Improved Regional Myocardial Blood Flow, Left Ventricular Unloading, and Infarct Salvage Using an Axial-Flow, Transvalvular Left Ventricular Assist Device

A Comparison With Intra-Aortic Balloon Counterpulsation and Reperfusion Alone in a Canine Infarction Model

Richard W. Smalling, MD, PhD; David B. Cassidy, MD; Robert Barrett, MD; Bruce Lachterman, MD; Patty Felli, BS; and James Amirian, BS

Background. It has been suggested that left ventricular unloading at the time of reperfusion provides superior infarct salvage over reperfusion alone. The purpose of this study was to show that the Hemopump transvalvular axial-flow left ventricular assist device provides superior left ventricular unloading, ischemic zone collateral blood flow, and infarct size reduction compared with intra-aortic balloon counterpulsation and reperfusion alone.

Methods and Results. Eighteen dogs were instrumented with regional myocardial function sonomicrometers in the ischemic and control zones. The left anterior descending coronary artery just distal to the first diagonal branch was instrumented with a silk snare and Doppler flow probe. Additionally, pressure catheters were placed in the left atrial appendage, left ventricular apex, and ascending aorta for hemodynamic measurements. Regional myocardial blood flow was determined by using 15-μm radioactive microspheres. Measurements were made in the control state, immediately after coronary occlusion, at 1 and 2 hours after coronary occlusion, with reperfusion, and 1 hour after reperfusion. In treated animals, left ventricular assistance was maintained during the entire period of occlusion and reperfusion. The Hemopump was associated with a significant decrease in left ventricular systolic and diastolic pressure, whereas mean arterial pressure was maintained. Intra-aortic balloon counterpulsation resulted in no significant changes in left ventricular systolic pressure and a modest decrease in left ventricular diastolic pressure. Regional unloading as assessed by sonomicrometers was significant in the Hemopump animals and absent in the balloon pump animals. Absolute regional myocardial blood flow in the ischemic zone increased slightly (p = 0.002) in the Hemopump animals and did not change in the balloon pump animals. Infarct size expressed as percentage of the zone at risk was 62.6% in the control animals, 27.22% in the balloon pump animals, and 21.7% in the Hemopump animals.

Conclusions. Mechanical unloading of the ventricle during ischemia and reperfusion appears to result in significant infarct salvage compared with reperfusion alone. The Hemopump appears to provide superior left ventricular systolic and diastolic unloading compared with intra-aortic counterpulsation in a canine model. (Circulation 1992;85:1152–1159)

Key Words • myocardial infarction • coronary disease • reperfusion injury • left ventricular assist device

The concept of salvage of ischemic myocardial tissue by reperfusion therapy has been suggested by animal1 and human2 studies. Some investigators have reported that the level of collateral flow to the bed at risk determines ultimate infarct size; others have suggested that the amount of collateral flow and degree of functional recovery are not correlated.4

An additional possible benefit of reperfusion therapy is the concept that late reperfusion may not salvage left ventricular (LV) tissue or function but may limit infarct expansion.5 Additionally, reperfusion may induce further myocardial damage; however, there is no clear consensus regarding the extent or possible modification of this problem.6 Recent interest has focused on the actions of free radicals and use of free radical scavengers at the time of reperfusion. Unfortunately, at the present time, these studies have yielded conflicting results possibly because of differences in models and agents used.7,8

With the development of interventional techniques for salvaging ischemic myocardium, mechanical support of
the ischemic left ventricle is another possible therapeutic modality. Some investigators have reported modest improvement in ischemic bed collateral flow by using intra-aortic balloon counterpulsation. Others have suggested there is minimal LV unloading or increase in ischemic zone collateral flow with balloon counterpulsation.

An extremely aggressive approach that uses total cardiopulmonary bypass, LV venting, and cardioplegia before reperfusion has demonstrated a decrease in infarct size to 12% compared with 44% of the region at risk by using reperfusion alone. This technique would be impractical for widespread application.

A small, axial-flow, transvalvular LV assist device (the Hemopump Cardiac Assist System, Johnson and Johnson Interventional Systems Co.) has been developed that is capable of significant LV unloading and circulatory support and is considerably less invasive than total cardiopulmonary bypass. We have previously demonstrated that this device improved collateral blood flow to ischemic tissue and reduced regional work. The purpose of this study was to show that the Hemopump provides superior LV unloading, improvement in ischemic zone collateral flow, and infarct size reduction compared with intra-aortic balloon counterpulsation and reperfusion alone.

Methods

Animal Instrumentation

Eighteen mongrel dogs of either sex weighing 25–33 kg were anesthetized intravenously with 30 mg/kg pentobarbital and maintained with Inovar-Vet (20 mg droperidol and 0.4 mg fentanyl/ml). The dogs were intubated and maintained on a volume ventilator. A left lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was isolated, and a silk snare was placed just distal to the first diagonal branch. A Doppler flow probe was placed proximal to the snare for monitoring coronary blood flow. Sonomicrometer crystals were implanted in the circumferential direction, midway between the base and the apex in the LV midwall in the distribution of the LAD and circumflex coronary arteries. A catheter was placed through a stab wound in the LV apex for measurement of LV pressure. A catheter was placed in the left atrium for injection of microspheres, and an additional catheter was placed in the ascending aorta for measurement of arterial blood pressure and for blood sampling during microsphere injections. In six animals, the Hemopump was placed through a low midline laparotomy into the common iliac arteries and advanced retrogradely under fluoroscopic control across the aortic valve. In six animals, a 40-ml Dataspoke intra-aortic balloon catheter was placed via cutdown on the left femoral artery and advanced under fluoroscopic control to the ascending aorta just distal to the brachiocephalic vessels. In the balloon pump animals, the contralateral femoral artery was instrumented with an arterial pressure catheter to ensure that the aorta was not totally occluded during intra-aortic counterpulsation. Six additional animals did not receive LV assist devices and were used as controls.

Control Measurements

After instrumentation and stabilization, baseline measurements of ECG, phasic and mean aortic pressure, LV pressure, and regional end-diastolic segment lengths and segmental shortening in the circumflex and LAD regions were recorded. Three to 5 million 15-μm radioactive microspheres (SEN-TRAC, DuPont) were injected in a volume of 1 ml through the left atrial catheter over 30 seconds, followed by 10 ml of normal saline. During the microsphere injection, arterial blood was continuously withdrawn from the ascending aorta for a period of 2 minutes with the use of a Harvard pump. After baseline control measurements, LV assistance was initiated in the Hemopump animals and the intra-aortic balloon animals. In the Hemopump animals, maximum flow was used (3.0–3.5 l/min, depending on mean arterial pressure and LV filling pressure). With the intra-aortic balloon pump, maximum augmentation was used provided that femoral artery pressure was not adversely affected. If it was evident that the intra-aortic balloon pump was occluding the aorta, the degree of augmentation was then reduced slightly from 40 ml to approximately 35 ml per beat. The above hemodynamic and microsphere measurements were repeated during LV assistance with the Hemopump or the balloon pump. After baseline measurements were obtained, the snare was tightened around the LAD to occlude it. Doppler flow measurements confirmed the occlusion of the LAD distal to the first diagonal. The ECG and rhythm were monitored with premature ventricular contractions being treated with intravenous lidocaine. Five minutes after LAD occlusion, hemodynamic and microsphere measurements were repeated on and off pump support.

After 2 hours of LAD occlusion, repeat hemodynamic measurements were obtained with and without LV assistance. The LAD snare was then released, and reperfusion was confirmed by Doppler flow measurements. Hemodynamic measurements were then repeated both with and without the LV assistance. LV assistance was continued for an additional 1-hour period of reperfusion in the Hemopump and intra-aortic balloon pump dogs. After 1 hour of reperfusion, measurements were repeated on and off assistance. Subsequent to the final hemodynamic measurements, the animals were killed with an injection of supersaturated potassium chloride. The hearts were immediately excised, rinsed in cold tap water, and trimmed of excess fat. The left ventricle was isolated, weighed, and sliced from base to apex in five to six 1-cm-thick sections. Each slice was then weighed and placed in freshly prepared 1% solution of triphenyltetrazolium chloride (TTC) and incubated for 45 minutes at 37°C to delineate viable and infarcted myocardium. Stained slices were then photographed for subsequent planimetry to determine infarct size. Microsphere flow measurements were obtained by dividing each slice into 1-g pieces that were identified and mapped on the photograph, thereby creating a flow map of each slice in 1-g subsections. The samples were analyzed according to the method of Heymann. The ischemic zone was determined to be that portion of the myocardium receiving less than 25% of blood flow delivered to the control (circumflex) region. The infarct size was expressed as a percentage of the region at risk determined by the low-flow segments. The area of the low-flow segments divided by the total area of each slice was multiplied by the weight of each slice and summed for the entire ventricle to determine.
the mass of tissue receiving low flow (region at risk). The infarct size fraction was determined by planimetricing the area of the TTC-negative-stained tissue in each slice and dividing by the total area of the slice. The infarct area fraction was multiplied by the weight of each slice and summed slice-by-slice to determine the mass of infarcted tissue. The infarct mass was then divided by the region-at-risk mass to determine the infarct size as a percentage of the region at risk.

**Statistical Analysis**

A sample size of six animals per group was chosen to detect large (50%) changes between the groups in perfusion to the ischemic zone, infarct size, and hemodynamic parameters. One animal was excluded from the analysis in the balloon pump group because of the presence of high collateral blood flow (>0.3 ml/g/min) to the ischemic zone during the control occlusion. The experiments were not done in a preconceived random fashion; however, there was considerable mixing of the groups studied so that each group was not studied consecutively.

All data were expressed as mean±SD and analyzed by using the paired (when applicable) or unpaired Student's t test. Statistical significance was assigned a probability value of less than 0.05.

**Results**

Representative tracings from one of the Hemopump animals are shown in Figures 1A and 1B. In the control state, institution of Hemopump LV assistance produced a diminution of LV systolic and diastolic pressure and a reduction in LAD as well as circumflex regional segmental end-diastolic dimension. During severe LAD ischemia, holosystolic paradoxical motion in the region of the LAD was uniformly demonstrated. LV end-diastolic pressure also increased in the majority of animals. With Hemopump LV support, however, LV segmental end-diastolic dimensions decreased, and there was minimal systolic paradoxical motion in the LAD region. Simultaneously, LV systolic pressure was markedly decreased and mean aortic pressure was maintained. As demonstrated by Figure 1B, at the end of a 2-hour LAD occlusion (during Hemopump support) the left ventricle ceased to eject, which provided a positive pressure gradient across the coronary collateral bed throughout the cardiac cycle.
Effect of Left Ventricular Assistance on Hemodynamics

The effect of Hemopump LV assistance during LAD ischemia on hemodynamic parameters is depicted in Table 1. In the control state and during progressive LAD ischemia, there was no change in heart rate throughout the experiment. Mean arterial pressure was fairly consistently increased by institution of Hemopump support. Similarly, LV systolic pressure was diminished as was LV end-diastolic pressure with Hemopump support. In Table 2, the effect of the intra-aortic balloon pump on hemodynamics during LAD ischemia is shown. Similar to the Hemopump, the balloon pump produced little change in heart rate throughout the period of the experiment. Mean arterial pressure was not significantly changed by the balloon pump; however, there was a trend toward modest systolic LV pressure reduction. Generally, LV diastolic pressure did not appear to be affected by intra-aortic balloon counterpulsation except at 1 hour after reperfusion, when there was a slight but significant decrease in diastolic pressure.

Table 3 depicts the hemodynamic parameters during LAD ischemia in control animals. In general, the values are similar to both intra-aortic balloon pump and Hemopump animals in the absence of LV assistance. There was little change in these parameters throughout the duration of the experiment.

Figures 2A and 2B demonstrate the end-diastolic segment lengths in the distribution of the LAD in the control state and at the end of a 2-hour LAD occlusion with and without LV assistance. All three groups were evenly matched in terms of resting end-diastolic segment length in the control state at approximately 15 mm. With Hemopump support, in the control state, there was a significant diminution of end-diastolic segment length, suggesting a significant degree of diastolic LV unloading. There was no change in end-diastolic segment length with intra-aortic balloon counterpulsation. After 2 hours of LAD occlusion, the end-diastolic segment length was significantly decreased with Hemopump support and was not changed with intra-aortic balloon counterpulsation.

Effect of Left Ventricular Assistance on Regional Myocardial Blood Flow

The absolute regional myocardial blood flow values obtained in animals with and without LV assistance during regional ischemia are shown in Table 4. Resting myocardial blood flows in each group are well matched in the control state (0.58–0.69 ml/g/min). With initiation of Hemopump support in the control state, there was a trend toward decreased regional myocardial blood flow presumably secondary to autoregulation in the face of decreased mechanical work of the left ventricle, as we have previously described. With occlusion of the LAD, regional blood flow dropped approximately 90% in each group. This is a typical value for blood flow measurements in the zone of central ischemia in a dog model. In the control regions opposite the risk regions, there was a trend toward increased regional myocardial blood flow. With intra-aortic counterpulsation, there was no appreciable change in risk region blood flow or control region blood flow; however, with Hemopump LV assistance, the risk region blood flow increased slightly at the same time control myocardial blood flow decreased.

Miura and Downey et al have suggested that ultimate infarct size is more closely correlated with the ratio of ischemic zone flow compared with control zone flow than to absolute ischemic zone flow. In an attempt to control for autoregulation caused by changes in myocardial work, the myocardial blood flow was then
expressed as a ratio of ischemic zone blood flow to nonischemic zone blood flow in Table 5. In each group in the control state, in the absence of ischemia, this ratio was 1, as anticipated. Similarly, with the onset of ischemia, the ratio dropped to approximately 10% of control flow as typically seen with severe ischemia in the dog model. However, in the Hemopump animals, the blood flow ratio improved significantly despite the fact that absolute blood flow to the risk region remained at depressed levels (0.10 ml/g/min).

**Effect of Left Ventricular Assistance on Infarct Size**

A summary of infarct size data in control, balloon pump, and Hemopump animals is shown in Table 6. In general, the heart weights were similar, as were the risk regions, with a trend toward increased risk region in the Hemopump animals. The infarct size expressed as percentage of the region at risk in control animals was 62.6±15%. With intra-aortic balloon counterpulsation, this was reduced to 27% (p=0.01). With Hemopump support, the infarct size was further reduced to 21.7% (p=0.001). Although there was a trend toward smaller infarct size in the Hemopump dogs compared with the balloon pump dogs, this did not achieve statistical significance. Group data are depicted in Figure 3.

**Discussion**

For the past decade, attempts at infarct salvage in acute myocardial infarction in humans have focused on the optimal methods of achieving reperfusion as well as prevention of reocclusion. During this period of time, many investigators have looked more closely at animal models for means of augmenting salvage of ischemic myocardium as well as prevention of reperfusion injury. An extensive review recently published by Opie discussed the roles of leukocyte plugging, free radical liberation by leukocytes and their deleterious effect on the endothelium, ultrastructure, and metabolism. In

---

**TABLE 3. Hemodynamic Parameters During Left Anterior Descending Coronary Artery Ischemia in Control Animals**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>5-Minute occlusion</th>
<th>2-Hour occlusion</th>
<th>Reperfusion</th>
<th>1-Hour reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats per minute)</td>
<td>102±19</td>
<td>115±28</td>
<td>107±19</td>
<td>103±18</td>
<td>104±13</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>101±17</td>
<td>95±13</td>
<td>85±16</td>
<td>84±12</td>
<td>94±14</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>117±14</td>
<td>110±14</td>
<td>98±16</td>
<td>99±12</td>
<td>109±12</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>6±2</td>
<td>8±2</td>
<td>5±2</td>
<td>5±2</td>
<td>7±4</td>
</tr>
</tbody>
</table>

LV, left ventricular.

---

**Figure 2.** Panel A: Bar graph shows end-diastolic segment length in the left anterior descending (LAD) distribution in the control state with and without left ventricular assistance. Panel B: Bar graph shows end-diastolic segment length in the LAD region at the end of a 2-hour LAD occlusion with and without left ventricular assistance. IABP, intra-aortic balloon pump.
addition, Opie discussed the mechanisms of calcium and oxygen paradox in terms of deleterious effects of large quantities of oxygen and calcium rushing into reperfused tissues. Although much work has been done in this area, a consensus regarding the best methods of prevention of reperfusion injury as well as attenuation of myocardial stunning17 has yet to be determined.

Survival Versus Ultimate Left Ventricular Function

Although thrombolytic therapy has been associated with improved survival in randomized trials, improvement in LV function has been more difficult to demonstrate. We have previously suggested2 that improvement in LV performance did not necessarily correlate with time from onset of pain (presumed arterial occlusion) to reperfusion. The Thrombolysis in Myocardial Infarction investigators subsequently demonstrated similar findings.19 The possibility that late reperfusion was associated with lower infarct expansion was investigated by Hochman and Choo.5 They found, in rats, that late (2 hours) reperfusion was associated with lesser infarct expansion than in rats undergoing permanent coronary ligation. The mechanism of this reduced infarct expansion, however, remains unclear.

Van Winkle and colleagues19 found that infarct salvage was produced in a rabbit model by LV unloading. However, for significant infarct salvage to occur, the unloading was found to be necessary throughout the entire period of ischemia and reperfusion. Unloading during reperfusion alone was not associated with a reduction in infarct size.

Possible Role of Mechanical Interventions

Most investigators agree that some element of reperfusion injury does occur. It has been suggested that the demand state, collateral blood flow, and LV distensile pressures all may affect this phenomenon. Intra-aortic balloon counterpulsation is the most accessible method of LV assistance available to the practicing cardiologist. However, careful animal investigations as to the mechanism of this device6,10 have failed to definitively demonstrate improved coronary perfusion with intra-aortic balloon counterpulsation. Clinically, intra-aortic balloon counterpulsation can improve aortic diastolic pressure and has been associated with a fall in LV filling pressures and stabilization of patients who have a borderline hemodynamic status. In acute ischemic syndromes, however, unless definitive revascularization follows temporary LV support with aortic counterpulsation, it is generally felt that the prognosis is unchanged with intra-aortic balloon pumping. After our initial experience with the Hemopump in defining its hemodynamic actions in animals, we felt a direct comparison with other conventional LV assist devices was warranted.

Comparison of Axial-Flow, Transvalvular Left Ventricular Assistance With Intra-Aortic Balloon Counterpulsation

As reported in this study, it is clear that the Hemopump results in superior unloading of the left ventricle with a significant reduction in LV developed systolic pressures during ischemia and that mean arterial pressure was maintained at control levels. Additionally, the LV filling pressures appeared to be reduced to a much greater extent with the Hemopump than with the intra-aortic balloon pump. As one would anticipate, the myocardial blood flow to the ischemic region was improved with the Hemopump compared with the intra-aortic balloon pump. Despite this improvement in myocardial blood flow, as well as improved hemodynamics with the Hemopump, the change in overall infarct size as expressed as a percentage of the zone at risk was not significantly different between the two treatments.

One possible explanation for the findings would be that the balloon pump did decrease the mechanical work of the ventricle somewhat. Minimal changes in mechanical work may significantly improve infarct salvage. Second, the absolute regional myocardial blood flow in the Hemopump animals with LV assistance still

| Table 4. Regional Myocardial Blood Flow With and Without Left Ventricular Assistance |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Absolute flows (ml/g/min)       |                 |                 |                 |                 |                 |                 |                 |
|                                | Control group   | IABP           | Hemopump group  |                 |                 |                 |                 |
|                                | Off             | On             | Off             | On             | Off             | On             |                 |
| Control region                 | 0.69±0.17       | 0.59±0.18      | 0.64±0.16       | NS             | 0.67±0.26       | 0.62±0.27       |                 |
| Risk region                    | 0.69±0.30       | 0.63±0.19      | 0.64±0.19       | NS             | 0.64±0.18       | 0.65±0.26       |                 |
| LAD ischemia                   |                 |                 |                 |                 |                 |                 |                 |
| Control region                 | 0.89±0.14       | 0.61±0.17      | 0.64±0.15       | NS             | 0.82±0.32       | 0.59±0.28       | 0.04            |
| Risk region                    | 0.06±0.03       | 0.53±0.03      | 0.05±0.03       | 0.009          | 0.05±0.01       | 0.10±0.02       | 0.002           |

IABP, intra-aortic balloon pump; LAD, left anterior descending.

| Table 5. Regional Myocardial Blood Flow Expressed as a Ratio of Ischemic Zone/Nonischemic Zone |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Control state   |                 | LAD ischemia    |                 |
|                                | Off             | On             | Off             | On             |
| Control                        | 1.00±0.25       | ...            | 0.08±0.05       | ...            |
| IABP                           | 1.08±0.18       | 0.99±0.13      | NS              | 0.09±0.04       | 0.07±0.03       | NS              |
| Hemopump                       | 1.00±0.13       | 1.00±0.25      | NS              | 0.07±0.03       | 0.21±0.12       | 0.02            |

LAD, left anterior descending coronary artery; IABP, intra-aortic balloon pump.
remains severely depressed despite the fact that the blood flow ratio improved rather dramatically. With Hemopump support, the collateral blood flow was only 0.10 ml/g/min, which is consistent with continued severe ischemia. This suggests that the most important effect of the Hemopump is the unloading effect in combination with reduced mechanical work and concomitant reduced oxygen consumption. Another potential mechanism for improved infarct salvage in the mechanical assistance group is the possibility that both assist devices depleted platelets, which may have improved microcirculatory blood flow, although we did not specifically evaluate the potential for this effect in the study.

The intra-aortic balloon counterpumping device requires synchronization with the patient’s heart rhythm for effective action. In critically ill patients, it is not uncommon for significant ventricular arrhythmias to occur. The Hemopump, being a continuous-flow device, seems to circumvent this difficulty in animals.

**Implications for Further Studies**

The mechanical interventions described in this study were initiated at the time of onset of ischemia. Clearly, this was not a clinically relevant study, given the fact that most patients presenting with severe ischemia or infarction are well into their course by the time they seek medical therapy. The maximum benefit of mechanical LV unloading might in fact occur not during reperfusion but in the subsequent several days after reperfusion during the period of infarct remodeling. Lower wall stress associated with significant LV unloading during this remodeling phase may well result in a smaller ultimate LV size, in addition to improved function. Whether LV unloading initiated just before reperfusion results in infarct salvage remains unclear at the present time.

Potential difficulties are the risk of leg ischemia associated with both intra-aortic balloon counterpulsation and the insertion of other LV devices, including the Hemopump, via the leg vessels. The Hemopump currently requires the use of a 12-mm woven Dacron graft for insertion similar to the early models of intra-aortic balloon devices. Because femoral artery cutdown (especially in the setting of thrombolysis) is a major source of potential complications, further animal studies are warranted prior to widespread human trials in acute myocardial infarction. Nonetheless, we are encouraged by these results and anticipate that regional mechanical LV unloading with further pharmacological intervention at the time of reperfusion may prove to be synergistic.

**References**


Improved regional myocardial blood flow, left ventricular unloading, and infarct salvage using an axial-flow, transvalvular left ventricular assist device. A comparison with intra-aortic balloon counterpulsation and reperfusion alone in a canine infarction model.

R W Smalling, D B Cassidy, R Barrett, B Lachterman, P Felli and J Amirian

*Circulation*. 1992;85:1152-1159
doi: 10.1161/01.CIR.85.3.1152

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 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/85/3/1152

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/