PULMONARY VASCULAR RESPONSES/Kealey and Brody

vasoconstrictor response to embolization;6-13 and (3) release of humoral vasoconstrictor substances by the emboli or processes secondary to the embolization.14

The large number of theories used to explain the etiology of respiratory distress syndrome probably results from the wide diversity of experimental models and conditions used to study the problem. The present study was undertaken with the following goals in mind: (1) to develop a reproducible, physiological model of diffuse pulmonary embolization; (2) to identify and separate the humoral and neurogenic contributions to the pulmonary vascular response to embolization, and (3) to determine the mechanisms responsible for these pulmonary responses.

Methods

Adult dogs of either sex weighing 17-25 kg were anesthetized with sodium pentobarbital, 30 mg/kg, and positioned in the field of a Siemens fluoroscope equipped with an image intensifier.

The dogs were then prepared and the lower lobe of the left lung was isolated and perfused in the manner described by Hyman.15 A special no. 18 French catheter (USCI 68336, U.S. Catheter Co.) was introduced via the left external jugular vein and guided fluoroscopically through the right side of the heart and into the lower lobar artery of the left lung. An occlusion balloon on the end of the catheter was then inflated with 1-2 ml of Renografin-60 for a visual check on position and inflation. An Intramedic polyethylene PE 100-side catheter was attached to the end of the no. 18 French USCI catheter in such a manner as to permit measurement of pressure distal to the inflated balloon. Blood was withdrawn from the inferior vena cava via a no. 20 French red rubber Robinson catheter that had been introduced through the femoral vein, passed through tygon tubing via a Sigmamotor T6S pump, and into the occluded, isolated left lower lobe. An inverted Erlenmeyer flask was placed in line in the tubing distal to the pump to damp the pressure pulse generated by the pump. Flow into the isolated lobe was in the range of 180-300 ml/min or approximately one-sixth of cardiac output. With the Sigmamotor pump, flow remained constant throughout the experiment. Cardiac output was determined by thermal dilution with a thermistor-equipped Swan-Genz catheter (93-120-6F, Edwards Lab.) placed in the pulmonary artery. This was used in conjunction with the 415-C cardiac output computer, designed and built by the Bioengineering Resource Facility at the University of Iowa. The distal part of the catheter was used to measure pulmonary artery pressure.

The right femoral artery was cannulated in order to monitor mean systemic arterial pressure. A no. 7 French pigtailed catheter (Squibb Co.) was introduced into the left femoral artery and placed in the left ventricle to monitor the left ventricular end-diastolic pressure (LVEDP). Catheter position was monitored by observing the pressure tracing.

All dogs were tracheotomized, intubated, and ventilated with a Harvard volume respirator with end-expiratory pressure at 2-4 cm H2O to prevent atelectasis. The dogs were ventilated with room air at a minute volume of 12-15 ml/kg body weight per min. This resulted in airway pressures that averaged between 6.5 and 8.2 mm Hg during the positive pressure respiratory cycle. The respiratory rate was set at 12-16 cycles/min. When required, a no. 18 French Bardic catheter with a no. 6 Flotex inflatable cuff was introduced into the left lower lobe bronchus under fluoroscopic control. The balloon was then inflated to allow independent ventilation of the left lower lobe. Harvard respirators, connected in tandem, were used to simultaneously ventilate the main lung (all lobes except left lower lobe) and the isolated left lower lobe. The minute volume of the left lower lobe under these conditions was one-sixth of the total minute volume calculated for that dog. Static compliance of the main lung and the left lower lobe was determined by separately inflating each part of the lung with a known volume of air and determining resultant pressure after elastic recoil of the inflated portion of the lung had occurred. Compliance was calculated by dividing the difference between end-inspiratory and end-expiratory pressures by volume (five-sixth tidal volume in the case of main lung and one-sixth tidal volume for the left lower lobe). When compliance measurements were made, the main lung and isolated lobe were inflated simultaneously with the tandem respirator to eliminate the influence of inflating one portion of the lung on the other.

All dogs received sodium heparin, 1000 U/kg, and were paralyzed with decamethonium bromide (Syncurine, Burroughs-Wellcome), 0.25 mg/kg. The dogs were given an intravenous infusion of Dextran-60 (6% solution) to ensure that the LVEDP was at a normal value of 5-10 mm Hg. This was done to minimize the influence of blood loss associated with filling the extracorporeal tubing. LVEDP remained in the normal range throughout the remainder of all experiments. The perfusion tubing itself was primed with Dextran-60 (6% solution).

In all experiments, the five lobes of the lung (main lung) were exposed to miliary embolization and we observed the resultant effects on the embolized main lung and the perfused protected nonembolized left lower lobe. Polystyrene copolymer beads (Dow Chemical Co.*) ranging in size from 44 to 84 μm, (mean 64 μm) and from 84 to 177 μm, (mean 130 μm) were used as emboli. The usual dose of 64-μm microemboli consisted of two 500-mg portions suspended in dextrose (5% in water) and was injected into a catheter placed in the superior vena cava via the right external jugular vein. This amount of beads was sufficient to raise main pulmonary vascular resistance acutely by 25-50% over control values. The usual dose of beads with a mean diameter of 130 μm was 500-700 mg. The same increment in pulmonary vascular resistance was used as an end point. Changes in pulmonary vascular resistance and left lobar vascular resistance were calculated by subtracting LVEDP from mean pulmonary and left lobar pressure and dividing by the respective

* The authors are indebted to Dr. Stanley Stryker (Dow Chemical Co.) for the generous supply of beads.
flows. For unknown reasons, control arterial pressure of the left lower lobe was somewhat higher than that of the pulmonary artery when the lobar flow was set at one-sixth of cardiac output.

Autologous clot emboli were prepared from 50 ml of arterial blood which was allowed to stand in a glass beaker in a warm water bath for 1–2 hours to achieve stability of the clot. The serum was then decanted and the clot minced with scissors. The clot was then placed in a plastic syringe and forced through the nozzle into a glass beaker. Random samples of the resultant mixture were placed on a glass slide and inspected with a light microscope. A microcytometer eyepiece was used to determine the size of individual fragments in the sample. This process of breaking up the clot and visual inspection of particles was continued until all observed fragments were less than 100 μm in any dimension. The usual dose of these autologous clot emboli was in the range of 4–10 g of the resultant mixture in order to raise main pulmonary vascular resistance by 25–50% above control values.

Denervation of the left lower lobe was accomplished through a left lateral thoracotomy under sterile conditions by sectioning all nerves found in the adventitia of the left lower lobar artery, vein, and bronchus. These dogs were allowed a 3-week postoperative recovery period prior to experimentation to allow recovery from the thoracotomy and for depletion of the endogenous neurotransmitter in the left lower lobe. Adequacy of denervation was evaluated in the following manner. Prior to neuromuscular blockade and after insertion of the endobronchial blockade tube, the left lower lobe was hyperinflated. Absence of a Herring-Breur reflex was taken as physiological evidence of denervation. Random samples of the main lung and the left lower lobe were taken at the end of the experiment, prepared in the manner described by Bjorklund et al. and examined for fluorescence due to catecholamines.

Statistical analysis was performed by a completely randomized design split plot analysis of variance. Dunnnett's test was used where appropriate. The level of significance was \( P < 0.05 \).

CONTROL EXPERIMENTS

A series of five dogs was used as a control group in which each dog was followed for a period of 1 hour during which time the following variables were monitored: mean systemic arterial pressure, mean pulmonary artery pressure, cardiac output, mean left lower lobar perfusion pressure, and LVEDP.

EMBOLIZATION OF MAIN LUNG

Four dogs were studied in which the main lung was embolized with polystyrene copolymer beads (64-μm). This series of dogs was then followed for a period of 1 hour during which all of the variables recorded in the control series were monitored. These dogs were compared with five that had undergone denervation of the lower lobe of the left lung and in which the main lung was embolized with 64-μm beads.

The role of the vagus nerve was studied in four dogs in which bilateral cervical vagotomy was performed prior to embolization of the main lung with 64-μm beads. Experiments to evaluate further the role of the autonomic nervous system included a series of four dogs in which ganglionic blockade was produced by infusion of hexamethonium, 10 mg/kg, over 20 minutes. The adequacy of ganglionic blockade was tested by comparing the systemic and pulmonary lobar arterial pressor response to 1 minute of bilateral common carotid occlusion before and after administration of hexamethonium. The main lung was then embolized with the standard dose of polystyrene copolymer beads with a mean diameter of 64 μm. These dogs were then followed for 1 hour.

The possibility that the response to embolization involved a cholinergic vasodilator was investigated. Six dogs received atropine sulfate, 0.25 mg/kg. Adequacy and specificity of blockade were determined by comparison of systemic and pulmonary lobar arterial pressor responses to 1 μg of intravenous acetylcholine and to 10 μg of nitroglycerin before and after atropine. The main lungs were then embolized with 64-μm beads.

The possibility of an adrenergic component of the pulmonary response to embolization was investigated. Four dogs were prepared in which β-adrenergic receptor blockade was produced by infusion of propranolol (1 mg/kg) over a 10-minute period. Specificity and adequacy of the β-blockade were determined by comparison of the change in mean systemic and pulmonary lobar arterial pressure in response to infusion of isoproterenol, 1 μg/kg, and nitroglycerin, 10 μg/kg, before and after propranolol. In three dogs, dose-response curves for isoproterenol (injected into the left lower lobe in doses of 1, 3, and 10 μg) were determined before and after propranolol (1 mg/kg). Responses to intralobar infusion of norepinephrine (1, 3, and 10 μg) and nitroglycerin (10, 30, and 100 μg) were also tested.

The histological changes resulting from miliary pulmonary embolization were studied by preparing four groups of dogs with three of either sex in each group. Each dog was screened to rule out respiratory illness by physical examination and by fluoroscopic examination of the lungs. Each dog was tracheotomized. A no. 7 French radio-opaque catheter (Cook Inc.) was introduced into the right external jugular vein and placed in the main pulmonary artery under fluoroscopic control. One dog of the group was chosen at random as the control animal and the others had 1 g of 64-μm polystyrene copolymer beads injected into the main pulmonary artery via the no. 7 French catheter. All dogs in a group were sampled at the same time interval. Groups were sampled 1, 2, 3, and 4 hours after embolization. At that time the dogs were ventilated with a Harvard respirator and thoracotomized. Prior to killing the dogs, random samples of lung parenchyma were taken, fixed, and stained with hematoxylin and cosin for light microscopy.

Results

A group of control dogs that received no emboli were studied for a 1-hour period. Data summarizing the
changes in cardiac output in these dogs and all other experimental groups are summarized in Tables 1-5. During the 1-hour period, control dogs showed no changes in cardiac output, systemic vascular resistance, pulmonary artery pressure, pulmonary vascular resistance, or vascular resistance in the isolated perfused left lower lobe. These data demonstrate that time alone had no influence on systemic and pulmonary hemodynamics. Although not shown, static complianc also was unchanged in both the main lung and the isolated lobe during this same 1-hour period.

When the main lung was embolized with 64-μm beads, pulmonary artery pressure and pulmonary vascular resistance rose. At this time there was no significant change in cardiac output, systemic vascular resistance, airway pressures, or compliance of the main lung. Two hours after embolization, compliance fell significantly by 25% and remained at this level until 4 hours.

The isolated left lower lobe, which was protected from embolization, showed a fall in vascular resistance of approximately 40-50%. There were no changes in the left lower lobar airway pressure or compliance, and LVEDP also was not altered. Thus embolization of the main lung was also not altered. Thus embolization of the main lung which is protected from the embolic insult. In five dogs an identical protocol was used except that the animals were studied for 4 hours after embolization. Main pulmonary vascular resistance was significantly elevated at 1 hour but had returned toward control at 2, 3, and 4 hours. The significant reduction in left lobar vascular resistance was sustained for the 4-hour period without changes in airway pressure, compliance, or LVEDP.

Experiments were undertaken to determine the mechanism by which this vasodilator response was produced. A series of experiments was performed on dogs in which the left lower lobe had been denervated 3 weeks prior to the study. Examination of samples obtained from these lobes at the end of each experiment revealed that fluorescence associated with catecholamine innervation in the vascular and bronchial trees was absent. Samples taken from lobes of the main lung showed normal adrenergic fluorescence patterns. As shown in the tables, typical hemodynamic responses to embolization were noted; however, the denervated lobe did not show a change in vascular resistance. The fall in vascular resistance produced by embolization of the main lung was also blocked by prior administration of hexamethionium and by bilateral cervical vagotomy.

The blockade of the left lobar vasodilator response produced by hexamethionium and by surgical denervation

### Table 1 Changes in Cardiac Output after Embolization of the Main Lung

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Initial value ± se (liters/min)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No emboli</td>
<td>2.0 ± 0.4</td>
<td>15 30 45 60</td>
</tr>
<tr>
<td>64-μm emboli*</td>
<td>2.5 ± 0.7</td>
<td>100 102 103 104 4 7</td>
</tr>
<tr>
<td>Denervated left lower lobe*</td>
<td>2.4 ± 0.4</td>
<td>101 110 97 86 5 40</td>
</tr>
<tr>
<td>Bilateral vagotomy*</td>
<td>2.7 ± 0.2</td>
<td>118 106 109 103 4 27</td>
</tr>
<tr>
<td>Systemic hexamethionium*</td>
<td>1.9 ± 0.1</td>
<td>95 104 138 127 4 54</td>
</tr>
<tr>
<td>Systemic atropine*</td>
<td>2.6 ± 0.2</td>
<td>101 112 96 95 4 14</td>
</tr>
<tr>
<td>Systemic propranolol*</td>
<td>2.1 ± 0.4</td>
<td>98 96 95 126 3 39</td>
</tr>
<tr>
<td>130-μm emboli</td>
<td>2.4 ± 0.7</td>
<td>103 115 116 97 5 22</td>
</tr>
<tr>
<td>Autologous clot emboli</td>
<td>2.0 ± 0.2</td>
<td>96 113 101 100 4 40</td>
</tr>
</tbody>
</table>

All values are expressed as percentage of initial value obtained just prior to embolization. No changes were statistically significant (P < 0.05); n = number of animals; CV = coefficient of variation. * Emboli (64-μm) administered via main pulmonary artery.

### Table 2 Changes in Systemic Vascular Resistance after Embolization of the Main Lung

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Initial value ± se (mm Hg/ liter per min)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No emboli</td>
<td>44 ± 7.3</td>
<td>15 30 45 60</td>
</tr>
<tr>
<td>64-μm emboli*</td>
<td>43 ± 4.3</td>
<td>101 93 90 95 5 15</td>
</tr>
<tr>
<td>Denervated left lower lobe*</td>
<td>44 ± 6.2</td>
<td>102 94 100 125 5 32</td>
</tr>
<tr>
<td>Bilateral vagotomy*</td>
<td>34 ± 4.9</td>
<td>75† 91 81 83 4 14</td>
</tr>
<tr>
<td>Systemic hexamethionium*</td>
<td>26 ± 4</td>
<td>77† 83† 66† 69† 4 39</td>
</tr>
<tr>
<td>Systemic atropine*</td>
<td>26 ± 3.1</td>
<td>78† 74† 64† 111† 4 51</td>
</tr>
<tr>
<td>Systemic propranolol*</td>
<td>41 ± 10</td>
<td>99 106 113 114 5 34</td>
</tr>
<tr>
<td>130-μm emboli</td>
<td>60 ± 8</td>
<td>105 77† 74† 76† 5 34</td>
</tr>
<tr>
<td>Autologous clot emboli</td>
<td>43 ± 4.8</td>
<td>95 88 97 100 4 27</td>
</tr>
</tbody>
</table>

All values are expressed as percentage of initial value obtained just prior to embolization; n = number of dogs; CV = coefficient of variation. * Emboli (64-μm) administered via main pulmonary artery. † P < 0.05.
The vasodilator response produced by embolization of specific cholinergic blockade appeared to be established. The main lung was unchanged by treatment with atropine. Thus perfusion pressure both before and after atropine. Thus the vasoconstrictor response was significantly reduced to 1.8 perfusion pressure by 2.7 mm Hg. After atropine this when injected directly into the lobe, increased lobar the main lung was examined. Acetylcholine (50 μg), blockade on the response of the lobe to embolization of the isolated lobe whereas norepinephrine produced dose-related vasconstriction. Propranolol produced a significant shift in the responses to isoproterenol (isoproterenol became one-thirtieth as potent). The specificity of β-adrenergic blockade was established by the failure of propranolol to alter the vasodilator responses produced by nitroglycerin. Of greatest interest was the observation that the vasoconstrictor effect of norepinephrine was significantly enhanced after propranolol. When the main lung was embolized with beads which averaged 130 μm in diameter, changes in pulmonary artery pressure and pulmonary vascular resistance similar to those observed in other experiments were produced. Although vascular resistance in the isolated lobe fell, as was the case with smaller emboli, the change was not statistically significant. When embolization was carried out with particles prepared from autologous clot material.

All values are expressed as percentage of initial value obtained just prior to embolization; n = number of dogs; CV = coefficient of variation.

* Emboli (64-μm) administered via main pulmonary artery.
† P < 0.05.
the typical fall in left lobar vascular resistance was obtained.

The groups of dogs that were embolized and sampled for histological study showed definite changes in the microscopic appearance of the pulmonary parenchyma. There was marked vascular congestion at 1 hour. These changes progressed to marked perivascular and interstitial edema at 2 and 3 hours after embolization. At 4 hours there was massive interstitial edema and cells and proteinaceous fluid in the alveolar spaces caused marked distortion of the pulmonary parenchymal architecture.

It is important to document that the perfused left lower lobe was in fact protected from embolization. Three lines of evidence were obtained. First, increased pressure was never observed in the perfused lobe when examined histologically (5 dogs). Second, beads were never found in the perfused lobe when the main lung was embolized. Third, the only experimental preparations considered to be satisfactory for inclusion in these studies were the ones in which the pressure in the lobar perfusion catheter fell to LVEDP when the pump was turned off, demonstrating isolation of the perfused left lower lobe from the remainder of the lung.

The experiments suggest that active neurogenic vasodilation of the pulmonary vasculature occurs in response to embolization of the lung by emboli less than 100 μm in diameter. This conclusion is based on several lines of evidence. Ganglionic blockade alone did not decrease lobar vascular resistance, indicating that the lobe does not possess adrenergic vasoconstrictor tone. Although not exactly comparable, resting lobar vascular resistance in the denervated lobe was also unchanged. Since the vasodilator response produced by embolization was abolished by both hexamethonium and chronic denervation, it must have been neurogenic in origin. Furthermore, these experiments demonstrate that an active vasodilator mechanism was responsible since the dilation could not be accounted for by withdrawal of vasoconstrictor tone.

This finding is at variance with the observations by several investigators that pulmonary embolization produces neurally mediated vasoconstriction of the pulmonary vasculature. At no time during any experiment was vasoconstriction of the perfused protected lobe noted. The experimental technique employed allows for isolation and perfusion of a lung lobe under physiological conditions in an intact animal. In addition it was possible...
to determine changes in lobar vascular resistance which were totally independent of any alterations induced directly by emboli trapped in pulmonary vessels. With two exceptions,10,11 previous studies on pulmonary embolization have measured changes in pulmonary hemodynamics in areas which have been embolized directly; i.e., it was not possible to separate changes in resistance produced by (1) mechanical obstruction, (2) local release of vasoactive substances, and (3) neurogenically mediated reflexes. Thus the results of the present investigation appear to have identified a component of the response that was masked in all other studies in which no portion of the lung was protected.

Niden and Aviado9 report on one experiment in which vasoconstriction was noted in the perfused left lower lobe when glass beads were injected into the right ventricle. Although the authors claim that the lobe was protected from embolization, their method of perfusion was not clearly described and no evidence was provided that beads did not reach the lobe.

Others have found results similar to those described here. Dunn,19 in very early studies on pulmonary embolization, concluded on the basis of measurements of pulmonary artery pressure that the failure of the pressure to be sustained after embolization was the result of pulmonary arteriolar dilation. Knisely et al.,2 using direct visualization, reported vasodilation of the pulmonary vasculature, including arterioles, in vessels not only distal to emboli but in vessels not directly downstream from emboli. Woolverton and Hyman18 studied vascular resistance changes in the perfused protected left lower lobe after embolization of the main lung. No response of the protected lobe was noted after embolization with large (150-250 \( \mu \)m) autologous clots. These data compare favorably with the present findings in which embolization with 130-\( \mu \)m particles did not significantly alter resistance in the protected lobe. Thus, the reflex and hormonal responses appear to be dependent on size of the embolus; small particles induce a net vasodilation, whereas no demonstrable effects are seen with larger emboli.

Acute cervical vagotomy prevented the pulmonary vasodilator response produced by embolization. This effect could have been the result of removal of either an efferent or an afferent pathway. Since atropine failed to influence the response, it is logical to conclude that vagotomy exerted its effect by removal of an afferent pathway originating in the lungs. Evidence already exists for the presence of sensory receptors in lungs which give rise to afferents carried through the vagus.20,21

Baroreceptors with vagal afferents in the extrapulmonary vasculature have been demonstrated by Coleridge and Kidd.22,23 These were localized in the area of the bifurcation of the main pulmonary artery and in the proximal portions of the right and left pulmonary arteries. Osorio and Roussek24 and Hyman25 have shown that nonocclusive distention of these arteries causes vasomotor response of the pulmonary vascular bed. Paintal26 and Mills et al.27 have demonstrated the presence of vagal receptors in the parenchyma of the lung. It is not clear whether they are demonstrating the same or a different receptor. However, it is clear that these receptors do exist and may be activated by a variety of stimuli including acute pulmonary hypertension, mililary embolization, noxious gases, and inhalation of small particles.20,21

There appear to be two ways in which vagal afferents arising from pulmonary vascular receptors might be involved in the reflex pulmonary vasodilator response observed in these experiments. If activation by distention of certain stretch receptors leads to vasodilation,24,25 then removal of distention in vessels beyond the site at which emboli lodge should lead to reflex pulmonary vasodilation if such receptors exist in smaller pulmonary vessels. Conversely, receptors might exist whose distention proximal to the emboli might also evoke reflex vasodilation.

The postembolic neurogenically mediated vasodilation, described in the experiments reported here, appears to consist of a central nervous system-mediated reflex involving vagal afferents and an adrenergic vasodilator efferent system. The vasodilating vasodilator does not appear to be involved, since no vasodilation was noted in dogs that had undergone previous surgical denervation of the left lower lobe. The blockade of postembolic lobar vasodilation by ganglionic blockade and by surgical denervation suggests that the efferent limb of the vasodilation is mediated through the autonomic nervous system.

The vasodilator response appears to be mediated by a \( \beta \)-adrenergic receptor mechanism. The evidence for this is as follows: (1) the vasodilation was prevented by pretreatment with the \( \beta \)-adrenergic receptor blocking agent, propranolol; (2) dose-dependent vasodilation was produced in the perfused left lower lobe with the prototype \( \beta \)-adrenergic receptor agonist, isoproterenol; (3) the vasodilator effect of isoproterenol is significantly reduced by propranolol; (4) the dose-dependent vasoconstrictor response of the lobe to intra-arterial administration of norepinephrine was potentiated by propranolol.

References

A Possible Change in the Rate-Limiting Step for Cardiac Norepinephrine Synthesis in the Cardiomyopathic Syrian Hamster

MICHAEL J. SOLE, ARVIND B. KAMBLE, AND M. NASIR HUSSAIN

SUMMARY The development of heart failure in the cardiomyopathic hamster is associated with a decrease in norepinephrine stores and parallel increases in cardiac sympathetic tone and tyrosine hydroxylase activity. Despite the increase in tyrosine hydroxylase, cardiac norepinephrine synthesis does not increase in heart failure. In this study, we have shown that an accumulation of cardiac dopamine accompanies the decline of cardiac norepinephrine. The abnormal content of norepinephrine and of dopamine in the decompensating hamster heart is restored to normal by peripheral ganglionic blockade. The acute increase in cardiac sympathetic tone induced by immobilization stress in control hamsters mimics the alterations in cardiac catecholamine distribution found in heart failure. Other investigators have demonstrated similar alterations in the catecholamine content of the rat submaxillary gland and adrenal medulla following an increase in sympathetic input to these organs. We conclude that the increase in cardiac sympathetic tone in the late stages of hamster cardiomyopathy appears to lead to a shift in the rate-limiting step for norepinephrine synthesis from the hydroxylation of tyrosine to the hydroxylation of dopamine. There is evidence that this shift which results in an accumulation of dopamine in the noradrenergic nerve terminals of the heart is a general manifestation of augmented sympathetic nerve traffic rather than a peculiarity of hamster cardiomyopathy.

The putative rate-limiting step for the biosynthesis of norepinephrine is the hydroxylation of tyrosine to dopa catalyzed by the enzyme tyrosine hydroxylase. We observed an increase in the activity of this enzyme in the myopathic hamster heart during cardiac decompensation. This increase in tyrosine hydroxylase correlated well with the increase in cardiac sympathetic tone. However, cardiac norepinephrine synthesis remained relatively constant, failing to reflect these increases. It is possible that, despite the measured increase in tyrosine hydroxylase activity in vitro, changes in precursor, product, and cofactor relationships obtaining in vivo obviated an increase in vivo synthesis. It also was possible that the hydroxylation of tyrosine was no longer the rate-limiting step for norepinephrine synthesis in the failing myopathic hamster heart and that the hydroxylation of dopamine became...
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