Response of the Intact Canine Left Ventricle to Increased Afterload and Increased Coronary Perfusion Pressure in the Presence of Coronary Flow Autoregulation

Mohanraj K. Karunanithi, BE, MBiomedE; Jason A. Young, BE, MBiomedE; Wally Kalnins, BE; Scott Kesteven, BSci, Grad Dip BiomedE; Michael P. Feneley, MD, FRACP

Background—Increased left ventricular (LV) contractile force or oxygen consumption has been documented with increased coronary arterial pressure (CAP) and flow (Gregg phenomenon). We investigated whether the increase in contractile force with increased LV afterload might be mediated by the concomitant increase in CAP when coronary autoregulation is intact.

Methods and Results—The LV of 6 autonomically blocked open-chest dogs was perfused through the left main coronary artery by a cannula with a side gate to the aortic root. With the gate open, CAP increased from 77 ± 20 to 93 ± 20 mm Hg (P < 0.05) with aortic constriction (AC). With the gate closed, CAP was maintained at a constant level of 100 mm Hg. A small reduction in the slope of the preload recruitable stroke work (PRSW) relationship was observed with AC, but this response was not altered by the coronary perfusion gate position. The end-systolic pressure-volume (ESPV) relationship shifted upward significantly with AC (P < 0.001), but this shift was not greater with open-gate perfusion than with closed-gate perfusion. Furthermore, with coronary autoregulation intact, wide changes in CAP (between 60 and 180 mm Hg, n = 5) did not alter either the PRSW or ESPV relationship. In contrast, when autoregulation was abolished with intracoronary adenosine (n = 6), both indexes of contractility increased progressively with increased CAP.

Conclusions—The concomitant increase in CAP with increased afterload in the intact canine LV does not contribute to the afterload-induced increase in contractile force. Coronary perfusion pressure per se does not influence LV contractile function. Coronary perfusion pressure influences contractility only when coronary flow changes. (Circulation. 1999;100:1562-1568.)

Key Words: contractility • ventricles • perfusion • pressure • physiology

Increased coronary perfusion pressure has been reported to increase left ventricular (LV) oxygen consumption and contractile function in a variety of experimental preparations (Gregg phenomenon). In the intact circulation, coronary perfusion pressure increases concomitantly with increased LV afterload. Consequently, increases in afterload might be expected to enhance LV contractile function, consistent with observations of a leftward/upward shift of the LV end-systolic pressure-volume relationship (ESPVR) in the intact heart. Similarly, the ability of the intact heart to maintain a virtually constant relationship between LV stroke work and end-diastolic volume (the preload recruitable stroke work [PRSW] relationship), despite increments in mean ejection pressure up to 200 mm Hg, indicates increased force-generating capacity with increased afterload.

We have reported, however, a 45% average increase in the slope of the right ventricular ESPVR with pulmonary artery constriction sufficient to increase right ventricular mean ejection pressure 70% in conscious dogs, while the slope and volume-axis intercept of the right ventricular PRSW relationship remained constant. Because pulmonary artery constriction does not increase coronary perfusion pressure, these observations cannot be explained by the Gregg phenomenon but are consistent with intrinsic “homeometric autoregulation” of contractility to increased afterload. Similarly, the ESPVR of the LV may also shift leftward with increased afterload in isolated heart preparations when coronary perfusion pressure is held constant, although this effect appeared quantitatively smaller than in the intact heart.

Thus, the upregulation of LV contractile force in response to increased afterload in the intact circulation might reflect both homeometric autoregulation and the Gregg phenomenon resulting from the concomitant increase in coronary perfusion pressure. It is not clear, however, that the Gregg phenomenon is due to increased coronary perfusion pressure per se. Although it has been established that increased coronary blood flow increases LV contractility even when coronary perfusion pressure is held constant, it remains controver-
sial whether the converse is true. In most studies of the Gregg phenomenon to date, including Gregg’s, increases in coronary perfusion pressure have been accompanied by increases in coronary flow due to deficient coronary autoregulation. Recent evidence indicates that myocardial oxygen consumption does not increase with increased coronary perfusion pressure when coronary autoregulation is intact.

The primary purpose of the present investigation was to determine whether the concomitant increase in coronary perfusion pressure with increased afterload in the intact circulation contributes to the upregulation of LV contractility. For this purpose, we devised a method of perfusing the intact canine LV through a coronary cannula that could be alternately opened to receive blood from the aortic root or closed to receive blood from a pump at constant pressure while LV afterload was increased by transient aortic constriction. In a second experimental protocol, we randomly altered the fixed coronary perfusion pressure to directly examine the influence of a wider range of coronary perfusion pressures on LV contractile function. In both protocols, coronary blood flow was maintained at a constant rate by intact coronary autoregulation. We then repeated the coronary perfusion pressure protocol in additional experiments after abolishing coronary autoregulation with intracoronary adenosine.

Methods

The experimental procedures were approved by our institutional ethics committee and conformed to the guidelines of the National Health and Medical Research Council of Australia.

Experimental Preparation

Six healthy adult dogs (weight 34 to 44 kg) were anesthetized with fentanyl (0.05 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) and halothane (0.5%) after induction with sodium pentobarbital (20 mg/kg IV). A left thoracotomy was performed and the pericardium opened. Ultrasonic transducers were positioned across the base-apex major (a), anterior-posterior minor (b), and septal–free-wall minor (c) diameters of the LV, as described previously. Pneumatic occluders were positioned around the inferior vena cava and the descending thoracic aorta. LV pressure was measured with a micromanometer (model MPC-500, Millar Instruments) introduced through the apex. Coronary blood flow was measured with flow probes (Doppler [Crystal Biotech] or Transonic [Transonic Systems Inc]) placed around the left anterior descending artery.

The tip of a coronary perfusion cannula (stainless steel, length 33 cm, flanged rubber tip with lumen diameter 3.4 mm) was inserted into the left main coronary artery via the brachiocephalic artery and secured by a ligature. The canine right coronary artery does not provide blood flow to LV myocardium.

Left coronary perfusion was maintained through a heparinized (10 000 U) circuit from 1 of the dog’s femoral arteries via a roller pump (Sarns model 5500) and a flask pressurized with oxygen to permit maintenance of a constant coronary arterial pressure. The flask was immersed in a water bath maintained at 37°C. The regulation of coronary arterial pressure was achieved by electronic feedback control of the pressure sensed from a micromanometer (Millar, model MPC-500) placed within the tip of the coronary perfusion cannula. The cannula was designed so that a gate in the wall near its distal end could be either opened to permit perfusion from the aortic root (open-gate perfusion) or closed to permit LV myocardial perfusion at a constant arterial pressure by the pressure regulation circuit (closed-gate perfusion).

Data Acquisition and Experimental Protocol

Protocol 1: LV Afterload Responses During Open-Gate and Closed-Gate Coronary Perfusion

After attenuation of autonomic reflexes with propranolol (1 mg/kg IV) and atropine (0.2 mg/kg IV), data were recorded under steady-state conditions and during transient vena cava occlusion induced by inflation of the pneumatic occluder for \( \approx \)10 seconds. The purpose of caval occlusion was to provide a wide range of variation in preload to permit subsequent derivation of the ESPVR and PRSW relationship.

The same protocol of sequential caval occlusions was conducted first under open-gate coronary perfusion conditions, when coronary arterial pressure increased normally with increased aortic root pressure during aortic constriction, and then under closed-gate coronary perfusion conditions, when coronary arterial pressure was maintained at \( \approx 100 \) mm Hg despite increased aortic pressure. We took care to ensure that the degree of aortic constriction was identical under both perfusion conditions by using the same volume to inflate the aortic occluder.

Protocol 2: LV Contractile Response to Various Levels of Coronary Perfusion Pressure

To examine the influence of coronary perfusion pressure per se on LV contractile performance over a broader range of pressures, caval occlusions were repeated in 5 dogs at each of various fixed levels of coronary arterial pressure ranging from 60 to 180 mm Hg. All caval occlusion data were collected after stable hemodynamic conditions were achieved at each level of coronary arterial pressure. The same protocol was repeated in 6 additional dogs (weight 28 to 41 kg) after abolition of coronary autoregulation with intracoronary adenosine (67 \( \mu \text{g/min} \)).

Data Analysis

Data were digitized in real time at 200 Hz. We calculated LV volume by fitting the 3 ultrasonically measured LV epicardial diameters to the formula for a general ellipsoid (\( \pi/6 \) a \( \cdot \) b \( \cdot \) c) and subtracting wall volume, which was determined by postmortem displacement in water. End-systolic pressure was defined as the time when the instantaneous pressure-volume ratio was maximal. Stroke work was calculated as the pressure-volume loop area for each beat. The PRSW relationship and ESPVR were determined by linear regression analyses, as described previously.

Statistical Analysis

The influence of the various interventions described above on the PRSW relationship and ESPVR was determined by multiple linear regression analyses. Dummy variables were used in the multiple linear regression analyses to account for the various interventions and for the interanimal variability. The general multiple linear regression model used was

\[
y = b_0 + b_1 \cdot x + b_1 \cdot \text{AC} + b_2 \cdot \text{Gate} + b_3 \cdot \text{AC-Gate} + \sum_{i=1}^{5} d_i \cdot D_i
\]

where AC and Gate are dummy variables coding for aortic constriction and gate position, respectively, using effects coding, and D\( _i \) represents dummy variables for each dog. The effects of afterload and the mode of coronary perfusion were represented by the coefficients \( b_1 \) and \( b_2 \), respectively (a coefficient not significantly different from zero would indicate no effect of the intervention). The coefficient \( d_i \) is the individual dog coefficient. For the PRSW
relationship, the dependent \( y \) and independent \( x \) variables were stroke work and end-diastolic volume, respectively. For the ESPVR, the dependent and independent variables were end-systolic pressure and end-systolic volume, respectively.

For protocol 2, the general multiple linear regression model applied was

\[
y = b_0 + b_1 x + b_2 \text{CAP} + b_3 \text{CAP} x + \sum_{i=1}^{d} d_i D_i
\]

where \( \text{CAP} \) is the coronary arterial pressure value.

Statistical analyses were performed with SPSS for Windows, version 6.1.

Results

Protocol 1: LV Afterload Responses During Open-Gate and Closed-Gate Coronary Perfusion

Representative dynamic data recordings obtained before and during aortic constriction under both open-gate and closed-gate coronary perfusion conditions are displayed in Figure 1. Steady-state hemodynamic data obtained before and during aortic constriction, under both open-gate and closed-gate coronary perfusion conditions, are summarized in Table 1. There were no significant differences in baseline steady-state hemodynamic parameters before aortic constriction between the open-gate and closed-gate perfusion states. Aortic constriction in the open-gate perfusion state increased LV mean ejection pressure from 93±22 to 116±21 mm Hg, resulting in a concomitant increase in mean coronary arterial pressure from 77±20 to 93±20 mm Hg (\( P<0.05 \)). In contrast, under closed-gate coronary perfusion conditions, the increase in LV mean ejection pressure from 92±20 to 123±22 mm Hg during aortic constriction was not accompanied by any change in the mean coronary arterial pressure, which was maintained at a constant level. The coronary flowmeter failed in 1 dog, but no significant changes in left anterior descending coronary artery blood flow were found between the open-gate and closed-gate coronary perfusion conditions in the remaining 5 dogs, indicating intact coronary autoregulation over the coronary perfusion pressure range examined.

Representative examples of pressure-volume loops obtained before and during increased LV afterload under both open-gate and closed-gate coronary perfusion conditions are shown in the upper panels of Figure 2. Superimposed on these loops are the corresponding ESPVRs. The PRSW relationships derived from the same loops are shown in the lower panels of Figure 2. The mean linear regression data for all dogs are summarized in Table 2. Under both open-gate and closed-gate perfusion conditions, there was a small but statistically significant (\( P<0.001 \)) downward shift of the PRSW relationship with aortic constriction, manifested by a reduction in the slope of the relationship with little change in

<p>| TABLE 1. Comparison of Closed-Gate With Open-Gate Perfusion Effects on Steady-State Hemodynamic Parameters Before and During Aortic Constriction |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Gate</th>
<th>HR, bpm</th>
<th>LVEDV, mL</th>
<th>LVSV, mL</th>
<th>LVMEP, mm Hg</th>
<th>LVS, erg ( \cdot 10^4 )</th>
<th>CAP, mm Hg</th>
<th>CBF, mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Open</td>
<td>104±15</td>
<td>60±28</td>
<td>20±10</td>
<td>93±22</td>
<td>270±149</td>
<td>77±20</td>
</tr>
<tr>
<td>AC</td>
<td>Open</td>
<td>99±14</td>
<td>72±25*</td>
<td>19±9</td>
<td>116±21*</td>
<td>296±164</td>
<td>93±20*</td>
</tr>
<tr>
<td>Control</td>
<td>Closed</td>
<td>103±17</td>
<td>61±22</td>
<td>24±10</td>
<td>92±20</td>
<td>304±155</td>
<td>100±23</td>
</tr>
<tr>
<td>AC</td>
<td>Closed</td>
<td>101±14</td>
<td>74±22*</td>
<td>20±9</td>
<td>123±22*</td>
<td>348±171</td>
<td>105±22</td>
</tr>
</tbody>
</table>

HR indicates heart rate; LVEDV, LV end-diastolic volume; LVSV, LV stroke volume; LVMEP, LV mean ejection pressure; LVS, LV stroke work; CAP, coronary arterial pressure; CBF, coronary blood flow through left anterior descending coronary artery; and AC, aortic constriction. Values are mean±SD.

\(*P<0.05\) vs control.
by guest on April 12, 2017 http://circ.ahajournals.org/ Downloaded from

The ESPVR shifted upward significantly (P<0.001) with aortic constriction under both open-gate and closed-gate coronary perfusion conditions, equivalent to an average 25.4±4.0 mm Hg increase in end-systolic pressure for a given end-systolic volume, but this was manifested by a flattening of the slope of the relationship accompanied by a marked leftward shift of the volume-axis intercept. The upward shift of the ESPVR with aortic constriction was not greater when coronary perfusion pressure was permitted to increase with increased afterload. In fact, the upward shift was somewhat smaller in the open-gate position, equivalent to 7.8±5.1 mm Hg less of an increase in end-systolic pressure for a given end-systolic volume (P<0.001).

Protocol 2: LV Contractile Response to Various Levels of Coronary Perfusion Pressure

Figure 3 shows the relationship between coronary blood flow and coronary arterial pressure in 5 dogs not administered adenosine and 6 dogs after intracoronary administration of adenosine. It can be seen that there was no relationship between coronary arterial pressure and coronary blood flow in the first group, indicating intact coronary autoregulation. In contrast, coronary blood flow increased with coronary arterial pressure in the second group, confirming that coronary autoregulation was abolished by adenosine administration.

Representative examples of the PRSW relationship and ESPVR obtained in these 2 groups of dogs at various levels of mean coronary arterial pressure, ranging from 60 to 180 mm Hg, are shown in Figure 4. As these examples demonstrate, under conditions of constant coronary blood flow, increasing coronary arterial pressure did not change either the ESPVR or the PRSW relationship significantly (the coefficient $b_2$ in Equation 2 was not significantly different from zero for either relationship). This lack of effect of coronary arterial pressure on contractility remained when the data were reanalyzed with a simpler statistical analysis that did not include the term for interaction between coronary arterial pressure and LV volume (CAP $\times$ LV in Equation 2). In contrast, when coronary autoregulation was absent, so that coronary blood flow increased in parallel with coronary arterial pressure, there was a progressive upward/leftward shift of both the ESPVR and PRSW relationship with increasing perfusion pressure (the coefficient $b_2$ in Equation 2 was significantly greater than zero; P<0.001).

Discussion

This study demonstrates that the concomitant increase in coronary perfusion pressure with increased afterload in the

![Figure 2. Top, Representative examples of pressure-volume loops obtained before (Control) and during aortic constriction (AC) under both open-gate and closed-gate coronary perfusion conditions. ESPVR is shown by line joining left uppermost corners of pressure-volume loops. Broken loops and lines indicate control. Solid loops and lines indicate AC. There is higher end-systolic pressure for any given end-systolic volume during AC under both open-gate and closed-gate conditions. Bottom, PRSW relationships derived from pressure-volume loops in top panels. There is a small depression of the PRSW relationship under both open-gate and closed-gate conditions.](image)

| TABLE 2. Comparison of Closed-Gate With Open-Gate Perfusion Effects on Linear Regression Data for Control State and Aortic Constriction |
|-----------------|-----------------|-----------------|
|        | PRSW            | ESPVR           |
| Gate   | $M_w$, erg mL$^{-1} \times 10^3$ | $V_{os}$, mL | $E_{es}$, mm Hg mL$^{-1}$ | $V_{os}$, mL |
| Control Open | 76.2±35.1       | 24.0±14.7       | 0.99±0.01       | 3.4±2.8       | 0.1±10.9       | 0.95±0.07       |
| AC     | 69.4±43.5*      | 21.2±12.5       | 0.94±0.12       | 2.8±2.9       | -15.5±23.2*    | 0.97±0.05       |
| Control Closed | 82.1±29.9       | 24.4±14.5       | 0.99±0.01       | 3.4±2.2       | 2.5±11.8       | 0.98±0.02       |
| AC     | 66.6±26.8*      | 22.4±13.8       | 0.98±0.01       | 1.7±0.8       | -39.5±27.8*    | 0.97±0.04       |

AC indicates aortic constriction; $M_w$, slope of PRSW; $V_{os}$, volume intercept of PRSW; $E_{es}$, slope of ESPVR; $V_{os}$, volume intercept of ESPVR. Values are mean±SD.

* Significant downward shift of PRSW relationship on multiple linear regression analysis (P<0.001) is due mainly to slope reduction.

† Significant upward shift of ESPVR on multiple linear regression analysis (P<0.001) is due entirely to leftward shift of volume-axis intercept while slope flattened.
Intact circulation with intact coronary autoregulation does not contribute to the upregulation of LV contractile performance. Thus, the normal upregulation of LV contractility in response to increased afterload is not a manifestation of the Gregg phenomenon. Moreover, this study demonstrates that provided coronary autoregulation is intact so that coronary blood flow does not vary with coronary perfusion pressure, coronary perfusion pressure does not influence LV contractile function. Thus, the Gregg phenomenon is not due to an increase in coronary perfusion pressure per se. We observed increased LV contractile function with increased coronary perfusion pressure only when coronary blood flow also increased.

Since Gregg’s original observation that increased coronary perfusion pressure in open-chest dogs increased myocardial oxygen consumption, many studies have demonstrated increased myocardial contractile function and/or oxygen consumption with increased coronary perfusion pressure and flow. Most of these studies have been conducted in isolated heart or isolated cardiac muscle preparations. Factors confounding the interpretation of many of these studies included the possibility that enhanced contractility with increased perfusion pressure and flow reflected correction of baseline ischemia, particularly in studies in which the control measurements were recorded with coronary perfusion pressures below 60 mm Hg, and the use of nonblood coronary perfusion solutions that may result in LV wall edema. In addition, some coronary perfusates contained calcium or induced increased intracellular calcium, thus further confounding the interpretation of contractility changes.

The most important confounding factor, however, in nearly all previous studies of the Gregg phenomenon, including that by Gregg, was that both coronary perfusion pressure and coronary flow increased simultaneously. Arnold and colleagues observed, in isolated guinea pig hearts, that increased coronary blood flow induced by hypoxia at constant perfusion pressure did not increase LV oxygen consumption or systolic pressure, but increasing the perfusion pressure of coronary dextran infusion at a constant flow rate increased both. The depression of contractile function by hypoxia, however, might have masked any increase in contractile function and oxygen consumption during increased coronary flow, whereas the infusion of hypertonic dextran may have enhanced contractility by inducing increased intracellular calcium.

Figure 3. Relationship between mean coronary blood flow and coronary arterial pressure in presence (left) and absence (right) of intact coronary autoregulation. Coronary blood flow data are normalized to baseline flow (autoregulation present) or flow at a coronary arterial pressure of 80 mm Hg (autoregulation absent). The different symbols represent different dogs.

Figure 4. Representative examples of ESPVRs (top) and corresponding PRSW relationships (bottom) obtained at various fixed levels of coronary arterial pressure, ranging between 60 and 180 mm Hg, in presence (left) and absence (right) of intact coronary autoregulation.
In support of coronary blood flow as the major determinant of contractile function, Abel and Reis demonstrated, in isovolumically beating canine hearts, increased oxygen consumption and maximal velocity of fiber shortening with increased coronary blood flow induced by adenosine at constant perfusion pressure, whereas neither parameter changed with decreased perfusion pressure at a constant blood flow rate. Goto and colleagues demonstrated that the ESPVR slope and unloaded oxygen consumption increased with increased coronary blood flow induced by adenosine at constant perfusion pressure in isovolumically beating rabbit hearts. Sunagawa and colleagues demonstrated, in isovolumically beating canine hearts, that the ESPVR was not dependent on coronary perfusion pressure provided that the pressure exceeded 67±22 mm Hg, below which coronary autoregulation was lost, but the highest pressure examined was only 120 mm Hg. Abel and Reis observed progressive increases in isovolumic peak pressure with step increases in coronary perfusion pressure from 45 to 175 mm Hg only when coronary blood flow also increased with each step in pressure.

From our findings and those discussed above, it appears that increased coronary blood flow is a necessary condition for the Gregg phenomenon, but this will occur with an increase in coronary perfusion pressure only when coronary autoregulation is deficient. This conclusion is supported by the recent finding of Bai and colleagues that effective coronary autoregulation in dogs minimizes increases in coronary vascular volume in response to increases in perfusion pressure, so that increased myocardial oxygen consumption in response to increased coronary perfusion pressure was seen only when coronary autoregulation was poor and coronary vascular volume increased significantly.

This nexus between the Gregg phenomenon, increased coronary blood flow, and increased coronary vascular volume is consistent with the view that the mechanism of the Gregg phenomenon is an increase in end-diastolic sarcomere length due to stretching by the engorged vasculature ("garden-hose" effect), but this is not the only possible interpretation. One study in an isovolumically contracting heart preparation and another in an isolated cardiac muscle preparation demonstrated large increases in force generation with increased perfusion pressure and flow that were not associated with significant increments in end-diastolic fiber length but were associated in 1 of the studies with an increased intracellular calcium transient. Both studies were subject to the limitations of nonblood perfusates and absent flow autoregulation summarized above. In 1 of the studies, flow rates were unphysiologically high, and force generation was much higher than that observed in blood-perfused preparations. Nevertheless, these studies raise the possibility that coronary vascular engorgement and increased wall volume are simply markers of the increased flow rate that is more directly responsible for the inotropic effect, possibly by increased washout of negatively inotropic agents or increased delivery or stimulated production of positively inotropic agents from the endothelium or myocytes.

Blood perfusion at 37°C and the presence of intact coronary autoregulation were 2 important advantages of our experimental preparation relative to most previous investigations of the Gregg phenomenon. The fact that the canine right coronary artery, unlike its human counterpart, does not supply any LV myocardium allowed control of LV myocardial perfusion pressure by cannulation of the left main coronary artery. In addition, the coronary perfusion cannula allowed us to switch rapidly between the open-gate and closed-gate perfusion conditions, thus minimizing any temporal variability in the baseline contractile state between the 2 perfusion conditions. Nevertheless, our experiments were conducted with the chest open under general anesthesia. These experimental conditions may have produced some depression of baseline contractility. The baseline slope of the ESPVR was indeed somewhat lower than reported values in conscious dogs after autonomic blockade. This may explain the small depression of the PRSW relationship with aortic constriction in the present study compared with the previously reported insensitivity of the relationship to larger increments in afterload in conscious animals. Presumably for the same reason, the relatively modest increments in LV mean ejection pressure with aortic constriction were the highest stable levels we could maintain in this preparation for the several minutes necessary to acquire the contractility data. It was for this reason, in part, that we used the second experimental protocol to achieve a much higher level of coronary perfusion pressure than could be achieved during aortic constriction.

In summary, in the intact canine circulation with intact coronary autoregulation, the concomitant increase in coronary perfusion pressure with increased afterload did not contribute to the upregulation of contractile force. Moreover, in the absence of any significant changes in blood flow, due to intact coronary autoregulation, wide variations in coronary perfusion pressure did not influence LV contractile function.

Acknowledgments
This study was supported by a project grant from the National Health and Medical Research Council of Australia.

References
Response of the Intact Canine Left Ventricle to Increased Afterload and Increased Coronary Perfusion Pressure in the Presence of Coronary Flow Autoregulation
Mohanraj K. Karunanithi, Jason A. Young, Wally Kalnins, Scott Kesteven and Michael P. Feneley

Circulation. 1999;100:1562-1568
doi: 10.1161/01.CIR.100.14.1562

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 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/100/14/1562

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/