Excessive Sympathetic Nervous System Activity Decreases Myocardial Contractility

(43030)

CHARLES F. PILATI, REBECCA S. CLARK, JACQUES GILLOTEAUX, FRANK J. BOSSO, PAUL HOLCOMB, AND MICHAEL B. MARON

Departments of Physiology and Anatomy, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio 44272

Abstract. **The objective of this study was to determine whether myocardial contractility is depressed by intense activation of the sympathetic nervous system. A massive sympathetic discharge was produced by injecting veratrine or sodium citrate into the cisterna magna of anesthetized rabbits (n = 10). Two and one-half hr later, the hearts were isolated and their left ventricular (LV) performance evaluated and compared with the LV performance of hearts isolated from control animals (n = 10). LV performance was evaluated from steady-state peak isovolumic systolic and end-diastolic pressures that were generated at various end-diastolic volumes (LV function curves). The relationship between peak LV systolic pressure (or the average peak developed LV wall stress) and LV end-diastolic volume was rotated downward ($P < 0.01$) in the hearts removed from rabbits treated with veratrine or citrate. The LV end-diastolic pressure or LV end-diastolic wall stress of these hearts was not different from control at any end-diastolic volume. The diminished ability of the experimental hearts to develop systolic pressure or wall stress suggests that intense sympathetic activation depressed contractility. Severely damaged myofibers, located largely in the subendocardium, were found in these hearts. Furthermore, the depressed contractility was not related to pulmonary edema since only 2 of 10 rabbits developed edema.** [P.S.E.B.M. 1990, Vol 193]

Neurogenic pulmonary edema (NPE) frequently occurs following trauma to the central nervous system (CNS) and results from intense activation of the sympathetic nervous system (SNS). In a canine model of NPE, Lang *et al.* (1) massively activated the SNS by injecting veratrine into the cisterna magna. The veratrine injection produced a transient systemic and pulmonary hypertension that lasted about 30 min. During the hypertensive episode, cardiac output remained constant, but after about 60 min began to decrease and continued to fall during the 3-hr time course of the experiment. Moreover, the decrease in cardiac output (and stroke volume) occurred whether or not pulmonary edema developed. This could mean that injuries to specific regions of the CNS, in addition to causing pulmonary edema, may lead to impaired left ventricular (LV) contractility. This hypothesis is consistent with the findings of several investigators (2–6) who observed ECG changes in stroke victims suggestive of myocardial ischemia or myocardial infarction, and areas of myocytolysis and necrosis in the hearts examined from these patients at autopsy. Similar histologic abnormalities have also been observed in cat hearts after hypothalamic stimulation (7) and in rabbit hearts after experimental subarachnoid hemorrhage (8). Although myocardial lesions have been observed in patients and in animals after CNS trauma, no studies have been conducted to evaluate the effects of these types of injuries on LV function. Therefore, the objective of the present study was to determine whether there is an acute decrease in LV contractility associated with CNS insults that massively activate the SNS.

Received June 8, 1989. [P.S.E.B.M. 1990, Vol 193]
Accepted November 22, 1989.

0037-9727/90/1933-0225$2.00/0

Materials and Methods

Animal Preparation and Procedures. Both a control (n = 10; weight, 2.76 ± 0.14 kg) and an experimental (n = 10; weight, 2.70 ± 0.11 kg) New Zealand White rabbit of either sex were studied simultaneously during each experiment. All surgical and experimental procedures were identical except that the experimental rabbit

was injected with either veratrine or sodium citrate intracisternally to activate the SNS. The control rabbit received no injection. The rabbits were anesthetized with thiamylal sodium (18 $mg \cdot kg^{-1}$ iv) followed by α-chloralose (40 $mg \cdot kg^{-1}$ iv). The tracheas were cannulated, and the animals were ventilated with room air at a frequency of 20 $breaths \cdot min^{-1}$ using a piston-type ventilator. End-inspiratory pressure was set at 15 cm H_2O. To determine if these ventilation parameters were appropriate, blood gases were measured during the first experiment and were: pO_2, 86 and 121 mm Hg; pCO_2, 28.2 and 21.7 mm Hg; and pH, 7.44 and 7.41 for the control and experimental rabbits, respectively. The right femoral arteries and veins were cannulated with 22-gauge intravenous placement units (Angiocaths; Deseret, Sandy, UT) and connected to polyethylene tubing (PE 90) to monitor arterial pressure, withdraw blood samples, and administer supplemental doses of anesthetic as needed. In the first six experiments, the SNS of the experimental rabbit was massively activated by injecting veratrine (80 $\mu g \cdot kg^{-1}$ in 0.3 ml of saline) into the cisterna magna through a 21-gauge needle. Since pulmonary edema did not develop in these experiments, sodium citrate (16 $mg \cdot kg^{-1}$ in 1.5 ml of saline) was substituted for veratrine in the final four experiments. Two of the four rabbits injected with citrate developed pulmonary edema. The intracisternal injection of either veratrine or sodium citrate caused a transient episode of hypertension that lasted from 10 to 30 min. In the final seven experiments, a 5-ml sample of arterial blood was taken from the control and the experimental rabbits at the peak of the hypertension (approximately 5 min after the veratrine or citrate injection) to determine the plasma concentrations of epinephrine and norepinephrine. The plasma concentrations of the two catecholamines provided evidence for increased sympathetic activity. Two and one-half hr after the intracisternal injection, the animals' blood was heparinized (1000 $units \cdot kg^{-1}$) and midline thoracotomies were performed. The hearts of both rabbits were removed and their LV functions compared by evaluating their abilities to generate pressure at several different LV end-diastolic volumes (preloads). The lungs were also removed at this time to determine lung extravascular water content. Three of the four rabbits injected with citrate did not remain alive for the entire 2.5 hr. In these experiments, the hearts and lungs were removed from both rabbits when the citrate-treated animal died.

Isolated Heart Preparation and Procedures. Hearts were quickly removed from both rabbits, immediately arrested in chilled (0°C) physiologic saline, and prepared for coronary arterial perfusion. The perfusion system (Fig. 1) consisted of a reservoir, placed above the heart at a level that provided a hydrostatic pressure head of 80 mm Hg and an in-line heat exchanger that warmed the perfusate to 30°C. A T-connector was inserted in the tubing leading from the heat exchanger so that the two hearts could be mounted on the perfusion system simultaneously. This ensured that both hearts were perfused with the same solution under identical conditions. The hearts were mounted on the perfusion system by cannulating the aortas retrogradely. Coronary arterial perfusion was accomplished by directing the bicarbonate-buffered perfusate from the reservoir toward the closed aortic valve, thus driving the fluid through the coronary arteries. The venous effluent discharging from the heart was collected in a container and pumped back to the reservoir. The hydrostatic level in the reservoir was kept constant with an overflow system between the reservoir and the collecting container. The perfusate was gassed with 95% O_2–5% CO_2 and had the following composition ($mmol \cdot liter^{-1}$): NaCl, 89.0; KCl, 5.0; $CaCl_2$, 2.0; $MgSO_4$, 1.0; $NaHCO_3$, 24.0; Na_2HPO_4, 1.0; CH_3COONa, 20.0; and dextrose, 10.0. The pH and pO_2 of this solution was 7.4 and approximately 550 mm Hg, respectively.

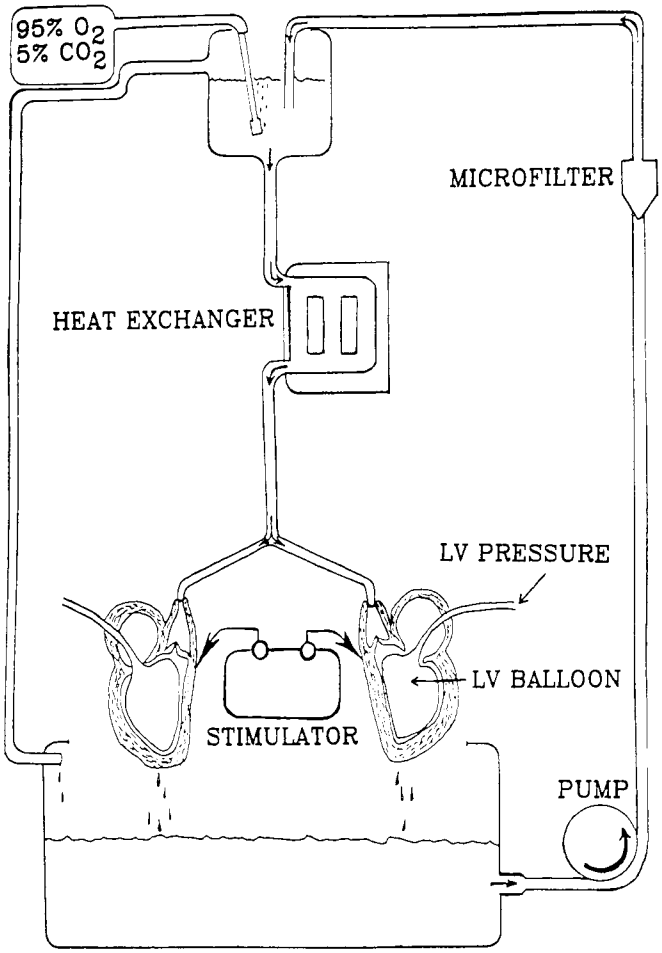

Figure 1. Schematic of the isolated heart preparation.

After the hearts were attached to the perfusion system, the atrioventricular nodes were crushed. Elec-

trodes were placed against the basal epicardial surface of each LV and the hearts electrically paced at 90 beats·min^{-1} (Grass SD9 stimulator). LV systolic and diastolic pressures of each isovolumically contracting heart were measured by placing a saline-filled balloon, connected to a pressure transducer, into the left ventricle through a small incision in the left atrium. LV preload could be changed by varying the volume of fluid in the balloon. Initially, enough fluid was added to each balloon to produce an end-diastolic pressure of 10 mm Hg, and the LV systolic pressure allowed to achieve steady state. When the systolic pressure of both hearts reached steady state, the volume in the LV balloons was decreased to 0.1 ml and the systolic and diastolic pressures were recorded. Then the balloon volumes were increased in 0.3-ml increments every 3 min until balloon volume was 1.6 ml. This provided systolic and diastolic pressure measurements at six different preloads along the ascending limb of Starling's curve. This procedure was performed on each heart in duplicate and the peak systolic and end-diastolic pressures for each preload were averaged over the two runs. LV performance was evaluated from LV function plots that were constructed from the mean steady-state peak LV systolic and end-diastolic pressures and from calculated mean developed (systolic minus diastolic) LV wall stresses. The pressure-volume relationship for the balloon alone was evaluated before each experiment and judged to be acceptable if no detectable pressures were generated by the balloon over the range of volumes used to assess LV function. At the end of each experiment, the atria and right ventricle were removed and the weight of the left ventricle was determined. In three experiments (two veratrine and one citrate), the hearts of the control and the experimental rabbits were fixed for microscopic examination prior to determining the weight of the left ventricle.

Calculation of LV Wall Stress. The average LV wall thickness was calculated for each heart at each balloon volume by making the following assumptions: the left ventricle is a homogeneous sphere, the specific gravity of the left ventricle is 1.05, and the intraventricular balloon is spherically shaped. This latter assumption permitted the chamber radius, r_i, to be calculated by setting the balloon volume (V_B) equal to (4/3) (π) (r_i)^3. The distance from the center of the balloon to the epicardial surface (r_o) was calculated by solving the following equation for r_o:

$$V_{LV} = 1.05\ M_{LV} = (4/3)\ (\pi)\ (r_o^3 - r_i^3) \qquad (1)$$

where V_{LV} and M_{LV} are the volume and weight of the left ventricle, respectively. The average circumferential and meridional LV wall stress (σ_c and σ_m, respectively) were calculated from the Laplace formulation by assuming a spherical shape for the left ventricle (9):

$$\sigma_c = \sigma_m = (pr_i^2 \cdot h^{-1}) \cdot (2r_i + h)^{-1} \qquad (2)$$

where p is the LV pressure (dynes·cm^{-2}) and h is the calculated average wall thickness ($r_o - r_i$).

Extravascular Lung Water Determinations. At the end of the experiment, the lung was removed from the thorax, the blood allowed to drain passively from the lobar vessels, and lung weighed. An equal volume of distilled water was added to the lung and this lung-water mixture was homogenized in a Waring blendor. Duplicate samples of the homogenate were centrifuged at 39,000g for 45 min at 5°C. The hemoglobin concentration of the lung supernatant samples and the hemoglobin concentration of duplicate samples of arterial blood were determined by the standard cyanmethemoglobin method. The water contents of the homogenate and the blood were determined by drying the samples to constant weight at 80°C. The blood content, the extravascular water content, and the bloodless dry weight of the lung were calculated from the equations of Pearce *et al.* (10). The extravascular water content was expressed as a function of the bloodless dry lung weight to normalize the extravascular lung water content for lungs of different size.

Plasma Catecholamine Analysis. Plasma epinephrine and norepinephrine concentrations were measured by high-performance liquid chromatography (Bioanalytical Systems, Inc., West Lafayette, IN). Samples of blood (5 ml) were collected in tubes containing 2.5 mg of sodium metabisulfite and 12.0 mg of EDTA and immediately chilled in iced water. The blood was centrifuged at 4°C and the plasma stored at −70°C until it was analyzed at a later time. The plasma catecholamines were adsorbed onto alumina at pH 8.5, eluted from the alumina with 0.1 M perchloric acid, and the acid extract injected into the high-performance liquid chromatography system containing electrochemical detection. The catecholamines were separated on a 10-cm reversed phase column using a mobile phase consisting of 75.0 mM monochloroacetic acid, 0.5 mM Na_2EDTA, and 1.0 mM sodium octyl sulfate. The pH of the mobile phase was adjusted to 3.0 with NaOH. The chromatography was performed at 28°C with column flow set at 0.9 ml·min^{-1}.

LV Microscopy. The hearts were fixed by perfusing the aortas retrogradely with 2% paraformaldehyde, 1.25% glutaraldehyde in 0.1 M cacodylate buffer for 5 min. The pH of the fixative was adjusted to 7.4 with NaOH. Blocks of tissue (<1 mm) were cut from the basal, middle, and apical regions of the LV-free wall and placed in fixative for an additional 90 min. The tissue was then washed in cacodylate buffer and post-fixed with 1% OsO_4, dehydrated in ethanol, and embedded in EMBED 812 (Electron Microscopy Sciences, Ft. Washington, PA). One-micrometer sections were cut and stained with toluidine blue (1%) and examined by light microscopy. Representative areas were selected and photographed with a Zeiss photomicroscope. Thin

sections were cut from these areas and collected on 100-mesh hexagonal copper grids (SPI, Inc., West Chester, PA). The sections were poststained with uranyl acetate and lead citrate and examined with a JEOL 100-S transmission electron microscope.

Statistics. Analysis of variance for two-factor experiments having repeated measures was used to determine whether the LV function of control and experimental rabbits was significantly different. The statistical significance of mean differences in plasma catecholamine concentrations was determined with a one-way analysis of variance. When significance was found, Neuman-Keuls *post hoc* testing was performed to determine which individual mean values were statistically different. All values reported in the text and figure legends are means ± SE.

Results

Hemodynamic Changes and Lung Water Content Associated with Veratrine or Citrate Injection. The effect of intracisternal injection of veratrine or citrate on mean arterial pressure is shown in Figure 2. Mean arterial pressure increased rapidly from 76.2 ± 6.7 to 140 ± 9.3 mm Hg when veratrine was injected into the cisterna magna. Once the pressor response had peaked, arterial pressure began to decrease, and, after 30 min, was not significantly different from the arterial pressure of control rabbits. After this time, the pressure stabilized at the control level for the remainder of this phase of the experiment. Injection of citrate caused mean arterial pressure to increase from 89.0 ± 3.7 to 161.0 ± 13.1 mm Hg in about 5 min. Then the pressure began to decrease rapidly and was not different from preinjection levels by 10 min. The pressure continued to decrease and was significantly less than control by 20 min. Three of the four animals of this group died within 60 min. The remaining rabbit survived the entire 150 min but its arterial pressure was only 35 mm Hg at this time.

The lung extravascular water content per gram of blood-free dry weight is shown in Table I. Extravascular water content did not increase in any of the veratrine-treated animals and increased significantly in only two of the four rabbits injected with citrate.

Plasma Catecholamine Analysis. Intracisternal injection of either veratrine or sodium citrate intensely activated the SNS as indicated by the large increases in plasma norepinephrine and epinephrine concentrations (Fig. 3). There was, however, one difference between the two chemicals. Although norepinephrine levels increased 10-fold with either veratrine or sodium citrate, the mean plasma epinephrine concentration did not increase significantly in the animals injected with veratrine but increased about 30-fold ($P < 0.01$) in the citrate-treated rabbits.

LV Function. LV function was diminished in the

Table I. Effect of Intracisternal Injection of Veratrine or Citrate on Lung Extravascular Water Content

Lung extravascular water content ($g\ H_2O \cdot g^{-1}$ blood-free dry wt)		
Control	Veratrine	Citrate
4.23	3.94	5.99
4.06	3.96	3.49
4.25	3.97	6.78
3.06	3.16	3.97
3.98	4.32	
4.20	3.87	
3.47		
4.24		
4.02		
4.10		
Mean 3.96	3.87	5.05
SE 0.12	0.16	0.79

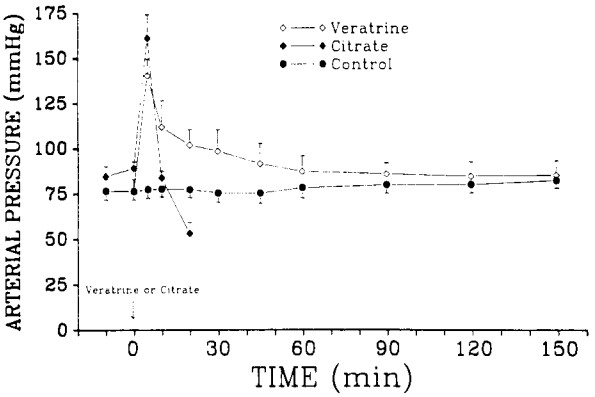

Figure 2. Mean arterial pressure after intracisternal injection of veratrine or citrate. Three of the four citrate-treated rabbits died before completing this phase of the experiment. Consequently, the pressure data shown for this group includes only those times in which all four rabbits were alive.

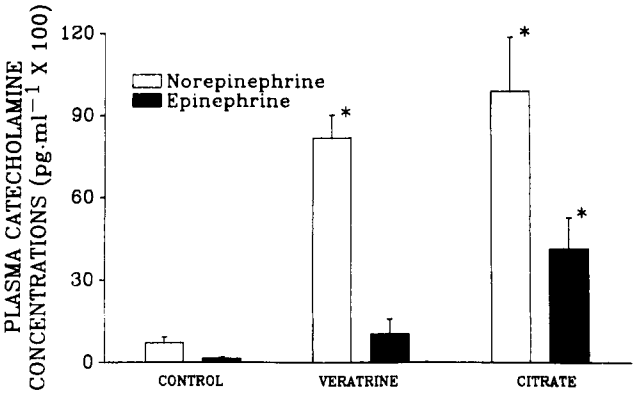

Figure 3. Effect of intracisternal injection of veratrine or citrate on plasma catecholamine concentrations. Catecholamines were measured in the final seven experiments from blood drawn at the peak of the pressor response. Control values were determined from blood taken at the same time (*$P < 0.01$ from control).

hearts isolated from rabbits that were injected with either veratrine or sodium citrate. This depression in function did not result from differences in perfusate delivery since coronary flow was the same in the control and the experimental hearts (33.2 ± 2.4 and 34.4 ± 2.0 $ml \cdot min^{-1}$, respectively). The intracisternal injection of either veratrine or citrate was equally effective in diminishing LV performance, and, consequently, the data were combined and are shown in Figure 4. The relationship between steady-state peak LV systolic pressure and LV end-diastolic volume was rotated downward ($P < 0.01$) in the hearts removed from the experimental rabbits compared with hearts taken from control animals. LV diastolic pressures were not different from control at any of the preloads studied. Thus, the passive properties of the LV chamber were not affected by the increased sympathetic activity. Figure 5 shows that the peak developed LV wall stress-LV volume relationship for the experimental hearts was also rotated downward compared with control ($P < 0.03$). This relationship

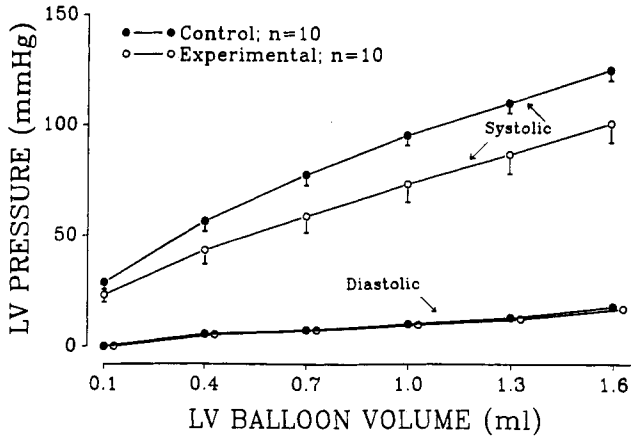

Figure 4. Systolic and diastolic function of experimental hearts compared with control. The ability of the experimental hearts to generate pressure was diminished by veratrine or citrate treatment but diastolic function was preserved.

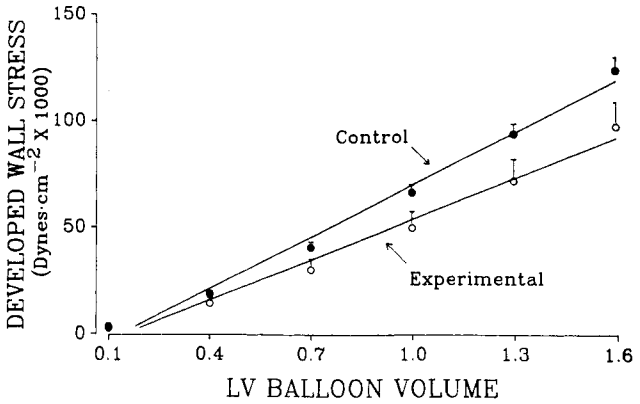

Figure 5. Peak developed circumferential and meridional LV wall stress after veratrine or citrate injection. The left ventricles of the experimental animals developed less wall stress at all levels of preload.

was linear with correlation coefficients of 0.995 and 0.992, respectively, for the control and the experimental hearts. The regression equations that describe the developed wall stress versus LV volume relationship are

$$\sigma_{Control} = 80.6\ V_{LV} - 10.6 \quad (3)$$

$$\sigma_{Experimental} = 62.9\ V_{LV} - 8.9 \quad (4)$$

where σ is the average circumferential and meridional LV wall stress (dynes·$cm^{-2} \times 10^3$) and V_{LV} is the LV volume. These equations were used to quantitatively compare the stress-volume data between the control and experimental hearts. Peak developed wall stress was equal ($\sigma_{Experimental} = \sigma_{Control}$) when the LV volume of the experimental hearts was 28.1% greater (80.6 ÷ 62.9) than that of the control hearts.

LV Microscopy. In contrast to control LV, LV from the veratrine- or citrate-treated animals showed myocyte damage characteristic of irreversible myocytolysis in many of the cells (Fig. 6). The damage, confined mainly to the subendocardium, was observed in several bundles of myofibers and was visible along

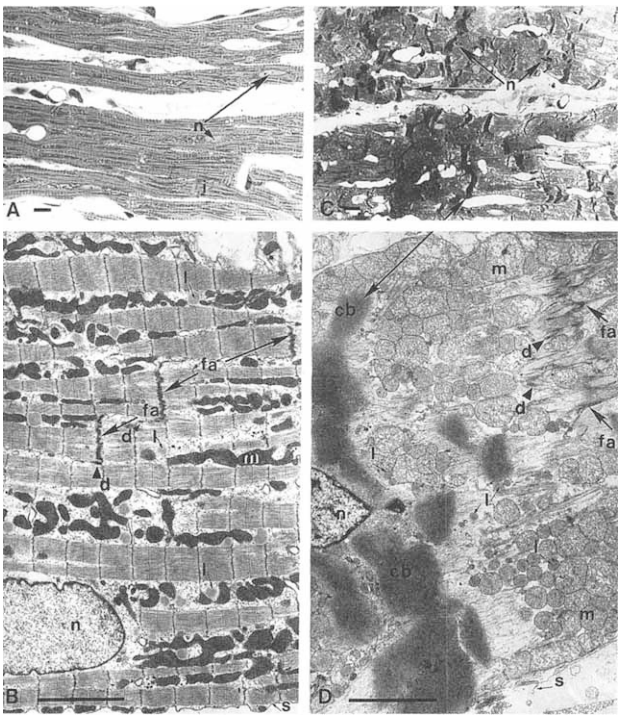

Figure 6. Representative photomicrographs of LV tissue from control and citrate-treated rabbits. Photomicrographs from control animals are shown on the left. In control LV, light microscopy shows a well-organized pattern of longitudinally oriented myofibers surrounded by the endomysium and their capillary bed (A). The ultrastructural characteristics are normal (B). Light microscopy of myocardium from a citrate-treated rabbit demonstrates thick abnormal banding and overall disruption of the myocytes (C). The ultrastructural changes (D) are consistent with irreversible myocytolysis and include sarcolemmal, mitochondrial, and myofibrillar damage. Scale bars are 10 μm (A and C) and 5 μm (B and D). cb, contraction bands; d, desmosomes; fa, fasciae adherentes; l, lipid inclusions; m, mitochondria; n, nucleus; s, sarcolemma.

the entire length of the cell. The nuclear chromatin was peripherally aggregated. The sarcolemma was discontinuous. Mitochondria were swollen (two to three times normal) and outer membrane blebs were frequently seen. The cristae were disorganized and often several were aggregated and appeared as dense structures. Granular densities were occasionally evident in the matrix. Loss of myofilaments was extensive in the deranged areas and mitochondria were often observed in the spaces previously occupied by the myofilaments. "Contraction" bands (2–4 μm) occurred extensively. The intercalated disks were wavy and less electron dense than in control myocytes and often displayed ovoid spaces at one or both sides. Fasciae adherentes and desmosomal junctions were, however, still intact in the damaged areas.

Discussion

Veratrine and citrate ion are substances that increase membrane Na^+ permeability (11), and when injected into the cisterna magna cause a massive activation of the SNS. Consequently, several investigators (12–16) have used these agents to produce experimental neurogenic pulmonary edema, a type of edema produced by excessive levels of sympathetic activity. In this study, we found that LV performance was also diminished in hearts isolated from rabbits after an intracisternal injection of veratrine or citrate. This is indicated by the downward rotation in the relationship between LV pressure development (or LV developed wall stress) and LV balloon volume. The downward shift in this relationship could have occurred if the intraventricular dimensions of the experimental hearts were larger than those of the control hearts, or if the contractile state of the experimental hearts was depressed. If the experimental hearts had larger LV chambers, sarcomere length (preload) would have been less at each balloon volume and, consequently, cardiac performance would have also been less at each balloon volume. To account for the differences in LV performance that we observed in this study, the LV chamber volume of the experimental hearts would have had to be about 28% larger than that of the control hearts. This is very unlikely since the rabbits that made up the two groups were selected randomly from a population of healthy juveniles of similar body weights and their LV weights were identical. Moreover, the fact that the diastolic pressures were the same in both groups at every LV end-diastolic volume studied suggests that the LV dimensions were not different. Thus, depressed contractility is the most reasonable explanation for the diminished LV performance exhibited by the hearts removed from the veratrine- or citrate-treated animals. The depressed LV function cannot be reasonably explained by a direct effect of veratrine on the myocardium. Although we do not know how much of the injected veratrine may have left the cisterna magna and entered the general circulation, if one conservatively assumes that the entire injected quantity (240 μg) was distributed uniformly in the extracellular space (approximately 500–600 ml), the plasma concentration of veratrine would have been within the range known to have positive inotropic actions (17, 18).[1] Moreover, since both groups of isolated hearts were perfused equally, differences in coronary flow also do not explain the diminished contractility. Furthermore, the diminished contractility was unrelated to pulmonary edema since edema developed in only 2 of the 10 treated rabbits.

The depression in myocardial contractility that we observed in this study should not be confused with the transient "relative" heart failure believed to play a major role in the development of NPE (19, 20). In this case, the term relative heart failure is used to describe the inability of a presummed normal left ventricle to pump blood against the excessive afterload produced by intense SNS activation. Consequently, central blood volume increases and pulmonary edema often occurs. This usually happens almost immediately after the onset of the sympathetic storm. In contrast, our results show that the inotropic state of the myocardium is also diminished by massive sympathetic activity. Since we evaluated LV function 2.5 hr after activating the SNS, we have no knowledge concerning the time course of this depression nor do we know to what extent it may reverse with time. However, the severe ultrastructural derangements (Fig. 6) suggest that at least a portion of the functional impairment is probably irreversible. It is not clear what role depressed contractility may play in the development of NPE. Since NPE usually develops immediately after the massive sympathetic outburst, depressed contractility is probably not a factor at this time. However, if the elevated pulmonary vascular pressures that accompany the intense SNS discharge injure the microvasculature or if permeability increases through some other mechanism, the diminished LV function could worsen the edema.

Although the mechanism responsible for the diminished LV function cannot be determined from our data, toxic concentrations of catecholamines could have been a major factor. Plasma levels of norepinephrine and epinephrine increased more than 10-fold in the blood sampled ~5 min after the intracisternal injection of veratrine or citrate, and catecholamines are known to produce biochemical (21, 22) and morphologic (22–31) aberrations and decreases in LV function (27, 30). Although the mechanism by which catecholamines injure the myocardium has not been resolved, the common findings of most investigators are sarcolemmal

[1] We have recently confirmed that the intravenous injection of 240 μg of veratrine does not alter the contractile state of our isolated heart preparation.

damage, contraction bands, swollen mitochondria, myocytolysis, and focal necrosis (22–31), and these derangements begin to develop within minutes after exposure to toxic concentrations (22, 24, 25). The ultrastructural damage we observed in the hearts from rabbits subjected to massive SNS activation appears to be identical. Interestingly, myocardial lesions, similar to those produced by exogenous administration of catecholamines, have also been found in patients who had died from intracranial trauma (2), and these types of injuries often cause elevated plasma catecholamine concentrations (32).

Previous studies have shown that myocardial lesions often develop following CNS trauma (2–8). To the best of our knowledge, our study is the first to link CNS injury and intense activation of the SNS with diminished LV contractility. Thus, decreased contractility may be relatively common in patients with intracranial injuries and could be a factor that determines their outcome.

This project was supported by the American Heart Association, Ohio Affiliate and by National Heart, Lung, and Blood Institute Grants HL-31070 and HL-43245.

The authors thank Kay Maender for her expert technical assistance.

1. Lang SA, Maron MB, Signs SA. Oxygen consumption after massive sympathetic nervous system discharge. Am J Physiol **256**:E345–E351, 1989.
2. Connor RCR. Heart damage associated with intracranial lesions. Br Med J **3**:29–31, 1968.
3. Greenhoot JH, Reichenbach DD. Cardiac injury and subarachnoid hemorrhage: A clinical, pathological, and physiological correlation. J Neurosurg **30**:521–531, 1969.
4. Hammermeister KE, Reichenbach DD. QRS changes, pulmonary edema, and myocardial necrosis associated with subarachnoid hemorrhage. Am Heart J **78**:94–100, 1969.
5. Marion DW, Segal R, Thompson ME. Subarachnoid hemorrhage and the heart. Neurosurgery **18**:101–106, 1986.
6. Norris JW, Hachinski VC, Myers MG, Callow J, Wong T, Moore RW. Serum cardiac enzymes in stroke. Stroke **10**:548–553, 1979.
7. Melville KI, Blum B, Shister HE, Silver MD. Cardiac ischemic changes and arrhythmias induced by hypothalamic stimulation. Am J Cardiol **12**:781–791, 1963.
8. Offerhaus L, van Gool J. Electrocardiographic changes and tissue catecholamines in experimental subarachnoid haemorrhage. Cardiovasc Res **3**:433–440, 1969.
9. Mirsky I. Elastic properties of the myocardium: A quantitative approach with physiological and clinical applications. Handbook of Physiology. The Cardiovascular System. Bethesda, MD: American Physiological Society, Vol **1**: p497, 1979.
10. Pearce ML, Yamashita J, Beasell J. Measurement of pulmonary edema. Circ Res **16**:482–488, 1965.
11. Shanes AM. Electrochemical aspects of physiological and pharmacological action in excitable cells. Pharmacol Rev **10**:59–273, 1958.
12. Jarisch A, Richter H, Thoma H.: Zentrogenes lungenoedem. Klin Wochenschr **18**:1440–1443, 1939.
13. Luisada AA. Mechanism of neurogenic pulmonary edema. Am J Cardiol **20**:66–68, 1967.
14. Maron MB. A canine model of neurogenic pulmonary edema. J Appl Physiol **59**:1019–1025, 1985.
15. Maron MB. Analysis of airway fluid protein concentration in neurogenic pulmonary edema. J Appl Physiol **62**:470–476, 1987.
16. Minnear FL, Kite C, Hill LA, van der Zee H. Endothelial injury and pulmonary congestion characterize neurogenic pulmonary edema in rabbits. J Appl Physiol **63**:335–341, 1987.
17. Krayer O, Acheson GH. The pharmacology of the veratrum alkaloids. Physiol Rev **26**:385–446, 1946.
18. Stearns NS, Maison GL. The action of veriloid upon the isolated mammalian heart. J Pharmacol Exp Ther **100**:238–243, 1950.
19. Sarnoff SJ, Sarnoff LC. Neurohemodynamics of pulmonary edema. I. Autonomic influence on pulmonary vascular pressures and acute pulmonary edema state. Dis Chest **22**:685–698, 1952.
20. Theodore J, Robin ED. Speculations on neurogenic pulmonary edema (NPE). Am Rev Respir Dis **113**:405–411, 1976.
21. Fleckenstein A, Janke J, Doring HJ, Pachinger O. Ca overload as the determinant factor in the production of catecholamine-induced myocardial necrosis. In: Bajusz E, Rona G, Eds. Recent Advances in Studies on Cardiac Structure and Metabolism. Baltimore: University Park Press, Vol **2**: p455, 1973.
22. Todd GL, Baroldi G, Pieper GM, Clayton FC, Eliot RS. Experimental catecholamine-induced myocardial necrosis. II. Temporal development of isoproterenol-induced contraction band lesions correlated with ECG, hemodynamic and biochemical changes. J Mol Cell Cardiol **17**:647–656, 1985.
23. Bloom S, Cancilla PA. Myocytolysis and mitochondrial calcification in rat myocardium after low doses of isoproterenol. Am J Pathol **54**:373–391, 1969.
24. Boutet M, Huttner I, Rona G. Permeability alteration of sarcolemmal membrane in catecholamine-induced cardiac muscle cell injury. Lab Invest **34**:482–488, 1976.
25. Csapo Z, Dusek J, Rona G. Early alterations of the cardiac muscle cells in isoproterenol-induced necrosis. Arch Pathol **93**:356–365, 1972.
26. Haft JI. Protection against epinephrine-induced myocardial necrosis by drugs that inhibit platelet aggregation. Am J Cardiol **30**:838–843, 1972.
27. Lee JC, Downing SE. Ventricular function in norepinephrine-induced cardiomyopathic rabbits. Am J Physiol **242**:H191–H196, 1982.
28. Milei J, Nunez RG, Rapaport M. Pathogenesis of isoproterenol-induced myocardial lesions: Its relation to human coagulative myocytolysis. Cardiology **63**:139–151, 1978.
29. Rona G, Boutet M, Huttner I, Peters H. Pathogenesis of isoproterenol-induced myocardial alterations: Functional and morphological correlates. In: Dhalla NS, Ed. Recent Advances in Studies on Cardiac Structure and Metabolism. Baltimore: University Park Press, Vol **3**: p507, 1972.
30. Werner JC, Lee JC, Downing SE. Preservation of left ventricular function by insulin in experimental catecholamine cardiomyopathy. Am J Physiol **238**:H257–H262, 1980.
31. Reichenbach DD, Benditt EP. Catecholamines and cardiomyopathy: The pathogenesis and potential importance of myofibrillar degeneration. Human Pathol **1**:125–150, 1970.
32. Neil-Dwyer G, Cruickshank J, Stott A, Brice J. The urinary catecholamine and plasma cortisol levels in patients with subarachnoid haemorrhage. J Neurol Sci **22**:375–382, 1974.