Role of Peripheral Vasodilation in the Hypotensive Response to Left Ventriculography in Anesthetized Dogs

DAVID D. SHAW, GERALD L. WOLF, AND HAROLD A. BALTAXE

SUMMARY Hypotension after left ventriculography (LVG) is believed to result from direct myocardial toxicity, peripheral vasodilation, or a combination of both. The contribution of each has not been established. Thus, LVG was performed in anesthetized dogs under conditions in which peripheral vascular reactivity (PVR) was altered pathophysiologically (aortic coarctation) or pharmacologically (acetylcholine infusion). Ventricular pressure (LVP), its first derivative (dP/dt), aortic pressure (AoP), and carotid and femoral flows were monitored. When PVR was normal, LVG was associated with significant hemodynamic changes which reached a maximum 25-35 seconds after injection. Left ventricular and aortic diastolic pressures were decreased by 22 and 48%, whereas carotid and femoral systolic flows were increased by 41 and 59%. During acetylcholine infusion, LVG did not cause systolic hypotension and peripheral flows were maintained strikingly constant. Similarly, LVG also was associated with insignificant changes in systolic pressures and carotid flow in the presence of aortic coarctation. These results demonstrate that the hypotension attendant with LVG is directly related to the augmentation in peripheral flow, suggesting that the response is mediated almost exclusively by peripheral vasodilation.


CHANGES in systemic hemodynamics and indices of myocardial performance in response to coronary arteriography and angiocardiography have received considerable investigative attention. Numerous studies in the intact animal (Austen et al., 1964; Benchimol and McNally, 1966; CHAHINE AND RAIZNER, 1976; FRIESINGER ET AL., 1965; Gootman et al., 1970; Hammermeister and Warbasse, 1973) have shown that intracoronary administration of contrast media is associated with a significant depression in indices of myocardial contractility. The time course of the response suggests a direct toxic effect on the contractile elements of the heart muscle. The hypotension observed after left ventriculography (LVG) previously has been explained on the basis of a direct myocardial effect coupled with intense peripheral vasodilation caused by hypertonic contrast media (CHAHINE AND RAIZNER, 1976; Hammermeister and Warbasse, 1973; ZELIS ET AL., 1970). However, since the time courses of the response to coronary arteriography and LVG differ markedly, changes in peripheral organ blood flow and resistance may be entirely responsible for the observed alterations in ventricular function following LVG.

Therefore, a series of experiments was designed to investigate the magnitude and temporal relationship of peripheral vasodilation in response to LVG under conditions of normal and altered peripheral vascular reactivity.

Methods

Seven mongrel dogs of either sex and weighing 20-27 kg comprised the study group. Anesthesia was induced with sodium pentobarbital (30 mg/kg, iv), and absence of the medial canthal reflex was maintained by supplemental injections of anesthetic. Through a left lateral thoracotomy, a 1-cm segment of the ascending aorta was dissected free of adhering fat, and a suitable length of umbilical tape.
was passed around the vessel and through a short piece of large bore vinyl tubing. By gently pulling on the umbilical tape, we could constrict the aorta to any desired degree. An end hole catheter was passed into the superior vena cava for administration of anesthetic and for drug infusion. All dogs were placed on intermittent positive pressure ventilation at 18–20 cycles/minute and a stroke volume of 15–18 ml/kg. An end-expiratory pressure of 4 cm H₂O was maintained when the thoracic cavity was opened.

LVG was performed using Renografin-76 (E.R. Squibb & Sons) (1.15 ml/kg) delivered through the Millar catheter at 8 ml/sec by a Medrad Mark IV injector (Medrad Corp.). (Injection pressures never exceeded 450 psi.) The following experimental protocols were performed on all seven dogs: (1) normal or control LVG, (2) LVG during intravenous infusion of acetylcholine chloride (Ach, 200 µg/min), and (3) LVG performed after an ascending aortic coarctation had been produced which minimally affected carotid flow but markedly decreased femoral flow.

Hemodynamic parameters were monitored continually throughout the response to each LVG, and a minimum of 15–20 minutes elapsed between successive contrast injections. Comparison of the hemodynamic changes in response to the three LVG's was made at the time of maximum ventricular systolic hypotension. If no systolic hypotension resulted from the LVG under altered peripheral vascular conditions (Ach infusion or aortic coarctation), then values were obtained at the time when hypotension was expected, as determined by the control LVG.

To verify that carotid chemoreceptor reflexes were intact during both Ach infusion and aortic coarctation, we injected a bolus of nicotine, 0.2 µg/kg, into the right common carotid artery of a single dog while monitoring systolic pressure and heart rate. In this same animal, we measured the hyperemic response to 20-second femoral artery occlusion in the control state and during Ach infusion and coarctation.

Statistical analyses were conducted on the data using Student’s paired t-test (Snedecor and Cochran, 1967).

Results

Left Ventriculography

The typical response to LVG is shown in Figure 1. As can be seen, all recorded parameters remained essentially unchanged for 10–15 seconds following injection of contrast medium. At this time, however, ventricular systolic pressure, dP/dt, and aortic pressures showed a progressive fall, reaching a nadir some 25–30 seconds after injection. Concomitant with the fall in pressures was a marked, sequential increase in flow in both carotid and femoral circulations which was maintained throughout the period of maximum pressure fall. Pressures and flows then showed a gradual return to preinjection values within 2–4 minutes. Table 1A summarizes the changes in recorded parameters at maximum ventricular systolic hypotension in response to LVG in the seven dogs studied.

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** Representative hemodynamic response to LVG in the anesthetized dog.
### TABLE 1  **Summary of Hemodynamic Changes Resulting from LVG under Conditions of Normal (A) and Altered Peripheral Vascular Reactivity (B and C) in the Seven Dogs Studied**

<table>
<thead>
<tr>
<th></th>
<th>A. Normal</th>
<th>B. Ach infusion</th>
<th>C. Ascending aortic coarctation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control 28 ± 2 sec</td>
<td>28 ± 2 sec</td>
<td>Control 26 ± 2 sec</td>
</tr>
<tr>
<td>Left ventricular pressure (mm Hg)</td>
<td>116 ± 5</td>
<td>79 ± 5</td>
<td>143 ± 6</td>
</tr>
<tr>
<td>Left ventricular + dP/dt (mm Hg/sec)</td>
<td>2273 ± 258</td>
<td>1576 ± 189</td>
<td>2750 ± 195</td>
</tr>
<tr>
<td>Aortic diastolic pressure (mm Hg)</td>
<td>97 ± 5</td>
<td>40 ± 4</td>
<td>94 ± 5</td>
</tr>
<tr>
<td>Aortic pulse pressure (mm Hg)</td>
<td>21 ± 2</td>
<td>39 ± 3</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>Peak carotid systolic flow (ml/min)</td>
<td>365 ± 77</td>
<td>450 ± 170</td>
<td>386 ± 117</td>
</tr>
<tr>
<td>Peak femoral systolic flow (ml/min)</td>
<td>327 ± 60</td>
<td>510 ± 125</td>
<td>252 ± 48</td>
</tr>
</tbody>
</table>

Control values were obtained prior to each injection and are compared to values obtained at the time of maximal systolic pressure fall resulting from the LVG (mean ± SEM) for each condition studied. Statistical probabilities were determined by Student's *t*-test for paired observations.

* P < 0.05; † P < 0.01; § P < 0.0025; ¶ P < 0.0005.

### Left Ventriculography during Ach Infusion

Intravenous infusion of Ach (200 μg/min; 7.5–10 μg/kg per min) was associated with significant changes in pressures and flows, as summarized in Table 2A and seen in Figure 2. Typically, Ach resulted in a large increase in femoral flow (+34%; *P* < 0.0025) but only moderate augmentation of systolic carotid flow (+22%; *P* > 0.05). Both ventricular and systemic pressures fell. The dogs became hemodynamically stable within 30 seconds after the infusion began. LVG performed at this time did not result in any further hypotension or augmentation of peripheral flow (Fig. 2). Aortic diastolic pressure did, however, show a modest fall (*P* < 0.05). Table 1B summarizes the hemodynamic changes resulting from LVG during Ach infusion for the seven dogs. The changes resulting from LVG alone and LVG during Ach infusion are shown in Figure 3 and demonstrate the significant attenuation of parameter changes after systemic vasodilation with Ach.

### Left Ventriculography with Ascending Aortic Coarctation

The production of an acute, ascending aortic coarctation was associated with significant hemodynamic changes both proximal and distal to the coarctation. These changes are shown in Table 2B. The degree of coarctation for each dog was adjusted to result in a marked damping of the aortic pulse pressure distal to the coarctation. This resulted in minimal changes in systolic carotid flow (+5%; *P* > 0.05) but markedly decreased femoral systolic flow (−28%; *P* < 0.0005). Figure 4 shows the response to LVG with aortic coarctation in one dog, and the results from all seven animals are given in Table 1C. From this table, it can be seen that ventricular systolic pressure showed a slight but

### TABLE 2  **Changes in Recorded Variables during Alteration of Peripheral Vascular Reactivity Pharmacologically [Ach infusion (A)] or Pathophysiologically [Ascending Aortic Coarctation (B)]**

<table>
<thead>
<tr>
<th></th>
<th>A. Effect of Ach infusion</th>
<th>B. Effect of aortic coarctation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before infusion</td>
<td>At maximum change</td>
</tr>
<tr>
<td>Left ventricular pressure (mm Hg)</td>
<td>123 ± 8</td>
<td>79 ± 5§</td>
</tr>
<tr>
<td>Left ventricular + dP/dt (mm Hg/sec)</td>
<td>2656 ± 405</td>
<td>1712 ± 241*</td>
</tr>
<tr>
<td>Aortic diastolic pressure (mm Hg)</td>
<td>99 ± 5</td>
<td>40 ± 4§</td>
</tr>
<tr>
<td>Aortic pulse pressure (mm Hg)</td>
<td>24 ± 3</td>
<td>39 ± 3§</td>
</tr>
<tr>
<td>Peak carotid systolic flow (ml/min)</td>
<td>369 ± 96</td>
<td>450 ± 170</td>
</tr>
<tr>
<td>Peak femoral systolic flow (ml/min)</td>
<td>380 ± 93</td>
<td>510 ± 125‡</td>
</tr>
</tbody>
</table>

Values (mean ± SEM) given at maximum change represent steady state conditions occurring approximately 30-60 seconds after initiation of each intervention. Statistical probabilities were determined by Student's paired *t*-test, with *n* = 7 for intervention.

* *P* < 0.05; † *P* < 0.01; § *P* < 0.0025; ¶ *P* < 0.0005.
PERIPHERAL VASODILATION DURING VENTRICULOGRAPHY/Shaw et al.

Response to LVG after pharmacological vasodilation with Ach (190 μg/min, iv). Ach resulted primarily in femoral vasodilation which became stable 30 seconds after the infusion was begun. LVG at this time did not result in systemic or ventricular hypotension (as seen in Fig. 1), nor did femoral or carotid flows increase.

Figure 2: Insignificant fall at 26 seconds, aortic diastolic pressure a significant decrease ($P < 0.0005$), and femoral flow a modest but significant increase ($P < 0.01$). In all aortic coarctation experiments, a characteristic fall in left ventricular systolic pressure and $dP/dt$ (both + and −) occurred immediately after the cessation of contrast injection (Fig. 4). Although not specifically investigated here, this most probably results from supernormal contrast perfusion of the coronary bed due to distal outflow obstruction.

Comparisons of the parameter changes resulting from LVG alone and LVG with aortic coarctation are presented in Figure 5.

Response to Chemoreceptor Stimulation and Reactive Hyperemia

The response to intracarotid nicotine during controlled ventilation in these animals included both mild tachycardia and more marked systolic hypertension (Table 3). During both interventions used to diminish vasodilator reserve, the nicotine response was intact. However, both interventions diminished the reactive hyperemic response (Table 4).

Discussion

It has been well established that contrast media administration results in profound hemodynamic (Austen et al., 1964; Benchimol and McNally, 1966; Chahine and Raizner, 1976; Friesinger et al., 1965; Gootman et al., 1970; Hammermeister and Warbasse, 1973; Zelis et al., 1970) and electrocardiographic (Coskey and Magidson, 1967; Eckberg et al., 1974; Frink et al., 1975; White et al., 1976) alterations, whether it is introduced into the left ventricle or directly into a coronary artery. The bradycardia attendant with coronary arteriography has been shown to be mediated by both a direct effect on sinus node function caused by hyperosmolality (Eckberg et al., 1974; White et al., 1976) and a coronary reflex mediated through the vagus.
Several possible mechanisms may be responsible for the hemodynamic alterations observed after both ventriculography and coronary arteriography. These include (1) a direct myocardial depressant effect; (2) peripheral vasodilation resulting from hyperosmolality of the contrast media; (3) electrolyte and body fluid shifts resulting from administration of hypertonic, hyperosmolar fluid; (4) reflex mechanism(s) originating in the heart, coronary arteries, and/or peripheral vascular beds; and (5) any combination of these possibilities.

Investigation of the effects of direct intracoronary injections has, to date, received considerable attention. The only vascular bed to be exposed to a significant amount of the contrast agent is the coronary circulation, and immediate alterations in cardiac function could be assumed, a priori, to result from either direct action on heart vasculature and muscle or reflex(es) originating within the heart itself. Both direct and reflex effects of coronary arteriography have been demonstrated in intact animals (Austen et al., 1964; Benchimol and McNally, 1966; Chahine and Raizner, 1976; Hammermeister and Warbaske, 1973; Zelis et al., 1976; Zelis et al., 1970) and the isolated heart preparation (Wolf et al., 1973). The hemodynamic response to intracoronary injection of contrast media (increased coronary blood flow, decrease in ventricular function) is rapid (5-10 seconds) and is dose dependent (Bookstein and Higgins, 1977). The bradycardia resulting from coronary arteriography appears to be mediated at least in part by a cholinergic reflex (Eckberg et al., 1974) and direct sinoatrial node depression (White et al., 1976). The hemodynamic alterations attendant with direct intracoronary injections demonstrate a time course similar to the opacification of the coronary vasculature as visually determined.

In contradistinction, LVG results in major alterations in systemic and ventricular function 25–35
seconds after contrast administration—a time when the coronary vasculature is no longer opacified. Furthermore, the fall in ventricular systolic pressure is more severe and lasts considerably longer after LVG than after intracoronary injection (Austen et al., 1964; Frink et al., 1975; Gootman et al., 1970; Hammermeister and Warbasse, 1973). These observations have lead to the speculation that changes in peripheral vascular flow and/or resistance may be a contributing factor in the resulting hypotension (Hammermeister and Warbasse, 1973; Zelis et al., 1976; Zelis et al., 1970). Unfortunately, previously published reports which have attempted to differentiate direct myocardial effects from peripheral vascular participation in the response to LVG have failed either to exclude reflux of contrast media into the coronary circulation during aortography (Chahine and Raizner, 1976) or to study the response to LVG as peripheral vascular reactivity is independently altered.

The present study was intended to investigate the hemodynamic responses to LVG under conditions in which peripheral vasodilator reserve (VDR) was abolished or severely compromised pharmacologically (Ach infusion) and pathophysiologically (aortic coarctation).

The basic mechanism and response to Ach and aortic coarctation are not the same (Table 2). Ach acts by direct arteriolar vasodilation with resulting augmentation in peripheral flow and pulse pressure, but lowered ventricular systolic pressure, dP/dt, aortic diastolic pressure, and peripheral resistance. Aortic coarctation, by affecting aortic pressure distally, results in decreased aortic diastolic and pulse pressures and peripheral flows, but with increased ventricular systolic pressure and dP/dt. The peripheral arterial dilation in this circumstance is due to attempted autoregulation intrinsically controlled by local mechanisms (Wolf and Wilson, 1974). With either intervention, directly measured VDR, elicited by 20-second arterial occlusion, showed a marked attenuation of vasodilator response.

Our data (Table 1) clearly show that by altering the peripheral vascular status, the response to LVG was markedly changed. Infusion of Ach proved to be the more reliable of the two interventions, since a more precisely controlled degree of vasodilation could be produced. The vasodilator properties of the contrast medium were not seen because the peripheral beds already were dilated. There was no hypotension in response to LVG in any of the seven dogs studied. Concomitantly, peripheral blood flow was maintained constant at pre-LVG levels.

Ionic contrast agents have been shown to elicit a carotid chemoreceptor reflex consisting of bradycardia and hypotension in conscious dogs (Higgins, 1979). Either this or other circulatory reflexes might be blunted by the maneuvers used here to diminish peripheral VDR. However, in both interventions, the expected response (Rutherford and Vatner, 1978) to intracarotid injections of nicotine was observed.

Ascending aortic coarctation proved to be a much more difficult intervention, since the precise degree of constriction was different for each dog. Due to the very large VDR in skeletal muscle beds (Wolf and Wilson, 1974), femoral reserve could not be abolished without creating ischemia in other beds with less reserve. Ischemia in beds such as the splanchnic and renal may have resulted in release of vasoconstrictor substances and/or a reflex increase in sympathetic nervous discharge. This would result in peripheral vasoconstriction which would restore VDR within the bed. Thus, when contrast media did reach the peripheral bed, moderate vasodilation could result by overriding the reflex constrictor response.

Although the mechanism and response underlying the two types of interventions used in this study are markedly different, the responses to LVG were consistently similar. When peripheral organ blood flow was prevented from increasing, no depression in ventricular function or systemic hypotension was observed.

The use of the term "myocardial depression" caused by contrast media administration must, at present, be restricted to alterations attendant with coronary arteriography or changes occurring within 10 seconds after LVG. Ventricular and systemic hypotension resulting from ventriculography or aortography occur at a time (25–35 seconds after injection) when ventricular function parameters are elevated rather than depressed (Chahine and Raiz-
ner, 1976). Additional support for this distinction has been obtained in our laboratory (Wolf and Shaw, unpublished observations) by performing a second LVG at the time of maximum hypotension and by analyzing ventricular silhouettes of both LVG's for ejection fraction and segmental wall motion. In all cases, these parameters are increased during the second LVG, indicating an enhanced myocardial contractile state at maximum systolic hypotension.

The results obtained in the present study indicate that augmentation in peripheral vascular flow occurs over a time course similar to the ventricular hypotension observed following LVG. When peripheral VDR was experimentally exhausted, LVG did not result in ventricular or systemic hypotension. Thus, in animals with normal coronary and peripheral circulations, ventricular systolic and systemic hypotension occurring 25–35 sec after LVG is mediated almost exclusively by peripheral vasodilation.

Acknowledgments

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