In search of afferent pathways of a cardiogenic hypertensive chemoreflex

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ABSTRACT Injection of serotonin (5-HT) into the left atrium or ventricle activates a hypertensive chemoreflex. The primary purpose of our study was to determine the afferent pathway(s) that mediates this response. A secondary goal was to localize the receptive sites of this reflex. We measured (1) changes in arterial pressure, (2) reflex vascular responses in skeletal muscle and paw, and (3) changes in renal nerve traffic that occurred after the left atrial or left ventricular injection of 5-HT. Injection of 5-HT (100 to 600 μg) into left atrium or ventricle produced large reflex increases in vascular resistance and sympathetic outflow. These responses were not reduced after bilateral cervical vagotomy. In separate experiments, increases in renal nerve traffic with left ventricular injection of 5-HT were assessed before and after cardiac sympathetic deafferentation. Interruption of cardiac sympathetic afferent pathways did not significantly attenuate increases in renal nerve activity with 5-HT. Injection of 5-HT (300 μg) into the aortic root produced large increases in arterial pressure but this was not observed after injections into the vertebral or common carotid arteries or descending aorta. Injection of 5-HT (100 μg) into the left main coronary artery (perfused via a Gregg cannula from an external reservoir) resulted in a depressor reflex (Bezold-Jarisch). In contrast, injection of 5-HT (200 μg) into the left ventricle when the drug was prevented from reaching the left coronary artery produced a large pressor response. We conclude that the left atrial, left ventricular, or aortic root injection of 5-HT elicits a hypertensive chemoreflex response from receptors that receive their blood supply from arteries other than the major branches of the left coronary artery. The afferent limb of this reflex does not travel in cardiopulmonary vagal or sympathetic afferent fibers. 


IT HAS BEEN suggested that stimulation of glomus tissue at the aortic root with serotonin results in a reflex increase in arterial pressure and tachycardia frequently preceded by bradycardia.1,2 This response to serotonin was first reported by Eckstein et al.1 Their original studies suggested that the blood supply to this glomus tissue originated mainly from the left anterior descending or circumflex branches of the left main coronary artery. In 1968, Rowen et al.3 reported in an abstract that bilateral cervical vagotomy abolished the reflex responses to injection of serotonin into the left coronary artery, although the subsequent full reports from this laboratory did not report data on effects of vagotomy.1,4

The existence of a cardiogenic hypertensive chemoreflex was confirmed by James et al.2 who reported that injections of serotonin into either the left atrium or small branches of the proximal left coronary artery produced a large rise in arterial pressure. James et al.2 also reported that bilateral vagotomy markedly attenuated but did not eliminate the acute hypertensive response to serotonin, although it abolished the chronotropic and dromotrophic effects on the heart. In a subsequent study from the same laboratory, Uthaler et al.5 reported that the vagi serve as the exclusive afferent limb for this reflex. However, neither of these two articles provided data to indicate the degree to which vagotomy attenuated or abolished the reflex responses. Zucker and Cornish6 recently studied the reflex cardiovascular and respiratory effects of serotonin in conscious and anesthetized dogs. These investigators found that bilateral cervical vagotomy reduced but did not abolish the blood pressure responses to serotonin.

A limitation of previous studies2,3,5,6 is that they...
relied primarily on changes in blood pressure before and after interruption of the vagi to determine whether the vagal nerves serve as the afferent pathway for this reflex. Tachycardia is a common component of the cardiogenic hypertensive chemoreflex and could contribute importantly to the rise in arterial pressure by inducing increases in cardiac output. As a result, sectioning of the vagi could reduce the pressor response to serotonin by reducing the tachycardia. Moreover, there may be changes in sympathetic outflow to various parts of the circulation that are not necessarily reflected in comparable changes in arterial pressure. Thus, changes in arterial pressure may not be a sensitive end point for studies evaluating afferent pathways of the reflex. Reflex changes in vascular resistance or sympathetic nerve traffic would seem preferable. Although Hageman et al.\(^1\) have observed increases in efferent sympathetic nerve activity after left atrial administration of serotonin, the effect of bilateral vagotomy on these responses was not reported.

The primary purpose of our study was to determine whether the vagal nerves serve as the afferent pathway for the serotonin-induced cardiogenic hypertensive chemoreflex. A secondary goal was to localize the receptive sites for the reflex. In addition to monitoring changes in arterial pressure, we measured reflex vascular responses in skeletal muscle and paw (as reflected by changes in perfusion pressure in constant flow-perfused preparations) and reflex changes in renal sympathetic nerve traffic. The distinctive features of this study are (1) the focus on reflex vascular and sympathetic nerve responses as opposed to changes in arterial pressure, and (2) the quantitative assessment of the effects of various interventions. The results of our experiments indicate that the vagi do not serve as the principal afferent pathway for the cardiogenic hypertensive chemoreflex.

### Methods

Studies were performed on mongrel dogs of both sexes weighing 16 to 24 kg. The dogs were anesthetized with \(\alpha\)-chloralose (100 mg/kg iv followed by 10 mg/kg hourly), intubated, and ventilated with a Harvard respirator with room air supplemented with oxygen. Arterial blood gases and pH were monitored at intervals and were maintained within physiologic limits by adjusting the ventilatory frequency or by administration of sodium bicarbonate. Before beginning the protocol, animals were treated with decamethonium bromide (0.3 mg/kg iv) to eliminate muscle movement. This was particularly important for experiments in which nerve recordings were performed. Body temperature was maintained by external warming at 37° to 39° C.

Arterial pressure was measured with a catheter in the right femoral artery connected to a Statham (P23AI) transducer. Mean arterial pressure was obtained by electrical averaging. Heart rate was monitored in some experiments by a cardiotachometer triggered by the QRS complex of the electrocardiogram.

**Isolated perfused muscle and paw.** The isolation and perfusion of the paw and muscle were described as previously.\(^8\) Briefly, the cranial tibial artery was exposed near the tarsus and collateral arteries at this level were ligated. In the same hindlimb, the gracilis muscle was dissected free from all of its vascular connections except for the gracilis artery and vein. The cranial tibial and gracilis arteries then were cannulated and perfused at constant flow with heparinized (500 U/kg intravenous) autologous blood from a brachial artery with the use of roller pumps. Flows were adjusted to produce perfusion pressures within 10 mm Hg of the mean arterial pressure and then were kept constant for the duration of the experiment. During constant flow perfusion, changes in perfusion pressure reflect changes in vascular resistance. The vascular responses of paw and muscle that we report were not due to local effects of serotonin since at least 1 min was required to traverse the perfusion circuit from the brachial artery cannula to muscle or paw. In contrast, peak reflex responses to serotonin were observed within 15 sec. The absence of significant collateral flow was evident from the consistent observation that perfusion pressures fell promptly to 10 to 20 mm Hg when the perfusion was interrupted.

**Nerve recordings.** The left renal artery was exposed via a retroperitoneal approach and a branch of the renal nerves was sectioned. The central cut end was placed on silver/silver chloride electrodes connected to a Grass probe (HIP511E) and amplified by a Grass P511 bandpass amplifier. Recordings were made from few fiber preparations obtained from the nerve. The

### Table 1

Responses of mean arterial pressure and paw and muscle vascular resistance to left ventricular injection of serotonin before and after vagotomy in closed-chest dogs \((n = 12)\)

<table>
<thead>
<tr>
<th>Dose of serotonin ((\mu g))</th>
<th>Mean arterial pressure (mm Hg) Before vagotomy</th>
<th>Paw vascular resistance (U) Before vagotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Response</td>
</tr>
<tr>
<td>150</td>
<td>92±16</td>
<td>+39±10(^A)</td>
</tr>
<tr>
<td>300</td>
<td>94±13</td>
<td>+30±16(^A)</td>
</tr>
<tr>
<td>600</td>
<td>91±12</td>
<td>+49±9(^A)</td>
</tr>
</tbody>
</table>

Values are mean ± SE.

\(^A p < .05\), significant change from control.
high-frequency cutoff of the bandpass amplifier was set at 1,000 to 3,000 Hz and the low-frequency cutoff was at 30 Hz. The amplifier output was audible over a loudspeaker and visible on a Tektronics D13 dual-beam storage oscilloscope. The output also was led into a nerve traffic analyzer that counted spike potentials exceeding a selected voltage (usually just above the noise). Each action potential that exceeded the voltage setting of the window discriminator (just above noise) generated a voltage step that was independent of spike amplitude. These normalized voltage steps were integrated to determine the number of spikes occurring over specific intervals. The counter was digital in design, and the relationship between integrator output and spike frequency was linear up to a frequency of 10 kHz. Integrated nerve activity was recorded continuously on a Gould recorder (Model 440).

**Localization of receptive region.** In five experiments we injected serotonin (300 μg) into the vertebral artery, common carotid artery, and the aortic root to localize the receptive region responsible for the responses.

**Origin of the blood supply to the receptive region for the cardiogenic hypertensive chemoreflex.** We performed 10 experiments in which serotonin (200 μg) was injected into the left ventricle but excluded from the left main coronary artery by perfusing the left main coronary artery with blood obtained from a reservoir. An immediate decrease in coronary perfusion pressure to less than 20 mm Hg when perfusion was interrupted was taken to indicate that there was no blood passing from the aorta to the left coronary artery when the cannula was positioned in the ostium of the left coronary artery. The reservoir was filled from the left femoral artery. Thus, we were able to inject serotonin (200 μg) into the left ventricle and to allow it either to enter the left coronary circulation (Gregg cannula removed from the left coronary ostium) or to be excluded from the left coronary circulation by positioning the Gregg cannula in the ostium of the left coronary artery. In these experiments serotonin (100 μg) also was injected into the left coronary perfusion circuit downstream of the reservoir with the Gregg cannula positioned in the orifice of the left main coronary artery.

We did four additional experiments to determine whether the cardiogenic hypertensive chemoreflex could be provoked from the right coronary vascular bed. We could not perfuse the right coronary artery with a Gregg cannula as was done for the left coronary. In these experiments a small catheter (PE-50) was passed retrogradely from a small peripheral branch to the origin of the right coronary artery. Its location was established during the experiment by gentle palpation and was confirmed at the conclusion of the study by injection of methylene blue. We injected 100 μg of serotonin (in 1 ml of saline) via this catheter, first with the right coronary artery in continuity with the circulation and then with the right coronary artery occluded during the injection. In the former circumstance, the serotonin was injected mainly into the aorta. In the latter circumstance, the serotonin was injected into the right coronary artery so that it could not reflux into the aorta. Immediately after the injection was completed the occlusion was released. We measured the changes in heart rate and arterial pressure that resulted from these injections. We also evaluated the responses to injection of vehicle under the same two conditions. The methylene blue was injected with the origin of the right coronary occluded and then after its release as described above for the serotonin injection. At the conclusion of the study each animal was killed, the heart was removed, and the extent of staining of the right coronary artery was determined.

**Statistics.** Changes in arterial pressure, paw and muscle perfusion pressure, and in renal nerve activity were determined before and after selective deafferentation in each protocol. Differences between control and deafferentation were determined by paired t test (for paired data, such as before vs after vagotomy) or by analysis of variance with a test for multiple comparisons to determine individual differences (for studies such as the nerve traffic recordings that required multiple deprivations). Data shown in tables and figures are the mean ± SE. Differences between means were considered significant at p < .05.

**Results**

**Reflex vascular responses.** In the initial series of 12 experiments, we examined the responses, in closed-chest dogs, to left ventricular injection of serotonin (at three different doses) before and after vagotomy. Serotonin produced abrupt increases in systemic arterial
pressure and in paw and muscle vascular resistances (table 1). The responses in paw and muscle that we observed were reflexly mediated because they were abolished by sectioning the sympathetic nerves passing to these beds.

There were no significant differences between the responses observed before and after vagotomy (table 1). The increase in muscle vascular resistance after injection of 150 μg of serotonin and the increase in mean arterial pressure after all three doses tended to be less after vagotomy (table 1), but these responses were not significantly different. Moreover, baseline muscle resistance and mean arterial pressure tended to be higher after vagotomy, which would tend to decrease responses to a superimposed vasoconstrictor and vasospressor stimulus.

In a separate group of five open-chest dogs, we examined the muscle vascular responses to left atrial injection of serotonin before and after vagotomy (figure 1 and table 2). The responses before and after vagotomy did not differ significantly. Thus, in two series of experiments, vagotomy did not significantly attenuate reflex vasoconstrictor responses in paw or muscle.

**Reflex responses of renal nerve traffic.** The responses of renal nerve activity to left ventricular injection of 100 μg of serotonin are summarized in table 3. Left ventricular injection of serotonin with all afferent pathways intact resulted in large increases in renal nerve activity. As previously reported, the increased in nerve activity could be characterized as large bursts of activity followed by a period of electrical silence.

The increases in renal sympathetic nerve activity with serotonin were not reduced by bilateral vagotomy alone or in combination with cardiac sympathetic denervation. Table 4 summarizes the latencies from the time of serotonin injection to the first evidence of increased renal sympathetic traffic with all reflex pathways intact, after bilateral vagotomy, and after the addition of sympathetic denervation. The latency was not changed by vagotomy and, although the number of observations was small, the addition of sympa-
Latency (in sec) from onset of injection of serotonin to earliest change in renal nerve traffic

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Intact</th>
<th>Vagotomy</th>
<th>Vagotomy plus sympathetic deafferentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>1.9</td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>34</td>
<td>3.0</td>
<td>3.4</td>
<td>2.5</td>
</tr>
<tr>
<td>42</td>
<td>2.3</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>2.2</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>2.5</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>63</td>
<td>3.2</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>2.51 ± 0.19</td>
<td>2.45 ± 0.23</td>
<td>2.57 ± 0.03</td>
</tr>
</tbody>
</table>

Experimental deafferentation appeared to be without effect on the latency.

To assess the efficacy of our procedure for interrupting cardiac sympathetic afferents, we determined in separate experiments the responses to epicardial application of bradykinin, which has been shown previously to activate cardiac sympathetic afferents and to result in pressor or depressor reflex responses. In three of six experiments, epicardial bradykinin elicited depressor reflex responses and in the other three experiments it gave rise to increases in arterial pressure. As previously reported, both pressor and depressor responses to bradykinin were abolished in all six experiments by interruption of the cardiac sympathetic afferent pathways, a procedure that did not significantly alter the response to serotonin. For example, in the three dogs with a pressor response, epicardial bradykinin produced changes in arterial pressure averaging 20 ± 11 mm Hg before vs -3 ± 4 mm Hg after sympathetic deafferentation. In the three dogs with a depressor response, bradykinin produced changes in arterial pressure averaging -24 ± 8 mm Hg before vs 2 ± 4 mm Hg after sympathetic deafferentation.

Localization of receptive region. In five experiments done in closed-chest dogs, we injected serotonin into the vertebral artery, the common carotid artery, and the aortic root to localize the receptive region for responses we observed. Neither vertebral nor common carotid artery injection of serotonin resulted in reflex hypertension (figure 2). In contrast, injection of serotonin into the aortic root resulted in a large increase in arterial pressure (figure 2). Although the data are not shown, injections of serotonin into the descending aorta failed to produce the increases in arterial pressure seen with injections into the aortic root.

Origin of the blood supply to the receptive region for the cardiogenic hypertensive chemoreflex. We performed 10 experiments in open-chest dogs in which serotonin was injected into the left ventricle but excluded from the left main coronary artery by perfusing the left main coronary artery with blood obtained from a reservoir.

Figure 3 shows portions of records from one of these experiments. Serotonin injected into the left ventricle...
reached both the aorta and the left coronary arterial circulation (left panel). As expected, serotonin elicited an increase in arterial pressure. We then perfused the main left coronary artery at constant pressure (from a reservoir) by placing the Gregg cannula in the ostium of the main left coronary artery. As shown in the center panel, injection of serotonin into the left ventricle under these conditions still produced a large pressor response, despite the fact that serotonin was excluded from the left coronary arterial system. Moreover, as shown in the right panel, when we injected serotonin directly into the main left coronary artery through the Gregg cannula, we failed to elicit a pressor response. Instead, we observed bradycardia and hypotension. Table 5 presents the mean data from 10 such experiments carried out in this fashion. Reflex depressor responses were always observed when serotonin was injected into the Gregg cannula positioned in the orifice of left main coronary artery. Thus, the receptive regions for this hypertensive reflex do not appear to receive their blood supply from the major branches of the left coronary arterial tree.

It could be argued that our experiments do not exclude the right coronary artery as the source of the cardiogenic hypertensive chemoreflex. To test this possibility, four experiments were conducted by use of a strategy similar to that employed for the left coronary. In each experiment a small catheter (PE-50) was passed from a small peripheral branch of the right coronary artery retrogradely to the origin of the right coronary artery. Serotonin (100 μg) was injected through the catheter with the right coronary in continuity with the circulation and then with the right coronary occluded at its origin. Responses of arterial pressure and heart rate to these injections of serotonin are summarized in figure 4. When injections were made with the right coronary in continuity with the circulation, large increases in blood pressure and heart rate were observed. These responses were most likely due to injection of serotonin into the aorta. For the second injection, a snare occluder was used to prevent the passage of serotonin into the aorta and the occlusion was released as soon as the injection of serotonin was completed. Thus, serotonin was restricted to the right coronary bed. These injections failed to change heart rate or blood pressure (figure 4). Right coronary occlusions and injections of saline with and without right coronary occlusion did not change arterial pressure or heart rate. At the conclusion of the study, the right coronary was occluded, methylene blue was injected, the occlusion was released, and the animal was killed. The right coronary arteries were stained to within 1 to 2 mm of their origin. Thus, serotonin does not produce a cardiogenic hypertensive chemoreflex from receptive areas that receive their blood supply from the right coronary artery. This is consistent with prior observations by Eckstein.

**TABLE 5**

Responses of mean arterial pressure to injection of serotonin: effects of excluding serotonin from left coronary artery with a Gregg cannula (n = 5)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control mean arterial pressure (mm Hg)</th>
<th>Change in mean arterial pressure with serotonin (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV 5-HT (200 μg) without Gregg cannula</td>
<td>90 ± 26</td>
<td>51 ± 17</td>
</tr>
<tr>
<td>LV 5-HT (200 μg) with Gregg cannula</td>
<td>85 ± 28</td>
<td>59 ± 8</td>
</tr>
<tr>
<td>LMCA 5-HT (100 μg)</td>
<td>79 ± 20</td>
<td>-12 ± 9</td>
</tr>
</tbody>
</table>

See text for explanation of data. Values are mean ± SE.

LV = left ventricular; 5-HT = serotonin; LMCA = left main coronary artery.

**FIGURE 4.** Mean arterial pressure and heart rate observed under control conditions (5-HT C) and after injection of 100 μg serotonin into the proximal right coronary artery. The responses observed with the right coronary in continuity with the circulation are illustrated with solid symbols and lines. The responses observed when serotonin was injected into the occluded right coronary artery (occlusion removed after injection) are illustrated with open symbols and broken lines. See text for discussion of results.

**Discussion**

Our findings confirm those reported previously by Eckstein et al.¹,⁴ and by James et al.² that there is a
hypertensive reflex response to injection of serotonin into the left atrium or left ventricle. The major new findings of this study are that (1) the afferent fibers suberving the cardiogenic hypertensive chemoreflex in the dog do not appear to travel in vagal or cardiac sympathetic afferent pathways, and (2) the receptive regions activated by serotonin receive their blood supply via vessels other than the major branches of the left (or right) coronary arterial system. Our discussion is focused on these two points.

**Afferent pathways.** We were surprised to find that vagotomy plus denervation of cardiac sympathetic afferent pathways failed to abolish the reflex responses to left ventricular or left atrial injection of serotonin. In addition, these denervations failed to alter the latencies of the nerve traffic responses. Our finding differs from prior conclusions by James et al.\(^2\) and Rowen et al.,\(^3\) but are consistent with the report of Zucker and Cornish\(^4\) that vagotomy did not abolish the hypertensive chemoreflex response to serotonin in open-chest anesthetized dogs. i.e., our experiments, we did not rely solely on changes in arterial pressure or in heart rate. We measured reflex vascular responses in skin and muscle and changes in renal nerve traffic before and after vagotomy and sympathetic deafferentation and we found that they were preserved after interruption of these afferent pathways. Unfortunately, our data have not identified the afferent pathway(s) for this response. The data suggest that if the response is indeed a reflex, the afferent limb traverses neural pathways that are unlike the classic vagal and sympathetic afferent pathways.

We tested the efficacy of the cardiac sympathetic deafferentation and found that the responses to epicardial bradykinin in dogs with prior vagotomy were abolished by sympathetic deafferentation. In addition, although not presented in the results, bilateral vagotomy abolished the hypotension and vasodilation resulting from intracoronary nicotine in muscle. Thus, the techniques we used to interrupt these afferent pathways were efficacious and yet the responses to serotonin we measured were not significantly attenuated.

The responses cannot be explained by stimulation of aortic or carotid chemoreceptors. Sectioning of the vagal nerves also interrupts the aortic depressor nerves that transmit aortic chemoreceptor afferents and this maneuver did not attenuate the reflex responses to serotonin. In addition, injection of serotonin into the carotid arteries did not provoke the reflex.

**Localization of receptive region.** We conducted three groups of experiments to provide insight into the location of the receptive areas involved in the cardiogenic hypertensive chemoreflex. In the first, serotonin was injected into the carotid and vertebral arteries and into the aortic root and descending aorta. In the second, left ventricular injection was performed with exclusion of serotonin from the left coronary circulation by the Gregg cannula. In the third group serotonin was injected into the right coronary artery by techniques that exclude serotonin from the aorta. The three sets of experiments suggest that the receptive regions are at the base of the heart or the root of the aorta, but receive their blood supply from arteries other than the major branches of the left main or right coronary arteries.

It has been suggested that the blood supply to the receptive regions of the cardiogenic hypertensive chemoreflex originates from the first few millimeters of the main left coronary artery.\(^2\) Thus, it might be argued that injections into the left coronary artery through the Gregg cannula were distal to the branches of the left coronary, which have been reported to supply the receptive region. However, it should be noted that in the histologic study by Eckstein et al.\(^1\) only 16% of vessels thought to supply this glomus tissue originated from the left main coronary artery, while 78% originated from the left anterior descending or circumflex coronary arteries or their branches. If these arteries are indeed supplying the receptive region, one would predict that in over three-fourths of our experiments (1) injection of serotonin into the left main coronary artery would produce the reflex, and (2) preventing left ventricular injections of serotonin from reaching the left anterior descending and circumflex coronary arteries would prevent or minimize the reflex. In none of our 10 experiments did either of these results occur. When we injected serotonin into the left main coronary artery via the Gregg cannula, we observed solely reflex depressor responses. This was probably the Bezold-Jarisch reflex mediated by cardiac receptors with vagal afferents. This type of response to intracoronary serotonin has been reported previously by James et al.\(^5\)

Our conclusion that the hypertensive response to left ventricular injections of serotonin does not originate from major branches of the left coronary system is consistent with the most recent report by Eckstein.\(^4\) In his article, Eckstein stated that "exclusion of the coronary blood supply to the aortic bodies resulted in a reduction of the control response of more than 50% in only two of 21 dogs."\(^4\) Thus, this author found that responses to left atrial serotonin were mediated mainly by receptors that receive their blood supply from vessels other than the left coronary circulation.

If the afferent limb of the reflex provoked by serotonin does not traverse traditional cardiac vagal and
sympathetic pathways, then where does it originate and how does it reach the nervous system? Might there be a direct line from the aortic arch to the spinal cord? Might there be direct effects of serotonin on preganglionic or even postganglionic sympathetic nerves? We anticipate that future studies will answer these questions.

In summary, our results suggest that the receptive sites of the cardiogenic hypertensive chemoreflex are located at the base of the heart or root of the aorta, but do not receive their blood supply from the major branches of the left coronary artery. Neither the vagi nor the sympathetic afferents serve as the principal afferent pathway for the reflex.

We thank John Hnida, Steve Yuih, and Pamela Hite for technical assistance and Janet Ellsworth, Anne Kioschos, Jacqueline Carter, and Shirley McCray for typing the manuscript.

References

Erratum

The last paragraph on page 1315, column 2, should have read as follows: “In summary, the afterload-corrected ESVI in patients with mitral regurgitation and ESVI in patients with valve lesions other than mitral regurgitation were independent predictors of outcome after valve replacement surgery for patients without coexisting coronary artery disease.”
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Circulation. 1987;75:643-650
doi: 10.1161/01.CIR.75.3.643

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