Effects of Intra-Aortic Balloon Counterpulsation on Cardiac Performance, Oxygen Consumption, and Coronary Blood Flow in Dogs

By Wm. John Powell, Jr., M.D., Willard M. Daggett, M.D., Alfred E. Magro, Jesus A. Bianco, M.D., Mortimer J. Buckley, M.D., Charles A. Sanders, M.D., Arthur R. Kantrowitz, Ph.D., and W. Gerald Austen, M.D.

ABSTRACT
The effect of intra-aortic counterpulsation (IACP) with a balloon upon myocardial oxygen consumption (MVo$_2$), coronary blood flow (TCF), and left ventricular performance was studied in 23 anesthetized canine right heart bypass preparations at constant heart rate and cardiac output. In nonhypotensive, non-TCF-limited preparations, IACP produced a fall in left ventricular peak systolic pressure (LVP) and a decrease in MVo$_2$ (-1.1 ± 0.2 (se) ml/min/100 g LV). In these animals there was little steady state change in TCF (-5.6 ± 5.9 ml/min), secondary to autoregulation by the coronary vascular bed. Left ventricular end-diastolic pressure (LVEDP) fell if elevated but exhibited little change if initially normal.

However, in hypotensive preparations, in which left ventricular performance was substantially limited by a decreased TCF, IACP produced a striking increase in TCF (+40.9 ± 8.6 ml/min) accompanied by an increase in MVo$_2$ (+1.2 ± 0.3 ml/min/100 g LV). Elevated LVEDPs fell substantially toward normal. Directionally similar changes in LVEDP could be produced by increasing TCF alone in the absence of balloon pumping. When TCF was maintained constant in the hypotensive, TCF-limited preparation, IACP produced a fall in peak LVP and LVEDP.

These data document two effects of intra-aortic balloon counterpulsation upon cardiac dynamics: (1) IACP can decrease left ventricular peak systolic pressure and LVEDP independent of changes in coronary flow; (2) a major effect of IACP in the hypotensive, failing, TCF-limited preparation is to improve cardiac performance by increasing TCF with an associated increase in MVo$_2$.

ADDITIONAL KEY WORDS
diastolic augmentation tension-time index autoregulation of coronary flow ventricular function
physiologic rationale (1-3). The development of an intra-aortic balloon pump simplifies substantially the application of this principle.

Previous investigations of the effects of external arterial counterpulsation, with particular reference to myocardial oxygen consumption and coronary blood flow, have yielded varying results (4-6). The present study is an attempt to clarify these divergent data and to elucidate underlying mechanisms of the action of intra-aortic balloon pumping. Specifically, a comparison was made of the effect of intra-aortic balloon counterpulsation on cardiac dynamics in two situations: (1) The low cardiac output, low coronary flow state which is associated with a high left ventricular end-diastolic pressure, and (2) the high cardiac output and coronary flow state with an associated low end-diastolic pressure.

Methods

Experiments were performed in 23 adult dogs of both sexes weighing between 28 and 64 kg, anesthetized with intravenous chloralose (60 mg/kg) and urethan (600 mg/kg). A tracheostomy was performed and ventilation with 100% oxygen with an Emerson constant-volume respirator. The chest was opened through a median sternotomy. A right heart bypass preparation, which has been previously reported (7), was employed.

After intravenous administration of Heparin, 3 mg/kg, the superior and inferior venae cavae were cannulated and the azygous vein was divided. The caval return was directed to a reservoir, through a bubble oxygenator and heat exchanger (37°C ± 0.5°C) and returned through a variable speed calibrated roller pump to the main pulmonary artery. The rate of pumping into the pulmonary artery controlled cardiac input. Deliberate decreases of the left ventricular input could then be made to obtain a low cardiac output and low coronary flow state, wherein myocardial performance was limited by the low coronary blood flow (8). The use of a bubble oxygenator allowed the option of switching to total cardiopulmonary bypass by altering the route of systemic perfusion from the pulmonary artery to the aorta (through the left subclavian artery). This was helpful in preventing irreversible distension of the left ventricle when the cardiac input was lowered to an extent that coronary flow was inadequate to support cardiac function. A ligature placed around the pulmonary artery completed isolation of the right heart which then received only coronary venous drainage.

Total coronary flow (minus left ventricular Thebesian flow) was led by siphon drainage from the cannulated right atrium and ventricle through a Shipley-Wilson rotameter (9) to the venous reservoir. The rotameter was calibrated at intervals during each experiment by timed volumetric collections of coronary venous blood. Although right ventricular and right atrial pressures were not monitored, the walls of both chambers appeared flaccid throughout the experiments and at no time was visible distension of either chamber noted. As a result of the different responses to balloon pumping which appeared related to the control level of coronary blood flow, the data were analyzed in terms of those animals in which control coronary blood flow was greater than, versus those animals in which control coronary flow was less than, the arbitrary figure of 50 ml/min/100 g left ventricle (wet weight).

Left ventricular pressure and left ventricular diastolic pressure were measured through a short, wide bore Y-shaped metal cannula inserted through the apex of the left ventricle. Proximal and distal aortic pressures were measured through short polyethylene catheters inserted into the aortic arch and distal aorta through the left carotid and right femoral arteries, respectively. In none of the experiments during counterpulsation was there a change in the animal’s peak systolic pressure relationship between the proximal and distal aorta. The largest peak systolic gradient seen across the balloon and catheter when the balloon was deflated was 15 mm Hg. All pressures were measured with Statham P23db transducers; the frequency response of the pressure measurement system was linear up to 30 cps. The rate of rise of left ventricular pressure \((dP/dt)\) was obtained by R. C. electronic differentiation of the full left ventricular pressure. Calibration of the \(dP/dt\) differentiator was accomplished by supplying a waveform of known slope to the differentiating circuit, which has a time constant of 0.001 sec and a cut off at 160 cps. In several experiments a mercury-in-silastic gauge (10) was used for the continuous measurement of the left ventricular external circumference.

In 13 of the larger animals a three-segment (20 cc capacity), and in 10 of the smaller animals a single-segment (15 cc capacity) Avco-M.C.H.1 \(^1\) intra-aortic balloon (11) was inserted through the left femoral artery into the thoracic aorta and positioned just distal to the left subclavian artery. The three-segment balloon had a capacity of 20 cc.

\(^3\)Avco-Evenett Research Laboratory-Massachusetts General Hospital.

Circulation Research, Vol. XXVI, June 1970
CARDIAC EFFECTS OF BALLOON COUNTERPULSATION

The continuous recording of the analyzer performance of each experiment by blood-gas determinations was pumped at a known constant rate through a multichannel Sanborn direct-writing oscillograph or an eight channel Beckman type S-II direct-writing oscillograph.

After the sinoatrial node was crushed, the heart rate was maintained constant during any one experiment by either atrial pacing or synchronous A-V pacing at an A-V interval of 90 to 100 msec by a Medtronic R Wave Coupled Pulse Generator (Model 5837).

Coronary arterial and venous blood was pumped at a known constant rate through a Guyton A-Vo2 analyzer which was calibrated for each experiment by blood-gas determinations done by the method of Van Slyke and Neill (12). The continuous recording of the analyzer permitted documentation of steady states in coronary A-V O2 difference. However, calculations of myocardial oxygen consumption (MVo2) were based on A-V O2 differences obtained directly with Van Slyke determinations. MVo2 was expressed as the product of minute coronary flow and coronary arteriovenous oxygen difference in milliliters per minute per 100 g of left ventricle (wet weight). MVo2 determinations (unless otherwise specified) were carried out after 13 to 20 minutes of counterpulsation to allow achievement of a steady state of both coronary flow and of the A-V O2 difference. Postpump control values were obtained between 7 and 11 minutes after balloon pumping had been discontinued. Although the recordings from brief runs of counterpulsation without oxygen determinations will be presented for illustration of the observed hemodynamic effects of intra-aortic balloon counterpulsation, all data plotted on the summary charts and present in the table represent experiments of the described duration. The hemodynamic effects in the experiments with and without oxygen determinations were similar.

Ventricular function curves were constructed as previously described (13). Mean aortic pressure during ejection was used as the mean systemic pressure for the calculation of stroke work. The tension-time index (TTI) was calculated according to the method of Sarnoff and co-workers (14). The duration of ejection is defined by the interval between the onset of aortic pressure rise and the dicrotic notch.

In three animals, the basic preparation was varied to allow for control of left coronary inflow. In these experiments the left coronary artery was perfused directly through a Gregg cannula from either the dog’s brachiocephalic artery (autoperfusion) or through a roller pump which allowed control of left coronary inflow. Coronary perfusion pressure was measured with a Statham P23db transducer attached to the coronary perfusion line.

Autonomic blockade was effected in all animals by the beta-receptor blocking agent propranolol (Inderal, 0.5 mg/kg) or by ganglionic blockade with mecamylamine hydrochloride (Inversine, 10 mg/kg), or both. Beta-receptor blockade was verified at the completion of the experiment by the absence of a chronotropic or inotropic response to 5 μg isoproterenol injected into the pulmonary artery.

Results

The hemodynamic effects of intra-aortic balloon counterpulsation (IACP) in the heart with a left ventricular end-diastolic pressure of less than 15 cm H2O are shown in Figure 1, which is representative of the effects seen in five experiments in four animals (Table 1, column 1). Peak systolic left ventricular pressure consistently fell in this group of animals and left ventricular end-diastolic pressure (LVEDP) and left ventricular circumference (LVC), when measured, changed little as a result of balloon pumping. Similarly, the maximal rate of rise of left ventricular pressure (max dP/dt) showed only insignificant small decreases under conditions wherein elevation of the LVEDP was not present in the control period. Of particular note in this

---

2Oxford Instrument Co., Jackson, Mississippi.

Circulation Research, Vol. XXVI, June 1970
Hemodynamic effects of balloon pumping in the heart with a left ventricular end-diastolic pressure (LVEDP) < 15 cm H$_2$O and a high coronary flow. LVP = left ventricular pressure; LVC = left ventricular circumference; LVDP = left ventricular diastolic pressure; AP = aortic pressure; LV dp/dt = rate of rise of left ventricular pressure; TCF = total coronary blood flow. Note lack of significant change in coronary flow.

Hemodynamic effects of balloon pumping in the heart with an LVEDP > 15 cm H$_2$O and a high coronary flow. Tracing from the same animal as that in Figure 1. Abbreviations as in Figure 1. Note lack of significant change in coronary blood flow.
TABLE 1
Effect of Intra-Aortic Balloon Counterpulsation as a Function of Coronary Blood Flow

<table>
<thead>
<tr>
<th>Flow &gt; 50 ml/min/100 g LV</th>
<th>Flow &lt; 50 ml/min/100 g LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal LVEDP*</td>
<td>Elevated LVEDP†</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>TCF (ml/min)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>+14.6 ± 8.8</td>
</tr>
<tr>
<td>Δ</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>MV0₂ (ml/min/100 g LV)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>8.5 ± 1.4</td>
</tr>
<tr>
<td>Δ</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>Peak LVP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>92 ± 15</td>
</tr>
<tr>
<td>Δ</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>TTI (mm Hg/sec)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1762 ± 273</td>
</tr>
<tr>
<td>Δ</td>
<td>&lt; 0.010</td>
</tr>
<tr>
<td>Max dP/dt (mm Hg/sec)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2473 ± 779</td>
</tr>
<tr>
<td>Δ</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>MER (ml/systolic sec)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>6.1 ± 1.8</td>
</tr>
<tr>
<td>Δ</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>LVEDP (cm H₂O)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>23.3 ± 2.5</td>
</tr>
<tr>
<td>Δ</td>
<td>&lt; 0.025</td>
</tr>
</tbody>
</table>

Abbreviations: LV = left ventricle; TCF = total coronary blood flow; MV0₂ = myocardial oxygen consumption; Peak LVP = peak left ventricular pressure; TTI = tension-time index; Max dP/dt = maximum rate of rise of the left ventricular pressure; MER = mean systolic ejection rate; LVEDP = left ventricular end-diastolic pressure; NS = not statistically significant; C = control; Δ = change. Values are means ± SE.

*Five experiments in four dogs.
†Six experiments in five dogs.
‡Seven experiments in six dogs.

A group of experiments was the observation that coronary blood flow did not change significantly (mean change: −14.6 ± 8.8 ml/min) during IACP.

Figure 2 is representative of the hemodynamic effects of balloon pumping seen in six experiments in five animals when elevated end-diastolic pressures (LVEDP > 15 cm H₂O) were induced acutely by increasing cardiac output. In these animals IACP consistently induced an initial fall in the left ventricular end-diastolic pressure which, however, was not sustained throughout the period of balloon pumping (Table 1, column 2). In addition, there was again no significant change in coronary blood flow (mean change: +2.0 ± 7.1 ml/min). Consistent correlates of the lack of change in coronary flow (−5.8 ± 5.9 ml/min) in the four hearts with normal LVEDP and the five hearts with elevated LVEDP were the presence of a "high" coronary flow in the control period and the appearance of autoregulation of coronary blood flow (Fig. 3) during balloon pumping.

In seven experiments in six animals in which...
coronary blood flow was initially "low," (in six experiments in five animals as a result of a sustained decrease of cardiac output) and in which systemic hypotension and failure were present, IACP caused consistent marked increases in coronary blood flow (mean change: +40.9 ± 8.6 SE ml/min) (Table 1, column 3). In this group of animals with initially low coronary flows, autoregulation of flow by the coronary vascular bed was effectively overcome by balloon pumping (Fig. 4). That these increases in coronary blood flow cannot be attributed solely to obstruction of the aorta as a result of balloon inflation is shown by the fall in left ventricular peak systolic pressure which accompanied a dramatic increase in coronary flow under conditions of severe hypotension and failure. Accompanying the increase in coronary blood flow in this group of animals was a substantial and sustained fall in left ventricular end-diastolic pressure. The effects of balloon pumping on coronary blood flow in those animals in which coronary flow was initially low (less than 50 ml/min/100 g LV) versus those animals in which coronary flow was high (greater than 50 ml/min/100 g LV) are summarized in Figure 5. The results are expressed as percent change in coronary blood flow.

In both the above groups of animals with initially high coronary flows, myocardial oxygen consumption (MVO₂) decreased significantly during IACP (-1.1 ± 0.2 ml/min/100 g LV; P < .005). These data are from 11 experiments in seven animals. In these animals TTI also decreased (-204 ± 69 mm Hg·sec/min) significantly (P < 0.025). In contrast, the animals in which coronary flow was initially low showed a significant increase in MVO₂ (+1.2 ± 0.3 ml/min/100 g LV) during balloon pumping (Table 1, column 3). In this group MVO₂ increased despite a decrease in TTI and LVEDP. The oxygen consumption data from each experiment are shown in Figure 6.

To understand better the influence of balloon pumping on ventricular performance, ventricular function curves were constructed from data from two animals in which coronary flow was initially normal and subsequently fell to low levels in association with hypotension and failure. Figure 7 is representative of the
CARDIAC EFFECTS OF BALLOON COUNTERPULSATION

FIGURE 5
Influence of intra-aortic balloon counterpulsation on coronary blood flow as a function of control coronary flow before initiation of balloon pumping. C = control; CP = during intra-aortic balloon pumping. Left panel: Animals in which control coronary flow was greater than 50 ml/min/100 g LV. Solid lines and solid circles show data from experiments with initially normal end-diastolic pressures; broken lines and solid or open circles indicate those with elevated control end-diastolic pressures. Broken lines and open circles show duration of CP, 6, 9 minutes. Right panel: Animals in which control coronary flow was less than 50 ml/min/100 g LV. In the right hand panel all dogs had elevated control left ventricular end-diastolic pressures. Other abbreviations same as in Figure 1.

results seen; the plot on the left (labeled A) shows that at a high coronary flow IACP results in a shift (arrows) downward along the same ventricular function curve. The quantitative decrease in LVEDP with counterpulsation is directly proportional to its control level. The points labeled B on the right show the effect of balloon counterpulsation on ventricular function when coronary flow is initially low. In this situation there is a substantial lowering of LVEDP with little change in ventricular stroke work. This latter effect is further illustrated in Figure 8 which depicts a tracing obtained from another animal with impaired coronary flow. This experiment which showed no change in peak left ventricular pressure with IACP was accompanied by the greatest increase of TCF seen in any of the experiments. This effect was reproducible three times in the same animal.

The suggestion of a relationship between TCF and the level of peak left ventricular pressure is supported by the data shown in Figure 9. In this experiment peak left ventricular pressure was initially lowered by the balloon with a concomitant fall in LVDP at a time when coronary flow had, as a result of autoregulation, increased little. Subsequently coronary flow increased progressively with...
Ventricular function consequent to balloon pumping. Solid circles = control points. Open circles = steady state LVEDP during balloon pumping. Arrows indicate drop of LVEDP as a result of balloon pumping. (A) in heart with coronary flow greater than 50 ml/min/100 g, LV; (B) in failing heart with limited coronary flow. See text.

Figure 7

Effects of balloon pumping on failing heart with limited coronary flow. Abbreviations as in Figure 1. Note the following with balloon pumping: (1) decrease of LVEDP and LVC; (2) increase of coronary flow and max dP/dt; (3) lack of change of left ventricular peak systolic pressure. Cardiac output = 1300 ml/min. (Stretching may account for distortion of the phasic changes of the circumference tracing.)

Figure 8

a parallel small increase in peak left ventricular pressure and max dP/dt, and a further fall in LVDP. Figure 10 offers an assessment of the independent effects of increasing TCF and of systolic unloading as a function of IACP upon ventricular performance and is illustrative of the data from each of three animals. Pre- and postcontrol panels numbered 1 and 4 show the expected increase in TCF with a small decrease in peak LVP, and a lowering of LVEDP with counterpulsation in the animal with an initially low coronary flow. When left coronary artery inflow was maintained constant as shown in panel 2, IACP resulted in directionally similar changes in both peak LVP and LVEDP. However, selective increase in left coronary inflow in the absence of IACP (panel 3) causes, in addition to a lowering of end-diastolic pressure, an increase in peak LVP and max dP/dt. Thus, in the low coronary flow state IACP contributed to a fall in LVEDP through both systolic unloading
 Sequential hemodynamic effects of balloon pumping. Abbreviations as in Figure 1. Note initial fall of LVEDP with onset of balloon pumping with little steady state change in coronary flow. Subsequent increases of coronary flow during balloon pumping are followed by a further fall of LVEDP and rise in peak LVP and max dP/dt.

Discussion

The data presented provide a basis for interpretation of the hemodynamic effects of intra-aortic balloon counterpulsation. These effects importantly relate to the functional state of the heart before the initiation of balloon pumping. If coronary blood flow and cardiac output are not initially low, autoregulation (15) of coronary flow occurs and counterpulsation is not associated with a steady-state change of coronary flow under the conditions described. However, if coronary blood flow is low in association with a low cardiac output, autoregulation does not occur and coronary flow increases with intra-aortic balloon counterpulsation.

This lack of autoregulation in the low coronary flow state is probably in large part secondary to overriding of the autoregulatory response by metabolic factors. It is unlikely that the sustained elevation of coronary flow is entirely secondary to a lowering of end-diastolic pressure consequent to "systolic unloading" by the balloon. Although Gregg (16) has suggested that extravascular compression may impede coronary flow, if this mechanism was solely responsible for the increased coronary blood flow observed during balloon pumping, then one would have expected coronary blood flow to increase during balloon pumping in hearts with a high cardiac output and high end-diastolic pressure but initially normal coronary flow. As was shown in Figure 2, this did not occur. It seems more likely that low coronary flow, per se, limits the performance of the heart and that diastolic augmentation, through raising the diastolic coronary perfusion pressure when the coronary vasculature is maximally or near maximally vasodilated, results in an increase of coronary flow. This increased flow through biochemical reconstitution of the myocardium contributes to the fall in end-diastolic pressure; the decrease of LVEDP in turn may further improve coronary flow.

The increases in myocardial oxygen consumption seen during counterpulsation in hearts which were coronary flow limited, in terms of performance, suggest that these hearts were also limited in terms of oxygen delivery. It has been demonstrated that at critically low levels of coronary flow there is a parallel relationship between coronary blood flow and myocardial oxygen consumption (17-19). Furthermore, as shown in Table 1, the increase in oxygen consumption noted with balloon pumping in the coronary flow limited
heart occurred despite either little change or a substantial decrease in those hemodynamic variables thought to influence myocardial oxygen consumption (14, 20-22).
These observations on oxygen utilization are supported by the findings of Hirsch et al. (6) who employed external arterial counterpulsation. In the present experiments intra-aortic balloon pumping in the coronary flow limited heart increased oxygen delivery with a parallel increase in oxygen utilization and an associated improvement of myocardial performance.

In the coronary flow limited heart both the effect of increasing coronary flow and the effect of systolic unloading can contribute to improved left ventricular performance. In the present study it has been possible to separate the relative contributions of systolic unloading and of increasing coronary flow secondary to intra-aortic balloon pumping. When the heart is severely coronary flow limited, balloon counterpulsation may, through an associated large increase in coronary blood flow, produce a salutary effect of sufficient magnitude to mask the unloading effect of balloon pumpng.

The present experiments were carried out under conditions wherein cardiac metabolism, intrinsic coronary vascular tension, and intramyocardial pressures were the dominant factors controlling coronary vascular resistance. They differ from the disease state in that heart rate, cardiac output, and autonomic activity were held constant. Whereas elevation of the end-diastolic pressure and hypotension in the present experiments were not the result of deliberately produced discrete myocardial lesions, the effect of intra-aortic balloon counterpulsation should be directionally similar in a pathologic situation characterized by hypotension and impaired myocardial function secondary to decreased coronary blood flow. In the present experiments this pathologic state was produced in most instances by lowering cardiac output and thus arterial pressure; it is of interest, however, that a large ventricular septal hematoma in one heart was associated with systemic hypotension and diminished coronary flow at a high cardiac output (see Fig. 8). Counterpulsation in this instance too produced a striking increase in coronary flow and improvement of ventricular performance.

The data presented indicate that the effects of intra-aortic balloon counterpulsation are most evident in those situations wherein myocardial performance and coronary blood flow are severely impaired. Not unexpectedly, this mode of mechanical cardiac support produces less striking hemodynamic effects in those instances in which intrinsic myocardial performance is not impaired. Intra-aortic balloon counterpulsation, through the mechanisms of systolic unloading and augmentation of coronary flow, can effectively assist and aid in the reconstitution of the failing coronary flow limited heart.

Acknowledgment

We gratefully acknowledge the technical assistance of Mr. Roy Teixeira, Mr. John Dewey, Mr. Marc Newman, Mr. John Hinckley and Miss Barbara Soscia.

References


Effects of Intra-Aortic Balloon Counterpulsation on Cardiac Performance, Oxygen Consumption, and Coronary Blood Flow in Dogs

WM. JOHN POWELL, WILLARD M. DAGGETT, ALFRED E. MAGRO, JESUS A. BIANCO, MORTIMER J. BUCKLEY, CHARLES A. SANDERS, ARTHUR R. KANTROWITZ and W. GERALD AUSTEN

Circ Res. 1970;26:753-764
doi: 10.1161/01.RES.26.6.753
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1970 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/26/6/753

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/