frequent sensitivity and calibration checks during recording. Calibrating pressures were substituted for arterial pressures by a quarter turn of a 3-way stopcock. During its return, when the stopcock core is momentarily positioned to block both calibration source and arterial needle from the transducer, the pressure on the transducer rises due to the minute inflow of purging saline. When transducer and artery are reconnected by abruptly completing the turn of the stopcock, the resultant stepwise fall in pressure sets up conditions for free oscillation in the recording system. The response of the registering equipment including the needle assembly, was tested under operating conditions in this manner.

In most studies the impactor was applied to the brachial artery at approximately the midhumerus where the artery is easily palpable and lies fairly close to the bone (fig. 2).

RESULTS

Records of intra-arterial pressure such as those of figure 3 show the transient pressure disturbances caused by the impactor. A trace indicating the moment of impact is above the blood pressure record. It is difficult to measure the time delay of the pulse onset because of the gradual onset of the rise from diastolic pressure. In contrast the transmission time of the impact pulses are more readily determined and the difference between the onset of the impact wave at the two positions can be measured for impacts which occur at various pressures. It will be noted that the time delay is less at high pressures than it is at low pressures. The impactor over the brachial artery is approximately 15 cm. proximal to the brachial needle, and 40 cm. proximal to the radial needle. In most experiments measurements were made between the site of impact production and a single radial intra-arterial needle. In these, a correction of the order of a few milliseconds was calculated by averaging 20 to 30 measurements of records which were made with the impactor placed over the radial artery adjacent to the open end of the needle. No
systematic variation was noted in the "zero correction time" at different pressures.

At a repetition rate of from 6 to 10 impacts/sec, several hundred impacts were superimposed on different momentary arterial pressures. Fewest impacts were obtained at pressures just below systolic. The manner of obtaining pressures lower than diastolic is described below. Time was measured to the nearest millisecond and pressure to the nearest millimeter Hg. The results of 1 experiment with relatively few impacts are shown in figure 4 as a plot of the transmission times of impact wave onset against the corresponding intra-arterial pressures. The data were grouped into class intervals, usually of 10 mm. Hg, and averaged. Table 1 presents coordinate values for corrected mean transmission times and mean pressures in another subject. Corrected transmission time divided by transmission distance, yields the reciprocal of wave velocity (fig. 5). An example of a velocity-pressure plot is shown (fig. 6). In a large number of subjects, the velocity of impact waves in the brachio-radial artery was about 10 M./sec. or less at

<table>
<thead>
<tr>
<th>Number of impacts (n)</th>
<th>Mean pressure (mm. Hg)</th>
<th>Transmission time of onset (msec.)*</th>
<th>Transmission time of peak (msec.)*</th>
<th>100 per cent rise time (msec.)</th>
<th>Average velocity ratio (peak/onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>37</td>
<td>27.1</td>
<td>30.6</td>
<td>11.4</td>
<td>.90</td>
</tr>
<tr>
<td>25</td>
<td>42</td>
<td>25.5</td>
<td>29.7</td>
<td>10.9</td>
<td>.92</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>20.3</td>
<td>22.1</td>
<td>10.5</td>
<td>.92</td>
</tr>
<tr>
<td>82</td>
<td>66</td>
<td>19.4</td>
<td>20.5</td>
<td>9.8</td>
<td>.95</td>
</tr>
<tr>
<td>155</td>
<td>74</td>
<td>18.9</td>
<td>19.7</td>
<td>9.6</td>
<td>.96</td>
</tr>
<tr>
<td>115</td>
<td>85</td>
<td>17.6</td>
<td>18.2</td>
<td>9.3</td>
<td>.97</td>
</tr>
<tr>
<td>49</td>
<td>92</td>
<td>17.4</td>
<td>17.5</td>
<td>8.8</td>
<td>.99</td>
</tr>
<tr>
<td>22</td>
<td>105</td>
<td>16.5</td>
<td>16.5</td>
<td>8.7</td>
<td>1.00</td>
</tr>
<tr>
<td>74</td>
<td>115</td>
<td>15.4</td>
<td>15.5</td>
<td>8.8</td>
<td>.99</td>
</tr>
<tr>
<td>28</td>
<td>121</td>
<td>15.1</td>
<td>15.2</td>
<td>8.8</td>
<td>.99</td>
</tr>
</tbody>
</table>

* Mean and standard deviation of distribution corrected for instrumental delay. (This "zero correction" time averaged 5.7 msec. to onset, and 14.4 msec. to peak, for 18 impacts generated immediately proximal to the radial needle. The range of 100 per cent rise time was 8 to 9 msec., and showed no detectable variation with pressure over a limited range.)
598 PRESSURE PROPAGATION IN HUMAN ARTERIES

Fig. 6. Relationship between impact wave velocity and pressure to illustrate reproducibility of procedure on the same and different days. Ordinate, impact wave velocity in M./sec.; abscissa, radial pressure in mm. Hg.

pressures below diastolic; 12 to 20 M./sec. at diastolic pressures in normotensive subjects, and 20 to 30 M./sec. in the region of systolic pressures. A consistent increase in velocity is observed with increasing pressure. In almost all instances the slope of the smoothed curve expressing velocity as a function of pressure decreases as pressure increases. The form of the curves obtained are generally similar to those published by Bramwell et al.11 and by Steele12 for the intact brachial artery using the cardiac pulse wave, and by Bramwell et al.4 for the isolated carotid artery. They do not confrom to data obtained from rubber tubing13 or to some of the relationships which have been predicted from theory.7 With our technic, pressure-velocity curves from rubber tubing and from isolated femoral arteries differ from the curves described above.

DISCUSSION

Wave Propagation in the Artery. To determine whether the intra-arterial pressure transient recorded at a distance from the impact site is predominantly or entirely a record of a disturbance propagated by the arterial structures rather than through extravascular material, these observations were made: 1. Impacts delivered to the arm were not well registered as pressure waves unless the impactor was very carefully positioned over the artery, indicating that no significant portion of the disturbance was produced by transmission of impacts through tissues other than the artery. 2. Digital occlusion of the artery between the impactor and the recorder obliterated the transmission of impacts to the recording needle. 3. Impact waves were not obtained unless the needle was in the arterial lumen. 4. The fact that the impact wave velocity varies with the intra-arterial pressure is additional evidence that this wave is determined by arterial phenomena and not to any significant extent by extra-arterial transmission. 5. The modification of transmission time by an externally applied cuff is further supporting evidence of this (see below).

Wave Form. After propagation for a distance, the waves show variation at different pressures, with a steeper rise at higher initial pressures. The peak of the transient is usually easier to identify than the onset, but “peak” velocity tends to be slightly less than that of the “onset,” especially at low pressures. We have therefore dealt primarily with the velocity of the onset of the disturbance.

It is evident that the steepness of pressure rise is not entirely determined by our impactor, but may be limited by the characteristics of the artery and the overlying tissues at the site of impact. In the radial artery at diastolic pressure the initial rate of rise of the impact wave averaged 2.5 mm. Hg/msec. (σd = ±1.3) in 18 subjects. The variation in this wave front due to change in pressure may be judged from table 1 to be about ±15 per cent. To this extent, the impactor created waves of substantially the same characteristics at all pressures or in different subjects.

Reproducibility. Several factors contributing to the variability of results were investigated: Impacts at the same, or nearly the same pressures, usually showed little variation in their transmission time (fig. 4). Where more than 70 measurements, within a 10 mm. Hg pressure interval, were obtained in a single sequence run, their distribution approximated a normal curve with a standard deviation of about 1 msec. Part of this spread may be due to the variation of time with pressure within the interval, or to
the errors of estimating pressure, as well as to the errors of estimating time. The residual variability is astonishingly small for a biological phenomenon. Some experiments show greater variability, and among these are instances where impacts are difficult to obtain or good placement cannot be maintained.

Removing, adjusting and replacing the impactor did not substantially alter the results obtained. If the included length of artery were altered the change in transmission velocity was generally proportional to the change in distance. In experiment no. 51, of table 1 over 600 impact transmission times, in 5 series, were measured in a 53-year-old male with minimal medial sclerosis of the brachial arteries. Initial placement was followed by a firmer apposition, removal, reapplication, and finally slight withdrawal, along the thrust axis. Columns 4 and 6 of table 1 indicate the relatively small variability which existed.

In figure 6 (from a 91-year-old man with marked calcific sclerosis and tortuosity of central and peripheral arteries) the lower full line represents the relation obtained from 101 recorded impacts. The impactor was then removed, subsequently repositioned, and 103 additional impacts recorded, with the results shown in the upper full line. Partial closure of the stopcock connecting needle with the transducer tubing, in order to damp the radial record for an additional .1.9 impacts gave no different results.

Experiments repeated on the same subject under the same conditions, but on different days, usually yielded similar results. In figure 6 the dashed line represents an experiment done a month previously. Under similar experimental conditions, the variability between runs was greater than for consecutive observations on the same day.

Additional evidences of validity and reproducibility were provided by the following studies: In most experiments the velocity was measured between the impactor site and a radial intra-arterial needle. The validity of this "single needle" technic was established by comparing the calculated velocity for the entire segment with simultaneously obtained records of the velocity measured between a second or brachial intra-arterial needle and the radial needle. In 5 experiments, the distance from impactor to radial needle averaged 39 cm. (range 35 to 42) while the distance included between the two needles average 25 cm. (range 23 to 27). The velocities calculated for the shorter distance were compared to the velocities at corresponding pressure for the total distance. The velocities of wave transmission measured between the needles in 3 experiments were slightly faster (av. = 1.5, 2.0 and 3.0 M./sec.), in 1 experiment slightly slower (0.7 M./sec.) and in 1 experiment there was no consistent difference. While a slightly faster velocity in the narrower distal arterial segment would not be unexpected, the average of 403 pairs of measurements shows that the calculated transmission time per unit distance was only 1.1 ± 0.1 msec./M. less for the shorter segment. Velocities obtained by a single needle technic, therefore, provide the same information as that obtained by using two sites of pressure recording.

In 3 of the foregoing experiments the effect on wave velocity of placing a needle in the artery was evaluated. A series of impacts were recorded with the radial needle in place, before as well as after the brachial needle was inserted. The transmission time from impactor to radial needle was not altered by the insertion of the needle in the brachial artery (fig. 5).

Because impacts were induced upon a varying, rather than a constant initial wall tension, the transmission time of impacts which were imposed on the steeply rising portion of the blood pressure curve were compared with the transmission time of impacts superimposed, at the same pressure, upon the rapidly falling part of the blood pressure curve. On the falling ambient, the impact induced pressure rises slightly slower, and the detection of onset of rise is more certain than on the rising ambient. No consistent difference was noted (table 2).

In order to study pressures below diastolic, two technics have been used. Occlusion of the axillary or subclavian artery for 3 to 15 sec. provided a simple means of attaining pressures below diastolic. The lowest pressures thus obtained were of the order of 25 mm. Hg. Records taken before the artery was occluded proximally for 2 min. by digital pressure, and immedi-
TABLE 2.—Impact Waves Riding on a Rising Ambient Pressure do not Travel Measurably Faster than on a Falling Ambient Pressure

<table>
<thead>
<tr>
<th>Number of impacts</th>
<th>Direction of ambient pressure</th>
<th>Average instantaneous pressure (mm. Hg)</th>
<th>Average recorded transmission time (of wave msec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. no. 51</td>
<td>rising</td>
<td>86.5</td>
<td>23.8</td>
</tr>
<tr>
<td></td>
<td>falling</td>
<td>87.8</td>
<td>22.6</td>
</tr>
<tr>
<td>Exp. no. 141</td>
<td>rising</td>
<td>122.1</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>falling</td>
<td>119.5</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Exp. no. 51

Exp. no. 141

FIG. 7. Effect of pneumatic sleeve 33 cm. long upon impact wave velocity over an intact arterial segment 42 cm. long. Abscissa, difference between recorded intra-arterial pressure and sleeve inflation pressure (both relative to atmospheric pressure) to demonstrate the similar velocities of impacts at the same "effective" pressure.

Fig. 7. Effect of pneumatic sleeve 33 cm. long upon impact wave velocity over an intact arterial segment 42 cm. long. Abscissa, difference between recorded intra-arterial pressure and sleeve inflation pressure (both relative to atmospheric pressure) to demonstrate the similar velocities of impacts at the same "effective" pressure.

FIGURE 7. Effect of pneumatic sleeve 33 cm. long upon impact wave velocity over an intact arterial segment 42 cm. long. Abscissa, difference between recorded intra-arterial pressure and sleeve inflation pressure (both relative to atmospheric pressure) to demonstrate the similar velocities of impacts at the same "effective" pressure.

TABLE 3.—Effect of Inflation of a Sleeve about the Arm upon Radial Arterial Pressure, Pulse Wave and Impact Wave Transmission (exp. no. 158, 51 yr. male)

<table>
<thead>
<tr>
<th>Pressure in sleeve (mm. Hg)</th>
<th>Number of pulse beats measured</th>
<th>Average radial pressure (mm. Hg)</th>
<th>Average carotid-radial time* (msec./M.)</th>
<th>Impact wave average transmission time (msec./M.) at radial pressures</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>86.6±0.5f</td>
<td>60</td>
<td>116</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>70.3</td>
<td>50</td>
<td>126</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>70.8</td>
<td>31</td>
<td>148</td>
</tr>
<tr>
<td>50</td>
<td>6</td>
<td>74.8</td>
<td>15</td>
<td>222</td>
</tr>
<tr>
<td>70</td>
<td>4</td>
<td>87.5</td>
<td>18</td>
<td>257</td>
</tr>
</tbody>
</table>

* Time from onset of carotid pulse rise to onset of radial pressure rise corrected for relative instrumental delay.

f Standard error of mean.

pressure, the transmission times under the sleeve were increased for cardiac pulses as well as impact waves. The pressure velocity curve obtained could be virtually superimposed upon that obtained without sleeve inflation, by subtracting inflating pressure from the recorded pressure (fig. 7). This would support the observations of Hemingway and McSwiney for cuff pressures well below diastolic pressure. But as inflation pressure was increased further, two changes were noted: 1. Impact transmission became poorer so that sharp radial impact waves were usually not obtained when the pressure differential across the artery was less than 20 mm. Hg. 2. The radial minimal or local "diastolic" pressure increased. Therefore the delay in the cardiac pulse transmission superficially appeared to become much greater, because as the systolic pressure wave reached the sleeve a rise in radial pressure did not occur until the local radial pressure was exceeded by the wave front. This produced an additional delay in the onset of the radial pulse (table 3) which is not to be interpreted as the delay time due to wave propagation through an open tube. At these low effective transmural pressures, therefore, the inflated sleeve method may introduce error in conventional measurements.
The inflated sleeve technic also provided a distribution of impact waves over a wider pressure range. Additional comparisons could be made of the velocity of waves superimposed on constant and changing baselines at the same relative pressure, and in support of other observations no consistent differences were observed.

SUMMARY

A method is described whereby transient sharp pressure waves may be induced in the intact brachial artery of man. The imposed wall stretch is relatively small and rapid. These waves travel along the artery, and their propagation characteristics may be studied by suitable intra-arterial pressure records. Since these waves are superimposed on the ambient arterial pressure, a determination of the relation of wave velocity to momentary arterial pressure is facilitated. A marked dependence of impact wave velocity upon pressure is consistently encountered. The method offers the primary advantages that sharper inflections permit measurements to be made with greater accuracy and over shorter distances than is possible for the cardiac pulse. The effect of variation in operative blood pressure may be determined without recourse to procedures which (aside from the pressure itself) may alter the vessel wall as well. The method is critically evaluated.

ACKNOWLEDGMENT

The capable assistance of Baymond Flath, Jesse Yaffa, Eleanor Roach, and Leon C. Perry were essential to the execution of these studies.

SUMMARY IN INTERLINGUA

Es describite un methodo que permitte le induzione de transiente acute undas de pression in le intacte arteria brachial del homine. Le tension parietal assi imponite es relative basse e rapide. Le undas percorre le arteria, e le characteristicas propagational pote esser studiate per medio del pertinente registroesiones de pression intra-arterial. Proque iste undas es superimponite al ambiente pression arterial, le determinacion del relation inter velocitate del unda e momentanea pression arterial es simplificata. Un marcate dependencia del velocitate del undas de impacto super le pres-
sion es regularmente a notar. Le metodo ha le major avantaggio que in illo le plus acute inflexiones permite mesureiones de plus alte grados de exactitude e pro plus curte distantias que in le caso del pulso cardiac. Le effetto de variationes del pression sanguinee pote esser determinate sin recurso a procedimentos que risca alterar non solmente le pression mesme sed etiam le pariete del vas in question. Es presentate un evaluatione critica del metodo.

REFERENCES

A Method Using Induced Waves to Study Pressure Propagation in Human Arteries
MILTON LANDOWNE

Circ Res. 1957;5:594-601
doi: 10.1161/01.RES.5.6.594

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/5/6/594

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/