Vagal Cardiopulmonary Reflexes After Left Ventricular Deafferentation

Anthony J. Minisi, MD; Theresa L. Cersley

Background Cardiac transplantation and chronic myocardial infarction interrupt vagal afferent nerve fibers, which originate mainly from the ventricles. Marked abnormalities of reflexes mediated by cardiopulmonary receptors with vagal afferent fibers have been demonstrated after both cardiac transplantation and chronic myocardial infarction. The relation between these reflex abnormalities and ventricular deafferentation is not known.

Methods and Results To further assess this relation, we investigated the effects of left ventricular (LV) deafferentation on the control of renal sympathetic nerve activity (RSNA) by the vagal cardiopulmonary reflex in chloralose-anesthetized, mechanically ventilated dogs with sinoaortic denervation. Responses of left atrial pressure (LAP) and RSNA to hemorrhage and volume expansion were measured before and after application of 88% phenol to either the inferoposterior LV (n=12) or the entire LV (n=14). In control experiments, measurements were made before and after application of saline to the LV (n=12). Reflex sensitivity (percent change in RSNA per mm Hg change in LAP) measured during volume expansion was mildly attenuated after both total (prephenol, -9.1 ± 0.7; postphenol, -6.6 ± 0.7; $P<.05$) and inferoposterior (pre, -12.5 ± 1.8; post, -8.1 ± 0.6; $P=.055$) LV deafferentation. Reflex sensitivity measured during hemorrhage was not significantly altered by inferoposterior or total LV deafferentation. Epicardial saline had no significant effect on reflex sensitivity values measured during either volume expansion or hemorrhage. Reflex inhibition of RSNA in response to intracoronary nicotine was abolished after phenol application, indicating adequate ventricular deafferentation. Phenol application had no significant effect on LAP–myocardial segment length relations measured by sonomicrometry (n=6).

Conclusions Interruption of vagal afferent input from the LV has only modest effects on the control of RSNA by the vagal cardiopulmonary reflex. These data indicate that there is considerable redundancy in the vagal cardiopulmonary reflex such that receptors from the lungs and other cardiac chambers can largely compensate for the loss of afferent input from the LV. (***Circulation.* 1994;90:2015-2021.**)

Key Words • nervous system • receptors • reflex • vagus nerve

Sensory receptors whose afferent fibers travel to the central nervous system in the vagal nerves are located throughout the cardiopulmonary region.[1] The vagal afferents act in conjunction with the arterial baroreceptors to modulate sympathetic and parasympathetic outflow from the central nervous system in response to a variety of physiological and pathological stimuli.

Cardiopulmonary receptors with vagal afferent fibers are present in the lungs, in all four cardiac chambers, and in the great veins. Although receptors in the atria, ventricles, and lungs each are known to exert an important tonic inhibitory influence over central sympathetic outflow,[2] the relative importance of afferent input from each of these regions has not been investigated systematically.

Recent observations indicate that afferent input from the ventricles may be of primary importance in determining the reflex response to alterations of cardiopulmonary pressures and volumes. Marked abnormalities in vagal cardiopulmonary reflexes have been demonstrated in patients with cardiac transplantation and in dogs with chronic myocardial infarction.[3-5] In both of these conditions, there is interruption of afferent fibers mainly from the ventricles, while atrial and pulmonary afferents remain largely undisturbed. These observations suggest that interruption of afferent input from only the left ventricle can result in marked abnormalities of vagal cardiopulmonary reflexes. However, the mechanism responsible for these abnormal reflexes has not been established, and the relation between ventricular deafferentation and abnormal vagal cardiopulmonary reflexes is unknown. Thus, our experiments were performed to determine the impact of left ventricular deafferentation on reflexes originating from the cardiopulmonary region.

Methods

Experiments were performed in anesthetized, mechanically ventilated dogs with sinoaortic denervation. The dogs were anesthetized with sodium thiamylal (25 to 30 mg/kg IV) followed by α-chloralose (80 mg/kg IV). Supplemental doses of chloralose (10 mg/kg IV) were administered hourly. The dogs were ventilated with a mixture of oxygen and room air. Arterial blood gases were monitored at intervals, and either the respirator settings were adjusted or sodium bicarbonate was administered to maintain pH between 7.35 and 7.45. The femoral artery and vein were cannulated for measurement of arterial pressure and for infusion of drugs and manipulation of blood volume. The left atrium also was cannulated to continuously monitor left atrial pressure (LAP). Body temperature was maintained by external warming. During the recording of nerve activity, muscular movement was eliminated with pancuronium bromide (2 mg IV).

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Surgical Preparation

To study the vagal cardiopulmonary reflex in isolation from reflexes mediated by the arterial baroreceptors, sinoaortic denervation was performed. A midline cervical incision was made to expose the carotid arteries and cervical vagi bilaterally. The carotid baroreceptors were denervated by isolation, ligation, and sectioning of all of the structures that course between the internal and external carotid arteries. Adequate carotid sinus denervation was confirmed by the lack of nerve traffic and arterial pressure changes during bilateral carotid occlusion. The aortic arch baroreceptors were denervated by sectioning of the cervical aortic depressor nerves bilaterally. With an operating microscope, these nerves were dissected free in the vagosympathetic trunk just caudal to the nodose ganglion near the junction of the vagus and the superior laryngeal nerves. The aortic nerves were identified by recording typical pulse synchronous baroreceptor activity. Although this method may not interrupt all aortic baroreceptor fibers,[6] it has been shown to result in acute, functional aortic denervation.[7]

After sinoaortic denervation, an incision was made in the left fifth intercostal space and a rib was removed to expose the heart. The pericardium was opened, and the heart was suspended in a pericardial cradle. Small cannulas (PE-50) were placed into branches of the anterior descending and circumflex coronary arteries for the intracoronary injection of chemicals. The epicardial surface was kept moist with warm saline at all times.

Renal Nerve Recordings

An incision was made in the left flank to expose the left renal artery. A small branch of the renal sympathetic nerves was dissected free from the renal artery and the surrounding connective tissue. The nerve was sectioned distally, and the nerve sheath was removed. The nerve was immersed in mineral oil and placed on bipolar platinum-iridium electrodes for the recording of action potentials as descibed in detail previously.[8] Briefly, the signal was amplified by a bandpass amplifier (model P511, Grass Instruments Co) with high-frequency cutoff set at 1000 to 3000 Hz and low-frequency filter at 30 to 100 Hz. The output of this amplifier was fed into an audio amplifier and a spike counter that counted and integrated all nerve spike activity whose amplitude exceeded a preselected voltage level (just above noise).

Experimental Protocols

Arterial pressure, LAP, and renal sympathetic nerve activity (RSNA) were measured continuously during manipulations of blood volume. Blood volume was reduced by hemorrhage and expanded by infusion of 10% dextran in normal saline. For hemorrhage, a total volume of 15 mL/kg was removed over a period of 8 minutes. For volume expansion, a total of 15 mL/kg was infused over a similar time period. Shed blood was reinfused, and infused volume was removed. The order of the experimental maneuvers was randomized, and sufficient time (15 to 30 minutes) was allowed between experimental maneuvers for stabilization of pressures and nerve activity.

The responses to hemorrhage and volume expansion were assessed before and after left ventricular deafferentation. Left ventricular afferents were interrupted by epicardial application of 88% phenol solution. Application of phenol in this manner has been shown to produce a layer of necrosis 0.25 mm in depth[9] and to interrupt ventricular vagal and sympathetic afferent fibers.[10] In one set of experiments (n=12), the effects of inferoposterior deafferentation were determined. In these experiments, phenol was applied with a cotton-tip applicator to the left atrioventricular groove and along the epicardium supplied by the branches of the circumflex coronary artery. In a second set of experiments (n=14), responses to blood volume manipulation were assessed before and after total left ventricular deafferentation. In these experiments, phenol was applied to the epicardium along both the anterior descending and circumflex coronary arteries. In a third set of control experiments (n=12), responses were assessed before and after epicardial application of 0.9% saline. In all experiments, the adequacy of ventricular deafferentation was determined by measurement of renal nerve responses to intracoronary injection of nicotine. In the inferoposterior and control experiments, nicotine (mean dose, 113±30 μg; range, 10 to 500 μg) was injected into the circumflex artery. In the total LV deafferentation experiments, nicotine was injected into both the circumflex (mean dose, 65±14 μg; range, 25 to 200 μg) and anterior descending (mean dose, 100±9 μg; range, 50 to 200 μg) coronary arteries.

In six experiments (four total and two inferoposterior deafferentation), the effect of epicardial phenol on left ventricular function was assessed by measurement of myocardial segment length changes during blood volume manipulations. Myocardial segment length was measured by sonomicrometry (Triton Technologies Inc). Sonomicrometry crystal pairs were placed perpendicularly through the epicardium to the mid-myocardial level at a distance of approximately 1 cm apart. To ensure that the intercrystal axis was circumferentially oriented and that shear-strain patterns were minimized, the position of the crystals was adjusted to yield the minimum end-systolic segment length and a waveform that did not contain large fluctuations in early diastole. At the completion of all of these experiments, crystal position and alignment were confirmed by direct inspection of the excised heart after fixation in formalin.

Data Analysis

Arterial pressure, LAP, and raw and integrated RSNA were recorded continuously on an electrostatic recorder (model ES1000, Gould Electronics). Baseline measurements were made immediately before either hemorrhage or volume expansion. Repeat measurements of renal nerve activity were made for each 0.5 to 1.0 mm Hg change in LAP that was elicited by hemorrhage or volume expansion. Since recordings were made from multiunit nerves in which the number of active fibers is variable, nerve traffic changes were expressed in terms of percent change from baseline values. These values of LAP and percent change in renal nerve activity were used to plot stimulus-response curves. The slopes of the linear portion of these curves were computed by linear regression and used as an estimate of the "sensitivity" of the vagal cardiopulmonary reflex (percent change in RSNA per mm Hg change in LAP; Fig 1).

For each group of experiments, the reflex sensitivity values that were measured during either hemorrhage or volume expansion were combined and mean±SEM were computed. The effect of inferoposterior, total, and sham ventricular deafferentation on mean reflex sensitivity values was assessed by paired *t* tests. To assess the adequacy of deafferentation, the mean maximal changes in renal nerve activity that were elicited by intracoronary nicotine were computed, and paired *t* tests were used to determine whether there were significant differences in these responses before and after epicardial phenol or saline. In all cases, a value of $P<.05$ was considered to be statistically significant.

For the sonomicrometry experiments, measurements of end-diastolic segment length and LAP were made at the end of each stage of hemorrhage and volume expansion. In these experiments, a solid-state transducer (Millar Instruments Inc) was placed into the left ventricle, and the output of this transducer was fed into a differentiator (Gould Electronics). End-diastolic segment length measurements were made at the onset of the positive dP/dt signal. The changes from baseline that occurred in end-diastolic segment length and LAP during blood volume manipulations were calculated. These values were combined and means±SEM were computed. Repeated-measures ANOVA was used to determine whether phenol

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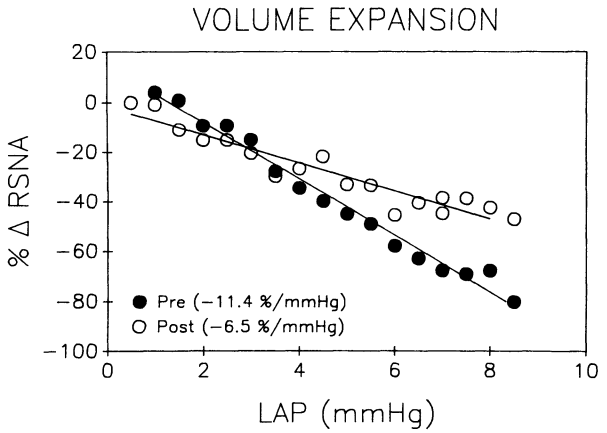

FIG 1. Graph showing results of volume expansion in a representative experiment from the inferoposterior deafferentation group. Left atrial pressure (LAP) measurements made during volume expansion are shown on the horizontal axis. Corresponding percent changes in renal sympathetic nerve activity (% Δ RSNA) are shown on the vertical axis. Volume expanded before (Pre, solid symbols) and after (Post, open symbols) phenol application. Reflex sensitivity values (slope determined by linear regression) are shown in parentheses.

application had a significant effect on the segment length–pressure relations.

Results

Baseline values of left atrial and mean arterial pressures and the changes that occurred in these pressures during blood volume manipulations are shown in the Table. There were no significant differences in baseline LAPs before and after epicardial phenol or saline. In addition, the changes in LAP were similar before and after epicardial phenol or saline, indicating that hemorrhage and volume expansion provided a comparable stimulus to the vagal cardiopulmonary receptors in all groups of experiments. Mean arterial pressures were significantly lower during the latter phases of the experiments, but the changes in mean arterial pressure that occurred with volume manipulations were similar before and after either epicardial phenol or saline.

Effect of Inferoposterior Deafferentation

The results observed during volume expansion in a single representative experiment from this group are shown in Fig 1. This figure also illustrates the methods used to analyze the experimental data. As expected, LAPs were elevated by volume expansion both before and after phenol application. These elevations in LAP elicited reflex decreases in RSNA. The slope of the relation between percent changes in RSNA and mm Hg changes in LAP (ie, reflex sensitivity) as determined by linear regression analysis was −11.4 (r=.99) before phenol. After phenol application, reflex sensitivity was reduced to −6.5 (r=.96).

Mean reflex sensitivity values (±SEM) for all animals in which epicardial phenol was applied to the inferoposterior left ventricle are illustrated in Fig 2. For volume expansion (left), there was a decrease in reflex sensitivity after inferoposterior deafferentation that just failed to reach statistical significance (pre, −12.5±1.8; post, −8.1±0.6; P=.055). The magnitude of this change in reflex sensitivity was modest in that reflex inhibition

Baseline Left Atrial and Mean Arterial Pressure Values and Changes From Baseline in Left Atrial and Mean Arterial Pressures During Blood Volume Manipulations in All Experimental Groups

	Hemorrhage		Volume Expansion	
	Pre	Post	Pre	Post
LAP				
Inferior	3.6±0.4	4.6±0.8	0.9±0.4	1.9±0.6
Total	6.5±0.6	7.0±0.8	2.9±0.7	3.8±0.6
Sham	7.1±0.7	6.5±0.7	4.5±0.7	4.1±0.4
Δ LAP				
Inferior	−4.4±0.3	−4.6±0.4	7.9±1.2	8.4±0.9
Total	−6.6±0.4	−6.2±0.6	11.0±0.7	10.9±0.9
Sham	−5.5±0.4	−5.0±0.5	8.2±0.8	8.8±1.0
MAP				
Inferior	139±5.2	118±5.7*	123±7.3	106±5.7*
Total	133±5.2	119±5.9*	115±6.2	96±6.6
Sham	139±7.0	122±6.1*	133±7.1	109±6.8*
Δ MAP				
Inferior	−62±6.7	−56±5.2	42±4.8	37±5.3
Total	−48±3.1	−53±4.9	30±4.4	39±2.9
Sham	−50±5.8	−53±7.8	21±4.3	26±6.3

Pre indicates before epicardial phenol or saline; Post, after epicardial phenol or saline; LAP, left atrial pressure (mm Hg); Δ LAP, change in left atrial pressure (mm Hg); MAP, mean arterial pressure (mm Hg); and Δ MAP, change in mean arterial pressure (mm Hg). Values represent mean±SEM.
*P<.05 Pre vs Post by paired t test.

of RSNA during volume expansion remained readily apparent despite interruption of vagal afferents from the inferoposterior LV. For hemorrhage (right), inferoposterior deafferentation had no significant effect on reflex sensitivity (pre, −17.8±2.4; post, −18.5±4.4; P=.88). Decreases in LAPs during hemorrhage elicited similar reflex increases in renal nerve activity before and after inferoposterior phenol application.

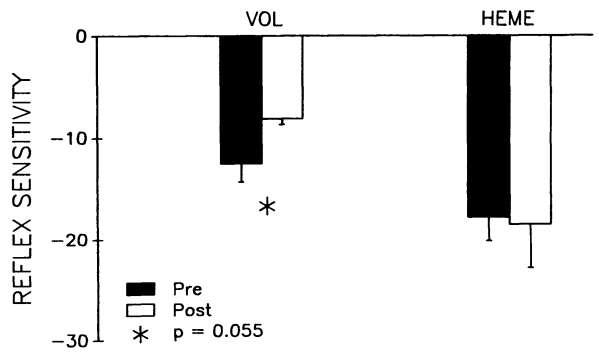

FIG 2. Bar graph showing mean±SEM reflex sensitivity values (percent change in renal sympathetic nerve activity per mm Hg change in left atrial pressure) computed from volume expansion (VOL, left) and hemorrhage (HEME, right) in the inferoposterior deafferentation group. Measurements made before phenol application (Pre) are shown in solid bars. Measurements made after phenol (Post) are shown in open bars.

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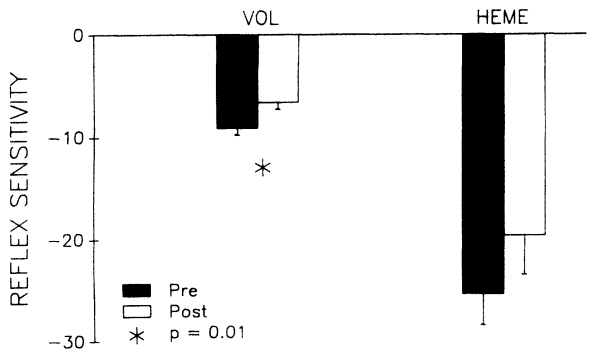

FIG 3. Bar graph showing mean±SEM reflex sensitivity values measured in the total left ventricular deafferentation group. Format is similar to Fig 2.

Effect of Total LV Deafferentation

Mean reflex sensitivity values (±SEM) for the group in which phenol was applied to the entire LV are shown in Fig 3. For volume expansion (left), there was a significant decrease in reflex sensitivity after total LV deafferentation (pre, −9.1±0.7; post, −6.6±0.7; P=.01). Although this decrease was statistically significant, the magnitude of the change in reflex sensitivity was modest. After application of phenol to the entire LV, elevation of LAP during volume expansion still resulted in substantial reflex inhibition of renal nerve activity. For hemorrhage (right), a decrease in reflex sensitivity also was observed after phenol application, but the magnitude of this change was small and it did not reach statistical significance (pre, −25.3±3.1; post, −19.6±3.8; P=.09). As was noted with volume expansion, the ability of the vagal cardiopulmonary reflex to increase RSNA in response to hemorrhage was well preserved after total LV deafferentation.

Effect of Sham Deafferentation

Mean±SEM reflex sensitivity values observed for the group in which saline was applied to the LV are shown in Fig 4. Elevation of LAP by volume expansion elicited similar reflex decreases in RSNA before and after epicardial saline (pre, −11.1±1.4; post, −11.3±1.4; P=.91). Similarly, epicardial saline had no significant effect on reflex increases in RSNA elicited by decreases in LAP during hemorrhage (pre, −17.7±2.8; post, −16.2±3.1; P=.62).

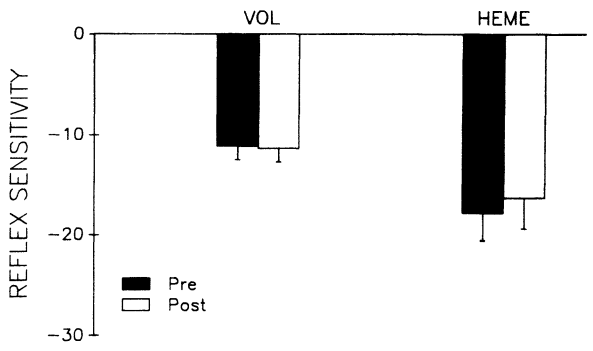

FIG 4. Bar graph showing mean±SEM reflex sensitivity values in the sham deafferentation group. Format is similar to Fig 2.

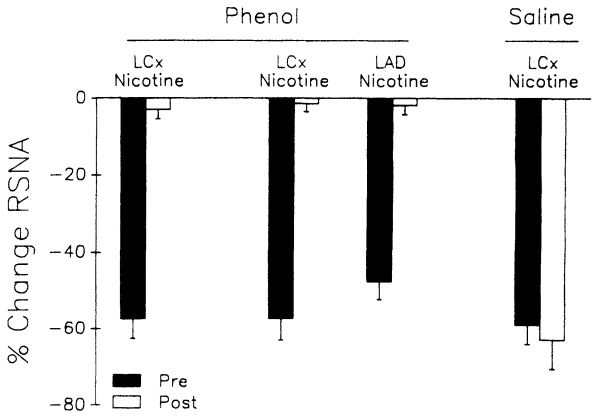

FIG 5. Bar graph showing mean±SEM maximal percent changes in renal sympathetic nerve activity (% change RSNA) observed during intracoronary nicotine injection. Responses were measured before (Pre, solid bars) and after (Post, open bars) either epicardial phenol or saline application. Responses to circumflex artery (LCx) injection in the inferoposterior deafferentation group (left), to LCx and anterior descending artery (LAD) injection in the total left ventricular deafferentation group (middle), and to LCx injection in the sham deafferentation group (right) are shown.

Responses to Intracoronary Nicotine

The percent changes in RSNA observed during injection of nicotine are shown in Fig 5. In the inferoposterior deafferentation group (left), injection of nicotine into the circumflex artery elicited large reflex decreases in RSNA (−57.5±5.2%) before phenol application. After phenol, this reflex sympathoinhibition was abolished (−2.9±2.5%), indicating that phenol effectively interrupted vagal afferent fibers in the inferoposterior LV. Similarly, in the total deafferentation group (middle), injection of nicotine into both the circumflex and anterior descending arteries resulted in inhibition of RSNA (circumflex, −57.4±5.7%; anterior descending, −47.5±4.8%). After phenol application, the responses to intracoronary nicotine were abolished, indicating that vagal afferent fibers from the entire LV were interrupted (circumflex, −1.3±2.2%; anterior descending, −1.8±2.4%). In the sham deafferentation group (right), responses to nicotine injection into the circumflex artery were not significantly affected by epicardial saline application.

Effect of Epicardial Phenol on LV Function

To determine whether epicardial phenol altered the mechanical stimulus provided to ventricular receptors by hemorrhage and volume expansion, myocardial segment length changes were measured before and after phenol application in six animals. The results of this analysis are shown in Fig 6. The relations between the changes in LAP and the changes in myocardial segment length elicited by hemorrhage and volume expansion were virtually identical before and after epicardial phenol application.

Discussion

The results of our experiments indicate that interruption of vagal afferents from the left ventricle has minimal effect on the control of sympathetic outflow to the kidney by the vagal cardiopulmonary reflex. To the best

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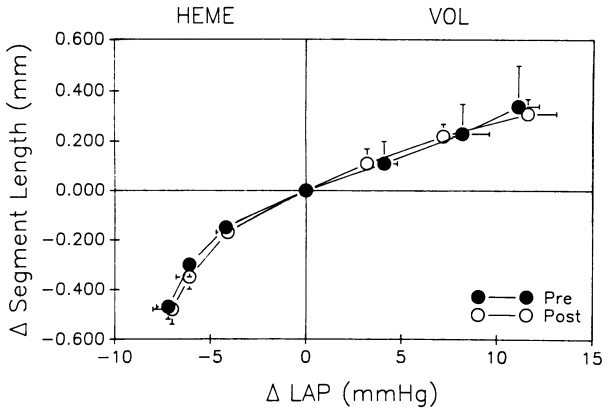

FIG 6. Graph showing myocardial segment length changes (vertical axis) during hemorrhage (HEME) and volume expansion (VOL). Changes in left atrial pressure (Δ LAP) are shown on the horizontal axis. Measurements made before (Pre, solid symbols) and after (Post, open symbols) epicardial phenol application.

of our knowledge, these are the first experiments to rigorously assess the reflex control of sympathetic outflow before and after deafferentation of left ventricular vagal afferents. Our experimental results are not surprising, considering the ubiquity of sensory receptors with vagal afferent fibers throughout the cardiopulmonary region. From an anatomic point of view, these receptors are known to be present in the lungs, in all four cardiac chambers, and in the great veins.[1] From a functional point of view, receptors in all of these areas have the potential to participate in the reflex control of sympathetic outflow. This latter point was demonstrated in early studies by Mancia and Donald.[2] They measured hemodynamic responses to vagal cold block in three groups of dogs in which only the atria, the ventricles, or the lungs were left with intact afferent innervation. In all three experimental groups, vagal cold block elicited large increases in arterial pressure, indicating that atrial, ventricular, and pulmonary receptors independently exert tonic inhibition of sympathetic outflow from the central nervous system. Although this is an important observation, these experiments provided no insight regarding the relative importance of afferent input from any one particular area of the cardiopulmonary region, nor did they assess the consequences that loss of afferent input from one region might have on reflex responses to physiological stimuli such as cardiac pressure or volume changes.

Several recent observations suggest that the ventricles, particularly the left ventricle, may be the most important source of vagal afferent input from the cardiopulmonary region. Striking abnormalities in vagal cardiopulmonary reflexes have been demonstrated both in humans with cardiac transplants[4,5] and in animals with chronic myocardial infarction.[3] Specifically, reflex increases in forearm vascular resistance elicited by low levels of lower-body negative pressure (LBNP) are markedly attenuated after cardiac transplantation in humans. Similarly, reflex increases in efferent RSNA elicited by hemorrhage are virtually abolished in dogs with chronic inferoposterior myocardial infarction. The mechanism responsible for these reflex abnormalities has not been determined. Both cardiac transplantation and chronic myocardial infarction interrupt afferent fibers that originate mainly in the ventricles, while afferent fibers that originate in the atria and the lungs remain largely undisturbed. However, a causal link between ventricular deafferentation and abnormal vagal cardiopulmonary reflexes has not been established. In fact, recent studies have raised questions about whether vagal cardiopulmonary reflexes are abnormal after cardiac transplantation. Jacobsen et al[11] observed reflex increases in muscle sympathetic nerve activity during low levels of LBNP in transplant patients. However, in their studies, even low levels of LBNP were associated with changes in arterial pressure, which likely engaged the sinoaortic baroreflex. When changes in arterial pressure during LBNP were prevented by concomitant infusion of phenylephrine, reflex increases in muscle sympathetic nerve activity were markedly attenuated. This observation supports the concept that vagal cardiopulmonary reflexes are abnormal after cardiac transplantation. Joyner et al[12] observed reflex increases in forearm vascular resistance during low levels of LBNP in patients with heart-lung transplants. However, the number of patients studied was small (three), and comparative measurements were not made in a control group.

Considering the complex pathophysiological state that exists after cardiac transplantation and chronic myocardial infarction, it is possible that there is no relation between abnormalities of the vagal cardiopulmonary reflex and interruption of ventricular afferent fibers. Nevertheless, the existence of a causal relation would have important physiological implications. Such a relation would indicate that ventricular afferent fibers are more important than atrial or pulmonary afferent fibers in determining the control of sympathetic outflow by the vagal cardiopulmonary reflex. As a result, severe disturbances in the reflex control of sympathetic outflow may complicate pathological processes that involve only the ventricles or perhaps only the inferoposterior wall of the left ventricle where the vagal receptors are preferentially distributed.[13,14]

The purpose of our experiments was to assess directly the effects of left ventricular deafferentation on control of sympathetic outflow by the vagal cardiopulmonary reflex. Epicardial phenol was used as an experimental tool to create a state of regional and global left ventricular deafferentation without otherwise altering ventricular function. Histologically, phenol applied to the epicardium in this manner has been shown to produce a layer of epicardial necrosis 0.25 mm in depth.[9] Barber et al[10] demonstrated that epicardial phenol can be used to interrupt both ventricular vagal and sympathetic afferent fibers. Our experimental results confirm their observations. We found that reflex sympathoinhibition resulting from activation of left ventricular vagal afferents by intracoronary nicotine was abolished by epicardial application of phenol. This indicates that epicardial phenol effectively interrupted left ventricular vagal afferent fibers in our experiments. Furthermore, epicardial phenol appeared to have no significant effect on left ventricular function. Relations between changes in cardiac filling pressure elicited by blood volume manipulation and changes in myocardial segment length were virtually identical before and after phenol application. On the basis of these findings, we conclude that this experimen-

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tal technique provides a model of pure left ventricular deafferentation that is unaffected by other confounding pathophysiological factors that may be present in more complicated states such as cardiac transplantation and chronic myocardial infarction.

Using this experimental technique, we found that the physiological consequences of both regional and global left ventricular deafferentation are small. Inhibition of renal nerve activity by the vagal cardiopulmonary reflex in response to elevation of cardiac filling pressures was attenuated after both inferoposterior and total left ventricular deafferentation. Statistically, this attenuation was more pronounced after global as opposed to regional deafferentation. In both cases, however, the magnitude of this attenuation was small. As a result, the physiological significance of this change in reflex sensitivity is probably minimal. Substantial reflex inhibition of renal nerve activity during volume expansion was observed after both inferoposterior and total left ventricular deafferentation. During decreases in cardiac filling pressures, neither regional nor global left ventricular deafferentation had a significant effect on the control of sympathetic outflow by the vagal cardiopulmonary reflex. After deafferentation, decreases in cardiac filling pressures continued to elicit large reflex increases in renal nerve activity.

Our experiments were performed in animals with sinoaortic denervation so as to facilitate evaluation of the vagal cardiopulmonary reflex and to eliminate potentially confounding effects of the arterial baroreflex. We measured the control of sympathetic outflow to the kidney by the vagal cardiopulmonary reflex in response to alterations of cardiac pressures and volumes. Hemorrhage and volume expansion were used to alter blood volume. Our goal was to assess the reflex control of sympathetic outflow in response to a physiological stimulus. The changes in cardiac filling pressures elicited by hemorrhage and volume expansion are comparable to the changes that may occur during common orthostatic stresses. The responses to these maneuvers were measured before and after phenol application. To ascertain whether the hemodynamic and reflex nerve traffic changes elicited by hemorrhage and volume expansion were reproducible, we performed control experiments in which the responses were measured before and after epicardial application of saline. The results of these control experiments indicate that epicardial saline had no significant effect on reflex sensitivity values for either hemorrhage or volume expansion (Fig 4). Therefore, we conclude that the responses to repetitive manipulations of blood volume are consistent.

Although we measured reflex responses to a mechanical stimulus (ie, blood volume manipulation), we used a chemical stimulus to confirm the adequacy of left ventricular deafferentation. Ideally, it would have been preferable to assess the extent of deafferentation with a mechanical stimulus that was selective for the left ventricle. From a technical point of view, it is extremely difficult, if not impossible, to apply a mechanical stimulus to the left ventricle without affecting the pressures in the lungs and other cardiac chambers. Therefore, a chemical stimulus was chosen because it could be delivered selectively to receptors located in the left ventricle. Nicotine was chosen as the chemical stimulus because previous studies in which vagal afferent activity was recorded directly indicated that this agent activated both mechanosensitive and chemosensitive sensory endings.[15,16] Thus, it is unlikely that our experimental results are related to an unrecognized failure of phenol application to interrupt mechanosensitive left ventricular vagal afferents. Although chemicals administered by the intracoronary route can potentially activate receptors located in the atria and the right ventricle, the reflex responses to intracoronary nicotine were abolished after phenol application to the left ventricle. On the basis of this observation, we would conclude that the contribution of atrial and right ventricular receptors to the reflex responses to intracoronary nicotine is minimal.

As alluded to above, epicardial phenol has been shown to interrupt sympathetic as well as vagal afferent fibers.[10] Sympathetic afferents do appear to have a significant role in reflex responses to pathological stimuli such as myocardial ischemia.[17-21] However, we think that there is little evidence that sympathetic afferents play a direct role in reflex control of sympathetic outflow during physiological changes in blood volume. Observations in both anesthetized and conscious dogs indicate that reflex changes in renal nerve activity elicited by hemorrhage and volume expansion are mediated entirely by the sinoaortic baroreflex and the vagal cardiopulmonary reflex.[22-24] After sinoaortic denervation and vagotomy, reflex changes in sympathetic outflow during blood volume manipulation are abolished. On the basis of these observations, we feel that the responses we measured in our dogs with sinoaortic denervation were mediated exclusively by the vagal cardiopulmonary reflex and that interruption of sympathetic afferents by epicardial phenol had no significant effect on our experimental results.

In summary, our data demonstrate that epicardial phenol effectively interrupts vagal afferent fibers originating in the left ventricle. Control of sympathetic outflow by the vagal cardiopulmonary reflex in response to elevation of cardiac filling pressures is attenuated after phenol-induced inferoposterior and total left ventricular deafferentation. However, the degree of this impairment is very mild. During decreases in cardiac filling pressures, left ventricular deafferentation has no significant effect on reflex sensitivity. From these results, we conclude that sensory input from the left ventricle is not essential to the function of the vagal cardiopulmonary reflexes. Residual receptors located throughout the cardiopulmonary region can compensate for the loss of afferent input from the left ventricle. As a result, reflex control of sympathetic outflow during changes in cardiac filling pressures is largely preserved despite left ventricular deafferentation. Finally, interruption of left ventricular afferent fibers does not replicate the marked reflex abnormalities that have been demonstrated after cardiac transplantation and chronic myocardial infarction. Thus, we speculate that these marked reflex abnormalities must be related to factors other than or in addition to ventricular deafferentation.

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