Adverse Effect of Therapeutic Vasoconstrictors in Experimental Acute Pancreatitis

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Alpha-adrenergic drugs commonly are used to treat hypotension resulting from severe acute pancreatitis. It was shown previously that although systemic arterial pressure is increased by phenylephrine, pancreatic microcirculatory perfusion is decreased. Because inadequate tissue perfusion may be critical in the progression of edematous pancreatitis to parenchymal necrosis, it was hypothesized that vasoconstrictors might be harmful in pancreatitis. Therefore the effect of phenylephrine on cerulein-induced mild pancreatitis were studied. Sprague-Dawley rats (n = 54) were randomly allocated to 6 experimental groups and subjected to the following infusion regimens: (1) cerulein (cae) + phenylephrine (phe), (2) cae + saline (NS), (3) NS + phe, (4) cae + phenoxybenzamine (pbz) + phe, (5) NS + pbz + phe, and (6) NS. Initial and terminal hematrocrit, serum amylase activity, and blood ionized calcium concentration were determined. The animals were killed 9 hours after starting the infusion. Macroscopic and histologic changes were scored by a 'blinded' pathologist. Phenylephrine increased the severity of cerulein-induced pancreatitis as manifested by statistically significant adverse changes in serum amylase, hematocrit, ionized calcium, peripancreatitic soap formation, and acinar cell vacuolization. These changes were antagonized by alpha-adrenergic receptor blockade with phenoxybenzamine. It is concluded that phenylephrine is deleterious in acute experimental pancreatitis, the first demonstration of such an effect by a pharmacologic vasoconstrictor, and suggested that microcirculatory changes may be important in the transition of mild to severe pancreatitis. Caution in the use of vasoconstrictor drugs in patients with acute pancreatitis is recommended.

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W HILE THE TRADITIONAL concept of acute pancreatitis is that the primary injury is enzymatic, there is increasing evidence that ischemia may be critical in the initiation of or progression to necrosis.[1] Experimental[2-5] and clinical[6-8] studies have indicated that the pancreas is highly susceptible to ischemic damage. Dynamic contrast-enhanced computed tomographic (CT) scans both in humans and in experimental animals have shown that reduced perfusion of the microcirculation early in the course of acute pancreatitis correlates with more severe pancreatitis and in particular with the development of areas of necrosis.[9] Variations in pancreatic perfusion therefore may alter the course of the illness.

Alpha-adrenergic vasoconstricting drugs commonly are used as an adjunct in treating the hypotension characteristic of severe early acute pancreatitis. However we have observed that phenylephrine, an alpha-1 receptor agonist, markedly reduces pancreatic microcirculatory perfusion in the rat[10] and have also noted an association between the increasing use of vasoconstrictors and pancreatic injury in patients undergoing cardiopulmonary bypass.[8] Therefore we investigated the effect of phenylephrine on the severity of cerulein-induced pancreatitis in rats.

Materials and Methods

The following studies were approved by the Subcommittee on Animal Care at the Massachusetts General Hospital.

Male Sprague-Dawley rats (Charles River Labs, Chelmsford, MA), weighing 320 to 350 g, were anesthe-

tized for vascular cannulation by administering intraperitoneal ketamine (44 mg/kg) and pentobarbital (20 mg/kg). Using aseptic technique a PE-10 polyethylene catheter (Becton-Dickinson, Parsipanny, NJ) was inserted into the right internal jugular vein for infusion of drugs. An additional PE-10 catheter was placed into the right carotid artery for blood sampling and arterial pressure monitoring. Both catheters then were tunnelled subcutaneously to the subscapular area and brought out through a lightweight flexible spring. The catheters were flushed with 0.5 mL of heparinized saline (10 U/mL) after insertion. The arterial catheter was subsequently flushed with 1 mL heparinized saline 6 and 18 hours after the operation. The animals were housed in individual stainless steel cages and allowed to recover overnight. The spring containing the catheters exited the cage through a hole on top and was connected to a swivel that permitted unrestrained movement of the animal. The animals were given water *ad libitum.* The experiments were performed on unanesthetized conscious animals in their home cages the next day.

Arterial pressure was monitored using a Spectramed (072911-00-075, Spectramed, Oxnard, CA) transducer linked to an 8-channel Hewlett-Packard Recorder 7758A (Hewlett-Packard, Downers Grove, IL). Mean arterial pressure (MAP) and pulse were recorded for 1-minute segments at each time point described below. Blood samples were collected through the arterial catheter and analyzed for serum amylase activity,[11] blood ionized calcium (ion-selective electrode "Nova 2," Nova Biomedical, Waltham, MA), and hematocrit.

In all animals 0.05 mL of blood was withdrawn for measuring baseline hematocrit and replaced by 0.2 mL of 0.9% NaCl 30 minutes before the assessment of baseline blood pressure and heart rate. Heart rate, pulse, and MAP were recorded while rats were resting quietly, starting approximately 18 hours after placement of catheters. The hemodynamic parameters were followed hourly as well as 10 minutes after starting the phenylephrine infusion and 10 minutes after administration of phenoxybenzamine, respectively. Throughout the experimental period, the arterial catheter was connected to a high-pressure infusion system delivering 0.9 mL per hour of heparinized saline (1 unit per mL). Nine hours after the start of the infusion, blood was withdrawn from the arterial catheter for determination of hematocrit, serum amylase activity, and ionized calcium concentration. The animals were killed by a lethal injection of intravenous pentobarbital.

Experimental Design

Fifty-four rats were distributed randomly to six experimental groups (Table 1). To study the effects of vaso-

TABLE 1. *Treatment Groups*

Group	Treatment
I	Cerulein + phenylephrine
II	Cerulein + normal saline
III	Normal saline + phenylephrine
IV	Cerulein + phenoxybenzamine + phenylephrine
V	Normal saline + phenoxybenzamine + phenylephrine
VI	Normal saline

constriction, 30 rats were allocated to experimental groups I to III. To investigate the effects of alpha receptor blockade, an additional 24 rats were allocated randomly to experimental groups IV to VI. The treatment groups are shown schematically in Figure 1 and described below.

Group I (cerulein + phenylephrine, n = 12): Acute edematous pancreatitis was induced by the intravenous bolus injection of 3 μg/kg of cerulein (Peninsula Labs., Belmont, CA) followed by a continuous infusion of 5 μg/kg/hr (0.48 mL/hr) for 6 hours. Four hours after commencing the cerulein infusion, phenylephrine HCL (neosynephrine, Winthrop-Brenon, New York, NY), diluted in NS, was infused at a rate of 3 mg/kg/hr, allowing for a constant total infusion volume of 0.94 mL per hour. The infusion was terminated 2 hours after completing the cerulein infusion (total of 4 hours of phenylephrine infusion). Animals were killed 1 hour after completing the phenylephrine infusion (*i.e.*, 9 hours after beginning the cerulein infusion).

Group II (cerulein + normal saline, n = 10): Acute edematous pancreatitis was induced as in group I. Four hours after commencing cerulein infusion, normal saline was infused for 4 hours at a rate of 0.94 mL/hr.

Group III (normal saline + phenylephrine, n = 8): Rats were given a 0.3-mL bolus of normal saline at the start of the experiment followed by an infusion of 0.48 mL/hr. Four hours after commencing the saline infusion, phenylephrine HCL was infused at a rate of 50 μg/kg/min (0.94 mL/hr) for 4 hours.

Group IV (cerulein + phenoxybenzamine + phenylephrine, n = 7): Cerulein infusion was begun as in group I. Three hours and 15 minutes after beginning cerulein infusion, 5 mg of phenoxybenzamine (5 mg/mL) in normal saline was infused over 15 minutes to establish alpha blockade. Four hours after beginning the cerulein infusion, phenylephrine infusion was begun in a manner identical to that of groups I and III.

Group V (normal saline + phenoxybenzamine + phenylephrine, n = 8): Animals were given saline infusion rather than cerulein. Phenoxybenzamine and phenylephrine were administered exactly as in Group IV.

Group VI (Normal saline controls, n = 7): Appropriate volumes of normal saline were used in identical volume
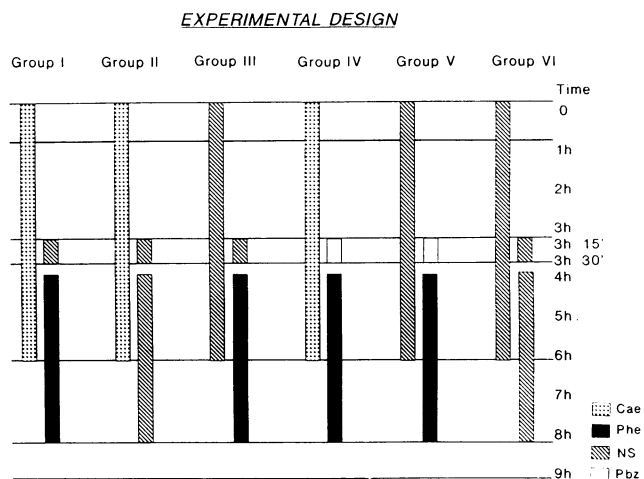
FIG. 1. Schematic diagram showing the sequence and combinations in which cerulein(cae), phenylephrine(phe), and saline(ns) were administered to the experimental group.

and time sequence as substitutes for cerulein, phenoxy-benzamine, and phenylephrine following the sequence of Group IV.

Morphology

After the animals were killed, postmortem examination of the abdomen was performed by a 'blinded' pathologist. Pancreatic edema and peripancreatic soap formation were graded according to the following scale: Pancreatic edema, + = confined to the tail, maximal the width of the spleen, ++ = head and tail, +++ = head and tail, the latter exceeding the width of the spleen; peripancreatic soap formation, + = 1 focus, ++ = 2 foci, +++ = confluent areas.

Thereafter the whole pancreas (with duodenum and spleen attached) was removed, fixed in 10% buffered formalin, and embedded in paraffin. Six histopathologic parameters were analyzed quantitatively from a single transverse section through the long axis of the pancreas: i.e., edema, parenchymal necrosis, inflammation, vacuolization, hemorrhage, and fat necrosis. Edema was scored as follows: 1+ if interlobular septae were expanded; 2+ if intralobular septae were expanded; and 3+ if individual acini were separated by edema. Parenchymal necrosis was quantified as follows: 1+ = 1 to 4 necrotic acinar cells per high-power field (HPF); 2+ = 5 to 10 cells per HPF; 3+ = confluent aggregates of more than 10 necrotic acinar cells. Inflammation was scored as follows: 1+ = 2 to 10 intralobular neutrophils per HPF; 2+ = more than 10 intralobular neutrophils per HPF without confluent aggregates or microabscesses; 3+ = confluent aggregates or microabscesses. Vacuolization was scored as 1+ if less than one third of the acinar cells in a HPF had prominent

cytoplasmic vacuoles; 2+ if between one third and two thirds of the acinar cells had vacuoles; and 3+ if more than two thirds had vacuoles. Hemorrhage and fat necrosis were scored as follows: 1+ = 1 focus per slide; 2+ = 2 foci per slide; and 3+ = 3 or more foci per slide.

Statistical Analysis

All values are expressed as mean ± standard deviation (SD). All parameters were tested for normal distribution. The following data were assessed by Student's t test: MAP, heart rate, and blood-ionized calcium. Because of large variance, especially in group I, serum amylase and hematocrit were subjected to Fisher's exact test. Probability values less than 0.05 were considered significant.

Results

Serum Amylase

As expected cerulein infusion caused a significant increase in the serum amylase activity (groups I, II, and IV) when compared with each of the experimental groups not receiving cerulein (Fig. 2). The addition of phenylephrine to cerulein caused a significantly higher amylase concentration than cerulein infusion alone (group I, 1076 ± 647 U/L versus group II, 709 ± 128 U/L (p < 0.05).

Blood-ionized Calcium

Blood-ionized calcium was significantly lower in group I (cae + phe) than group II (cae + ns) (p < 0.05) (Fig. 3). The difference between group I and group IV approximated significance (p = 0.05), suggesting that phenoxybenzamine partially counteractivated the effect of phenylephrine.
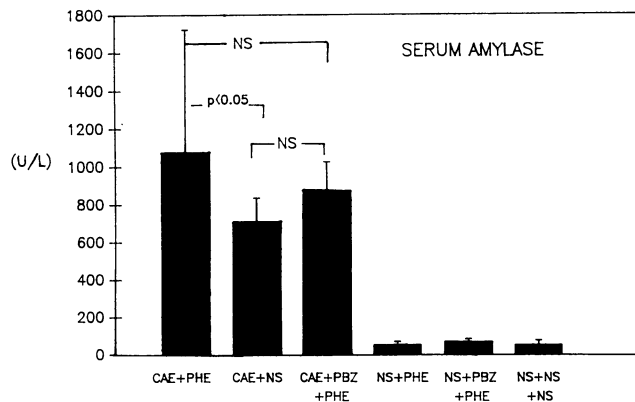

FIG. 2. Serum amylase activity in animals receiving cerulein plus phenylephrine infusion was significantly higher than animals receiving cerulein and normal saline infusion. Phenylephrine infusion alone did not alter control levels of serum amylase.
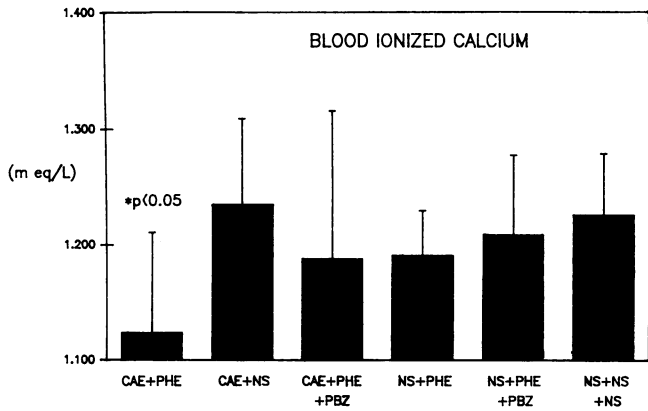
FIG. 3. Blood ionized calcium was significantly lower in rats receiving cerulein and phenylephrine that rats receiving cerulein + normal saline.

Hematocrit

The mean hematocrit level in group I increased by 4.75% ± 13.7% in contrast to all other groups, which showed decreases in the hematocrit (Fig. 4). This difference was statistically significant (p < 0.05 by Fisher's exact test). There was no significant difference between group II and group IV. Thus phenylephrine superimposed changes on cerulein-induced pancreatitis that were abolished by phenoxybenzamine.

Gross Pathology

Significantly more peripancreatic fat necrosis was observed in group I (cae + phe) than in groups II (cae alone) or IV (cae + pbz + phe) (Table 2). This observation is again consistent with an adverse effect of phenylephrine on cerulein pancreatitis and blockade of the effect by phenoxybenzamine. There were no other significant differences in the macroscopic appearances among the
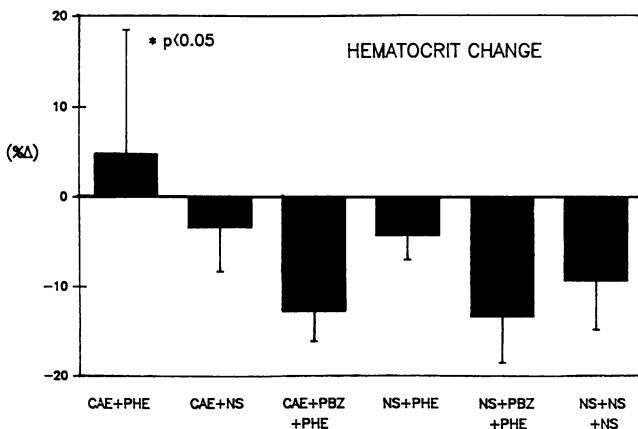

FIG. 4. Hemoconcentration, manifested as an increase in the mean hematocrit, occurred only in animals receiving cerulein and phenylephrine infusion.

TABLE 2. Gross Pathology

Group	Edema	Peripancreatic Fat Necrosis
I	12/0	4/8*
II	10/2	0/12
III	1/7	0/8
IV	6/1	0/7
V	0/8	0/8
VI	0/8	0/8

* = p < 0.01 vs. all other groups.
Data are expressed as a ratio: number of rats with changes >1+/number of rats with changes ≤1+. Peripancreatic soap formation was greatest in animals receiving cerulein and phenylephrine.

groups with acute pancreatitis. The pancreas appeared normal on gross inspection in the control groups (III, V, and VI).

Histology

Pancreatitis was seen only in animals that received cerulein infusion (groups I,II, and IV) (Table 3). The extent of edema, inflammation, hemorrhage, and necrosis did not significantly differ among the groups with acute pancreatitis. Microvascular thrombosis and vasculitis were not frequently observed. Significantly more vacuolization was seen in rats receiving cerulein plus phenylephrine (group I) compared to those receiving cerulein alone (group II). This change was not abolished by alpha receptor blockade (group IV). In three rats the quality of the histologic preparation was not suitable for analysis.

Hemodynamics

Phenylephrine infusion (50 μg/kg/min) increased MAP from 110 ± 11 mmHg to 144 ± 10 mmHg (Fig. 5A). There was a concurrent decrease in heart rate (423 ± 39 to 336 ± 57 beats/min (Figure 6A). Mean arterial pressure promptly returned to baseline with cessation of phenylephrine infusion. Phenoxybenzamine infusion caused a

TABLE 3. Histology

Group	Edema	Inflammation	Necrosis	Vacuolization
I	12/0	9/3	8/4	12/0*
II	10/0	7/3	4/6	4/6
III	3/5	0/8	0/8	0/8
IV	7/0	6/1	2/5	7/0*
V	0/8	0/8	0/8	0/8
VI	0/7	0/7	0/7	0/7

* = p < 0.05 vs. group II.
Data are expressed as a ratio: number of rats with changes >1+/number of rats with changes ≤ 1+. Cerulein and phenylephrine produced significantly more vacuolization than cerulein alone. This change was not abolished by phenoxybenzamine.
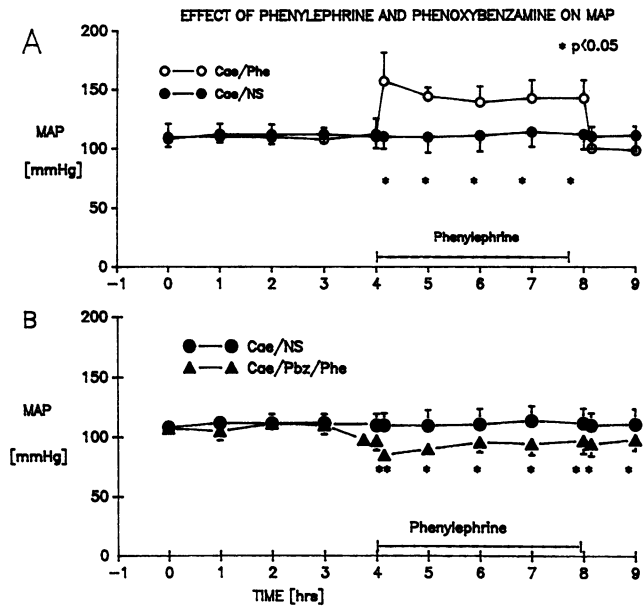
FIG. 5. Intravenous infusion of phenylephrine caused an immediate and significant increase in MAP (A). Alpha-adrenergic blockade by phenoxybenzamine caused a decrease in MAP. The addition of phenylephrine in the presence of alpha blockade caused a further decrease in MAP due to unmasking the weak beta agonist activity of phenylephrine (B).

decrease in MAP from 110 ± 7 mmHg to 97 ± mmHg (p < 0.05). The addition of phenylephrine in the presence of established alpha blockade by phenoxybenzamine led to a further decrease in MAP (Fig. 5B). Accompanying the decrease in blood pressure was an increase in heart rate (Fig. 6B).

Mortality

One rat in group IV died shortly after beginning the intravenous infusion, presumably due to catheter-related embolism. No other deaths occurred during the experimental period.

Discussion

The importance of reduced blood flow in the pathogenesis of acute pancreatitis has been investigated in a variety of ways. In 1948 Popper[2] demonstrated that short-term arterial occlusion following the induction of edematous pancreatitis (by duct ligation and hyperstimulation) led to the development of necrosis. Pfeffer's[3] work focused attention on the importance of the microcirculation. He demonstrated that obstruction of terminal arterioles by the intra-arterial injection of 8 to 20 μ microspheres caused hemorrhagic pancreatitis. In contrast larger microspheres produced only pancreatic edema, presumably because collateral flow was capable of maintaining microcirculatory perfusion. Subsequent investigators have confirmed

that microcirculatory disturbances occur in the pathogenesis of experimental pancreatitis.[12-17] Intravital microscopy has demonstrated directly capillary blood flow impairment within 60 minutes of the induction of biliary pancreatitis.[18]

Clinical evidence also supports the importance of ischemia in the pathogenesis of pancreatitis. In 1978 Warshaw and O'Hara[6] noted a high incidence of pancreatitis in cardiac surgical patients who were in a low output state. This relationship was confirmed in subsequent studies.[7,8] Recently contrast-enhanced CT has been used to study pancreatic perfusion and the subsequent development of pancreatic necrosis. The extent of hypoperfused pancreas on admission CT scans predicts the subsequent development of pancreatic necrosis, abscesses, and death.[9]

Phenylephrine is an alpha adrenergic agent widely used to produce vasoconstriction in critically ill patients. Phenylephrine increases total peripheral resistance and can be accompanied by considerable hemodynamic changes, including a decrease in cardiac output and reduced splanchnic blood flow.[19,20] In rats it causes increases in MAP and total peripheral resistance and a decrease in cardiac output at doses between 3 and 10 μg/kg/min.[19] Despite increased MAP, doses greater than 25 μg/kg/min
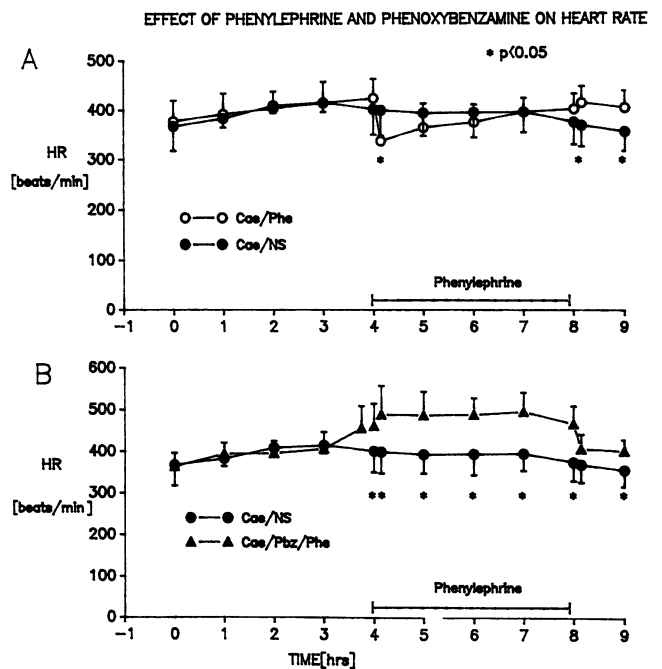

FIG. 6. Phenylephrine infusion initially caused bradycardia in conjunction with an increase in MAP when compared to animals receiving cerulein infusion alone. However, after completion of the infusion, animals that had received cerulein plus phenylephrine had a significantly increased tachycardia, presumably due to intravascular volume contraction (A). Phenylephrine infusion in the presence of alpha blockade by phenoxybenzamine accentuated tachycardia due to inherent weak beta agonist activity of phenylephrine.

decrease splanchnic perfusion.[21] This finding has been ascribed to vasoconstriction and has been demonstrated in experimental preparations as well as in humans.[20–25] We have shown with intravital microscopy in the rat that phenylephrine reduces pancreatic microcirculatory flow to 36% of controls.[10] Recently, using reflectance spectroscopy, we also have found that oxyhemoglobin levels in pancreatic tissue decrease by 25% and deoxyhemoglobin levels increase correspondingly during phenylephrine infusion.[26]

In the current study, a dose of 50 μg/kg/min was used to produce splanchnic vasoconstriction. This dose is well tolerated by the rat for up to 6 days.[27] In our model the hemodynamic effect of phenylephrine was documented by an increase in MAP of 30 to 40 mmHg accompanied by bradycardia[19,28] (Figs. 5 and 6). These changes were completely abolished with alpha receptor blockade by phenoxybenzamine as previously described.[29,30] The characteristic decrease in blood pressure and increase in heart rate were augmented by the subsequent addition of phenylephrine. This was due to the weak beta-agonist activity of phenylephrine.

In this study phenylephrine administration increased the severity of cerulein-induced pancreatitis. This finding was confirmed by higher serum amylase activity, hemoconcentration, hypocalcemia, an increase in pancreatic soap formation, and an increase in acinar cell vacuolization.

In certain experimental models, serum amylase activity correlates with the severity of pancreatitis (in contrast to most clinical situations). In Sokolowski's model using short-term ischemia of the pancreas, the serum amylase level correlated well with varying degrees of pancreatic injury.[4] In the cerulein model of pancreatitis, serum amylase levels parallel the histologic changes.[31–33] Therefore it seems appropriate, in our model, to interpret the significantly higher amylase in group I (cerulein + phenylephrine) as an indication of more severe pancreatitis.

Hemoconcentration is a common finding in patients presenting with acute pancreatitis and the volume of intravenous fluid necessary to reverse this change is generally accepted as a parameter reflecting the severity of the disease.[34] In our studies hemoconcentration was only observed in the animals that received cerulein and phenylephrine. Mild hemodilution was observed in all other groups. This fact provides further evidence of more severe pancreatitis in group I.

Hypocalcemia is also a well-established prognostic marker for the severity of pancreatitis.[34] Although many mechanisms have been proposed to account for hypocalcemia, no single explanation has been widely accepted. While it is tempting to attribute hypocalcemia to sequestration of calcium in areas of fat necrosis, human autopsy studies have shown that the quantity of calcium in soap formation is insufficient to account for the observed changes.[35,36] Nonetheless, in rats, the extent of intra-abdominal fat necrosis correlates with severity of pancreatitis.[4,5,37] In these experiments hypocalcemia was only observed in animals receiving both cerulein and phenylephrine. Rats receiving both cerulein and phenylephrine also had the most pronounced peripancreatic soap formation. These data provide further evidence that phenylephrine caused a worsening of cerulein-induced pancreatitis.

Morphologic changes of pancreatitis were only seen in animals receiving cerulein. The histologic changes of pancreatitis were similar to those described originally by Lampel and Kern[38] and Tani.[33] Phenylephrine alone or in combination with phenoxybenzamine did not cause pancreatitis. In the cerulein model of pancreatitis, vacuolization is a relatively early change, seen within the first 9 hours of the illness. In contrast inflammatory cell infiltration is more prominent at a slightly later time period (9 to 12 hours). Those animals receiving phenylephrine in addition to cerulein demonstrated more vacuole formation than other groups receiving cerulein alone or in combination with phenoxybenzamine. The 9-hour period of observation in our study was too brief to evaluate the full extent of inflammation and necrosis, but the increased vacuolization seen in group I is histologic evidence of more severe pancreatitis.

It seems most likely, in consideration of the known effects of phenylephrine on the pancreatic microcirculation, that the observed harmful effects of phenylephrine on otherwise mild cerulein-induced pancreatitis are due to impairment of pancreatic perfusion, rather than some other unspecified action on acinar cell membrane receptors. Despite increased MAP both cardiac output and splanchnic blood flow have been documented to decrease under similar experimental conditions.[21] Although we did not quantitate pancreatic perfusion in this study, the proposed mechanism is supported by the abolition of these changes by phenoxybenzamine. Despite a significant decrease in MAP in animals receiving phenoxybenzamine + phenylephrine + cerulein, most of the changes indicative of more severe disease were prevented. A previous study using an identical dose of phenoxybenzamine demonstrated that pancreatic perfusion was preserved in the presence of alpha blockade, despite a decrease in MAP of 32 mmHg.[39] Furthermore it has been shown that improvement of pancreatic perfusion during biliary pancreatitis reduces the extent of parenchymal injury.[40]

The present study demonstrates that mild interstitial pancreatitis can be worsened by the systemic administration of phenylephrine. While there is much previous evidence that ischemic injury may be an important factor

in the aggravation and progression of acute pancreatitis, this is the first demonstration that a pharmacologic agent causing reduced blood flow can augment the injury. Whether this phenomenon is due to direct action on the pancreatic microcirculation or an indirect action *via* globally diminished splanchnic blood flow is not shown by these experiments. In either case the protection afforded by alpha adrenergic blockade supports the hypothesis that pancreatic hypoperfusion is the mechanism of action. These experimental results lead us to suggest that vaso-constrictor agents may worsen pre-existing pancreatitis in humans and therefore should be avoided if possible.

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