Effect of Distension of the Gallbladder on Plasma Renin Activity in Anesthetized Pigs

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Background—Gallbladder pathology has been associated with cardiovascular disease. Recently, we showed that gallbladder distension in anesthetized pigs reflexly increased heart rate, arterial pressure, and coronary and renal vascular resistance through efferent sympathetic mechanisms. Renin release is affected by sympathetic output, and angiotensin liberation may result in vasoconstriction. This study was undertaken to determine whether gallbladder distension primarily causes a reflex change in plasma renin activity (PRA) and to assess its influence on observed pressor and coronary responses as well as on regional vascular resistance.

Methods and Results—In 34 α-chloralose–anesthetized pigs, balloons positioned within the gallbladder were distended for 30 minutes with volumes of Ringer’s solution equal to those of withdrawn bile. In 19 pigs, gallbladder distension at constant heart rate, arterial pressure, and renal flow increased PRA in the absence of changes in urinary sodium excretion. This increase was abolished by cervical vagotomy, section of renal nerves, or blockade of β-adrenergic receptors. In another 15 pigs, blockade of angiotensin II receptors significantly attenuated the pressor and coronary, mesenteric, and iliac vasoconstrictive responses to gallbladder distension.

Conclusions—The present study showed that innocuous gallbladder distension primarily caused a reflex increase in PRA. This increase, which involved afferent vagal pathways and efferent sympathetic mechanisms related to β-adrenergic receptors, contributed significantly to the pressor and coronary, mesenteric, and iliac vasoconstrictive responses to gallbladder distension. (Circulation. 2000;101:2539-2545.)

Key Words: gallbladder ■ renin ■ reflex ■ blood pressure ■ vasoconstriction

Some reports have indicated an association between gallbladder and cardiovascular diseases in humans.1–3 In anesthetized patients, distension of the gallbladder or distortion of its wall was found to cause tachycardia.4,5 In experimental animals, distension of the gallbladder and stimulation of its mechanoreceptors are known to activate afferent vagal or splanchnic nerve fibers.6–9 Also, rapid biliary tract distension in anesthetized dogs was found to cause a reduction in myocardial blood flow that was abolished by vagotomy10 and in anesthetized ferrets to increase blood pressure.11 Gallbladder distension is also reported to increase blood pressure or produce inconsistent hemodynamic changes in anesthetized cats.6,12

Recently, innocuous gallbladder distension in anesthetized pigs was shown to cause reflex tachycardia, pressor responses, and renal and coronary vasoconstriction that involved afferent vagal pathways.13,14 The efferent limb of these responses involved sympathetic pathways. The tachycardia involved β-adrenergic effects, whereas pressor and renal and coronary vasoconstrictive responses were mediated by α-adrenergic effects.14–16 It is possible that this widespread sympathetic activation might affect renin release from kidneys17 and the liberated angiotensin hormone, which can have a potent vasoconstrictor effect.18

Therefore, the present study was planned to determine the primary reflex effect of innocuous distension of the gallbladder on plasma renin activity (PRA) and the mechanisms involved. Also, the study planned to assess the possible contribution of the hormone angiotensin to the observed pressor and regional vasoconstrictive responses, which include that of the coronary circulation.

Methods

The experiments were carried out in 34 pigs weighing 64 to 72 kg that were supplied by an accredited dealer (Azienda Cornelia srl, San Pietro Mosezzo, Novara, Italy). Food was withheld from all animals on the morning of the experiments, which were carried out in accordance with the Decreto legislativo 27 gennaio 1992, n. 116 (Attuazione della Direttiva n. 86/609/CEE in materia di protezione degli animali utilizzati a fini sperimentali o ad altri fini scientifici). As previously reported in detail,14 pigs were anesthetized with ketamine (20 mg/kg IM, Parke-Davis) followed in 15 minutes by a bolus of α-chloralose (100 mg/kg IV, Sigma) and were artificially ventilated with oxygen-enriched air by respiratory pump (Harvard 613, Harvard Apparatus). Anesthesia was maintained by continuous

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infusion (0.5 to 1.0 mg · kg⁻¹ · min⁻¹ IV) of 1% α-chloralose in saline solution.

Pressures in the ascending aorta and right atrium were obtained through right femoral artery and right external jugular vein catheters connected to pressure transducers (Statham P23 XL, Gould). Through left-sided thoracotomy, the heart was paced via the left atrial appendage by a stimulator (model SS8800, Grass Instruments; 3 to 5 V, 2 ms). Through a midline abdominal incision, an electromagnetic flowmeter probe (model BL 613, Biotronex Laboratory Inc) was positioned around the left renal artery, and in some pigs, a probe was also positioned either around the anterior descending coronary artery or superior mesenteric and left external iliac arteries. A plastic snare was placed distal to each probe for zero blood flow assessment. Each probe was calibrated in vitro at the end of experiments. The ureters were catheterized to collect urine and measure its sodium concentration with a flame photometer (model System E2A, Beckman). As previously described in detail, a balloon catheter was used to distend the gallbladder slowly with Ringer’s solution maintained at 38°C and to measure the pressure in the balloon. The volume of bile withdrawn was measured for use as the distending volume, and distending transmural pressure was calculated as the difference between balloon pressure inside and outside the gallbladder.

In preliminary experiments, aortic blood pressure responses were prevented without changing cardiac pressures by a pressurized reservoir as previously described. Coagulation of blood was avoided by intravenous injection of heparin (Parke-Davis; initially 500 IU/kg, subsequently 50 IU · kg⁻¹ · 30 min⁻¹). Arterial blood samples were used to measure the pH, PO₂, PCO₂ (IL 1304, IL Instrumentation Laboratory), and hematocrit. The acid-base status and rectal temperature were monitored and kept within normal limits, as previously reported.

PRA was assayed by a method previously described. Briefly, left renal vein blood samples (5 mL) were obtained to measure PRA (ng Ang I · mL⁻¹ · h⁻¹) by radioimmunoassay with an antibody supplied by Sorin Biomedica. Each sample was split to provide duplicates for assessment of variability of measurement in terms of individual differences.

Mean ABP and right atrial blood pressure, pressure in the balloon, and mean and phasic blood flows were monitored and recorded together with HR by an electrostatic strip chart recorder (Gould ES 2000, Gould). HR was obtained from the ECG with a ratemeter (ECG/Biotech amplifier, model 13-4615-65A, Gould). Regional vascular resistance was calculated from ABP and blood flow.

At the end of the experiments, each animal was killed by injection of 40 mg/kg sodium pentobarbitone IV (Siegfried).

**Experimental Protocol**

The experiments were performed after ≥30 minutes at steady state with respect to measured hemodynamic variables. In each pig, gallbladder distension was performed by distending the intravisceral balloon by a volume of Ringer’s solution equal to that of bile withdrawn. Initially, 2 preliminary distensions, each lasting 1 minute, were performed in each animal without controlling any hemodynamic variable and while preventing changes in ABP. In all subsequent experiments, HR changes were prevented by atrial pacing, and the gallbladder was distended for 30 minutes. PRA was assessed during the last minute of the control period before distension, during the last minute of distension, and 30 minutes after release of distension. The volume and sodium concentrations of collected urine were measured during the last 10 of the 30 minutes. The response to distension was calculated as the difference between values during distension and the average of those obtained before and after distension. Any change in PRA caused by gallbladder distension was considered a response only when it was reversed by release of the distension.

The 34 pigs were divided into 2 main groups. In the first (19 pigs), the effect of distension on PRA was studied after a control period of 30 minutes at steady state after blockade of •-adrenergic receptors with phentolamine (Ciba-Geigy; 1 mg/kg IV). In the same experimental model, this dose abolished pressor and renal vasoconstrictor responses to gallbladder distension. In 4 of these pigs, the gallbladder was distended in 3 steps by volumes the highest of which corresponded to that of the aspirated bile.

The reflex nature of PRA response to gallbladder distension was examined by repeating the distension after 30 minutes at steady state in 15 of the 19 pigs after bilateral cervical vagotomy (5 pigs), bilateral section of the renal nerves (5 pigs), or after β-adrenergic blockade by propranolol (0.5 mg/kg IV, Sigma; 5 pigs).

In the second group of 15 pigs, the influence of changes in PRA on hemodynamic responses to gallbladder distension was investigated. Distension experiments were performed before and after blockade of angiotensin II receptors with losartan (bolus of 0.1 mg/kg followed by IV infusion of 0.1 mg · kg⁻¹ · min⁻¹, Merck). This dose has been shown to block the pressor effect of renovascular hypertension and pressor response to angiotensin II in salt-depleted dogs, and is twice that used to attenuate the pressor effect of angiotensin II in anesthetized dogs. The blocking effect was confirmed in preliminary experiments by reducing pressor responses to angiotensin II infusion by ~50% without a drastic effect on baseline blood pressure levels. Experiments of gallbladder distension were repeated after steady-state values of hemodynamic variables were attained after ~40 minutes of losartan infusion. RBF changes were avoided by injection of phentolamine into the renal arteries (7 mg for each artery), and a secondary influence of baroreceptor activity was minimized by denervation of carotid sinuses.

We examined the effect of gallbladder distension on ABP (5 pigs), on CBF (5 pigs), and on MBF and IBF (5 pigs). In these experiments, changes in regional perfusion pressure were minimized by an aortic constriction with a plastic snare placed around the thoracic aorta close to the diaphragm. Blood pressures proximal and distal to the constriction were measured.

**Statistical Analyses**

Student’s paired t test was used to examine changes in measured variables caused by gallbladder distension. The relationship between gallbladder transmural pressure and changes in PRA was examined by the least-squares procedures for linear correlation analysis. A value of P < 0.05 was considered statistically significant. Group data are presented as mean ± SD (range).

**Results**

In all pigs, recordings commenced ~5 hours after the induction of anesthesia. The pH, Po₂, and Pco₂ of arterial blood were 7.39 ± 0.02 (7.36 to 7.42), 120 ± 9.1 (103 to 137), and 39.3 ± 1.2 (37 to 42) mm Hg, respectively, and the hematocrit was 37.7 ± 1.8% (33% to 41%). The distending volume of Ringer’s solution used was 63.4 ± 16.3 (35 to 105) mL, and the transmural pressure was 13.2 ± 3.7 (8 to 21) mm Hg. This value of transmural pressure was not significantly different (P = 0.40) from that measured inside the gallbladder before it was emptied.

The initial gallbladder distension increased mean aortic blood pressure (ABP) by 11.6 ± 2.7 (6 to 17, P < 0.0005) mm Hg and heart rate (HR) by 6.6 ± 1.9 (4 to 12, P < 0.0005) bpm from control values of 102.3 ± 11.6 (80 to 128) mm Hg and 110.4 ± 11.5 (89 to 130) bpm. At constant ABP, HR increased by 11.1 ± 2.5 (8 to 18, P < 0.0005) bpm, and renal blood flow (RBF) decreased by 44 ± 21 (24 to 67, P < 0.0005) mL/min from control values of 412 ± 44 (310 to 510) mL/min. These responses were as previously described and determined HR responses for use with atrial pacing.

**First Group of Experiments**

In the first group, phentolamine decreased ABP by 24.4 ± 9.1 (10 to 46, P < 0.0005) mm Hg. This was accompanied by HR...
In 15 pigs in which distending transmural pressure was 12.5±4.1 (8 to 22) mm Hg, changes in hemodynamic variables and in urinary sodium excretion (USE) were small and insignificant (Table). However, in each pig, gallbladder distension increased PRA (Figure 1); group increases were 2.50±1.61 (0.98 to 7.58, P<0.0005) ng angiotensin (Ang) I·mL⁻¹·h⁻¹ from control values of 4.83±2.57 (2.56 to 13.12) ng Ang I·mL⁻¹·h⁻¹. Each PRA response was greater than its measurement variability; group variability was 0.45±0.24 (0.12 to 0.95) ng Ang I·mL⁻¹·h⁻¹.

In the remaining 4 pigs, the gallbladder was distended in 3 steps by volumes of 52.5, 67.5, and 82.5 mm Hg, respectively. Increasing the distending volume augmented the response of PRA (Figure 2). The 3 group increases were 1.90±0.48 (1.21 to 2.24, P<0.0025), 2.57±0.63 (1.64 to 3.02, P<0.0025), and 3.07±0.74 (2.01 to 3.61, P<0.0025) ng Ang I·mL⁻¹·h⁻¹, respectively, from control values of 4.80±0.95 (3.91 to 6.12) ng Ang I·mL⁻¹·h⁻¹. Each PRA increase was greater than its measurement variability; for each, this was 0.56±0.07 (0.48 to 0.65), 0.56±0.31 (0.24 to 0.93), and 0.27±0.08 (0.17 to 0.36) ng Ang I·mL⁻¹·h⁻¹. Changes in measured hemodynamic variables and USE were small and insignificant (P>0.20). The responses of PRA to the distending volumes were significantly different from each other (P<0.0025). Also, there was a significant linear trend (r=0.86, P<0.0005) between PRA responses and gallbladder transmural pressure.

Figure 1. Response of PRA to distention of gallbladder in 15 pigs. Values obtained during test period of distension are plotted on ordinate against control values on abscissa. Continuous line is line of equality.
Experiments After Vagotomy

In 5 pigs, cervical vagotomy increased HR by 11.4±1.2 (7 to 15, P<0.0005) bpm, without significantly changing ABP and RBF; their changes were 1.2±7.8 (−11 to 8, P>0.35) mm Hg and −2±18 (−31 to 15, P>0.40) mL/min. During subsequent experiments, transmural pressure was 14.2±5 (8 to 20) mm Hg, and changes in measured hemodynamic variables and USE were small and insignificant (Table).

Vagotomy abolished PRA responses to gallbladder distension, and any resulting changes were within the variability of its measurement; this variability was 0.49±0.16 (0.29 to 0.76) ng Ang I · mL⁻¹ · h⁻¹, and PRA changes were −0.08±0.32 (−0.63 to 0.13, P>0.30) ng Ang I · mL⁻¹ · h⁻¹ from control values of 4.63±0.73 (3.85 to 5.39) ng Ang I · mL⁻¹ · h⁻¹. In the same pigs, PRA responses before vagotomy amounted to 2.14±0.89 (1.26 to 3.64, P<0.0025) ng Ang I · mL⁻¹ · h⁻¹ from control values of 4.12±0.78 (3.46 to 5.41) ng Ang I · mL⁻¹ · h⁻¹. A comparison between individual responses of PRA before and after vagotomy is shown in Figure 3.

Experiments After Section of the Renal Nerves

In 5 pigs, renal nerve section decreased RBF by 37±26 (10 to 71, P<0.025) mL/min without significantly affecting HR and ABP; their changes were 1.8±4.9 (−3 to 10, P>0.20) bpm and 0.4±5.9 (−7 to 5, P>0.40) mm Hg. During experiments after renal nerve section, the heart was paced to the same frequency as that before section. Transmural pressure was 11.6±2.1 (9 to 14) mm Hg, and changes in measured hemodynamic variables and USE were small and insignificant (Table).

Renal nerve section abolished PRA responses to gallbladder distension, and any resulting changes were within the variability of its measurement; this was 0.63±0.25 (0.30 to 1.05) ng Ang I · mL⁻¹ · h⁻¹, and PRA changes were 0.03±0.16 (−0.19 to 0.22, P>0.30) ng Ang I · mL⁻¹ · h⁻¹ from control values of 2.59±0.62 (1.71 to 3.22) ng Ang I · mL⁻¹ · h⁻¹. In the same pigs, PRA responses before the intervention were 2.39±0.84 (0.98 to 3.17, P<0.0025) ng Ang I · mL⁻¹ · h⁻¹ from control values of 3.91±1.48 (2.56 to 6.35) ng Ang I · mL⁻¹ · h⁻¹. A comparison between individual responses of PRA before and after renal nerve section is shown in Figure 4.

Experiments With Propranolol

In 5 pigs, propranolol decreased HR by 27.4±11 (18 to 38, P<0.0025) bpm and increased ABP by 10±2.9 (7 to 14, P<0.0025) mm Hg. RBF decreased by 27±11 (15 to 41, P<0.005) mL/min. Transmural pressure was 11.4±3.5 (8 to 17) mm Hg. Changes in measured hemodynamic variables and USE were small and insignificant (Table).

Blockade of β-adrenergic receptors abolished PRA responses to gallbladder distension, and any resulting changes were within the variability of its measurement; this was 0.44±0.25 (0.15 to 0.80) ng Ang I · mL⁻¹ · h⁻¹, and PRA changes were −0.01±0.20 (−0.20 to 0.32, P>0.45) ng Ang I · mL⁻¹ · h⁻¹ from control values of 3.61±1.75 (2.36 to 6.65) ng Ang I · mL⁻¹ · h⁻¹. In the same pigs, PRA responses to gallbladder distension before blockade amounted to 2.96±2.67 (1.05 to 7.58, P<0.05) ng Ang I · mL⁻¹ · h⁻¹ from control values of 6.48±3.89 (3.74 to 13.12) ng Ang I · mL⁻¹ · h⁻¹. A comparison between individual responses of PRA before and after blockade of β-adrenergic receptors is shown in Figure 5.

Second Group of Experiments

In the second group, gallbladder transmural pressure was 13.4±3.3 (9 to 20) mm Hg. Losartan did not significantly change measured hemodynamic variables (P>0.15) during the steady state, but it reduced all observed hemodynamic
responses caused by gallbladder distension (Figure 6). In all these experiments, injection of phentolamine into the renal arteries prevented RBF from changing significantly ($P>0.25$).

**Response of ABP**

In 5 pigs, gallbladder distension at constant HR before losartan increased ABP by 13.8±2.4 (11 to 17, $P<0.0005$) mm Hg from a control value of 101.6±7.7 (93 to 112) mm Hg. After losartan, the same distension increased ABP by 7.8±1.8 (6 to 10, $P<0.0005$) mm Hg from control values of 101.4±6.1 (95 to 110) mm Hg, with a reduction in pressor response of 43.8±4.7% (39.4 to 51.2 mm Hg · mL$^{-1}$ · min$^{-1}$, $P<0.0005$).

**Response of Coronary Blood Flow**

In 5 pigs, gallbladder distension at constant HR and ABP decreased coronary blood flow (CBF) by $9.9\pm2$ (6.9 to 12.2, $P<0.0005$) mL/min from control values of $54.4\pm4.3$ (48.6 to 60.3) mL/min and increased coronary resistance by 0.43±0.13 (0.33 to 0.66, $P=0.0025$) mm Hg · mL$^{-1}$ · min$^{-1}$ from control values of 1.93±0.39 (1.49 to 2.47) mm Hg · mL$^{-1}$ · min$^{-1}$. After losartan, the same distension decreased CBF by $5.3\pm1.9$ (2.9 to 7.7, $P=0.0025$) mL/min from control values of $55.2\pm5$ (47 to 60.5) mL/min and increased coronary resistance by $0.20\pm0.08$ (0.13 to 0.33, $P<0.005$) mm Hg · mL$^{-1}$ · min$^{-1}$ from control values of 1.91±0.41 (1.49 to 2.55) mm Hg · mL$^{-1}$ · min$^{-1}$; the vasoconstrictive response was reduced by $53.5\pm6.5$% (47.2 to 60.5 mm Hg · mL$^{-1}$ · min$^{-1}$, $P<0.0005$). Changes in coronary perfusion pressure were small and insignificant ($P>0.30$). An example of these coronary effects is shown in Figure 7.

**Response of Mesenteric and Iliac Circulations**

In 5 pigs, gallbladder distension at constant HR and ABP decreased mesenteric (MBF) and iliac (IBF) blood flow by $111\pm36$ (68 to 153, $P<0.0025$) and $18\pm7$ (11 to 29, $P<0.0025$) mL/min from control values of $902\pm128$ (750 to 1091) and $102\pm14$ (85 to 121) mL/min, respectively. These corresponded to increases in vascular mesenteric and iliac resistance of $15.5\pm5.8$% (7.7 to 22.2, $P<0.0025$) and $20.6\pm7.4$% (12 to 31.9, $P<0.0025$) mm Hg · mL$^{-1}$ · min$^{-1}$ from control values of $0.11\pm0.03$ (0.09 to 0.15) and $0.99\pm0.14$ (0.88 to 1.20) mm Hg · mL$^{-1}$ · min$^{-1}$. After losartan, the same distension decreased MBF and IBF by $60\pm20$ (40 to 82, $P<0.0025$) and $9\pm3$ (7 to 14, $P<0.0025$) mL/min from control values of $898\pm137$ (752 to 1103) and $103\pm16$ (89 to 125) mL/min. Mesenteric and iliac resistance increased by $8\pm2$% (5.6 to 11.1, $P<0.0025$) and $9.7\pm2.5$% (6.9 to 13.6) mm Hg · mL$^{-1}$ · min$^{-1}$ from control values of $0.11\pm0.02$ (0.09 to 0.15) and $0.98\pm0.12$ (0.87 to 1.16) mm Hg · mL$^{-1}$ · min$^{-1}$, with a reduction of the vasoconstrictive responses by $46.1\pm10.6$% (27.3 to 53.5, $P<0.0005$) and $51.4\pm6$% (42.5 to 57.4, $P<0.0005$) mm Hg · mL$^{-1}$ · min$^{-1}$, respectively. Changes in blood pressure distal to the aortic constriction were small and insignificant ($P>0.20$). An example of these effects is shown in Figure 8.

**Discussion**

The present investigation showed for the first time that gallbladder distension in anesthetized pigs primarily caused a reflex PRA increase in the absence of secondary interference from changes in HR, ABP, RBF, cardiac pressures, and USE. This reflex involved vagal afferent pathways, and its efferent limb was in the renal nerves and involved $\beta$-adrenergic receptors. In addition to reproducing the reflex pressor and coronary vasoconstriction responses previously shown in the same experimental model to involve $\alpha$-adrenergic mechanisms, 14,15 a reflex mesenteric and iliac vasoconstriction also occurred in response to gallbladder distension. Furthermore, this reflex activation of the renin-angiotensin system (RAS) contributed significantly to the pressor and regional vasoconstriction responses to gallbladder distension.
Response of PRA
In the present study, the observed PRA increase was a primary effect caused by gallbladder distension and not by other interfering factors. The reflex changes in hemodynamic variables that could secondarily affect PRA were prevented, and there were no changes in cardiac filling pressures, which may activate atrial receptors and change PRA. Furthermore, the urinary bladder was emptied and ureters were cannulated to prevent activation of bladder receptors and its resulting effect of changing hemodynamic variables, efferent renal nerve activity, and renin release. The supposition that PRA increase was primarily related to gallbladder distension was supported by the ability to augment this increase by incrementing the level of gallbladder distension.

Reflex Mechanisms
The afferent pathway of PRA response to gallbladder distension involved the vagus nerves; the response was abolished by bilateral cervical vagotomy. It has been shown that the gallbladder and the biliary ducts are innervated by afferent vagal and splanchnic nerve fibers, although mechanoreceptors that discharge in the splanchnic nerves are believed to subserve nociception or reflexes related to gastrointestinal function. We used distending volumes and transmural pressures that were similar to those measured in the gallbladder before it was emptied and were considered unlikely to elicit nociceptive responses. As previously found by the same methods, such an innocuous gallbladder distension caused reflex hemodynamic responses that involved the vagus nerves.

Figure 7. Example of experimental recordings showing effect of distension of gallbladder before (A) and after (B) blockade of angiotensin II receptors with losartan. From top: HR, mean ABP proximally and distally with respect to an aortic constriction, mean and phasic RBF, mean right atrial pressure (RAP), mean and phasic CBF, and pressure in intravisceral balloon (BP).

Figure 8. Example of experimental recordings showing effect of distension of gallbladder before (A) and after (B) blockade of angiotensin II receptors with losartan. From top: HR, mean ABP proximally and distally with respect to an aortic constriction, mean and phasic MBF, mean right atrial pressure (RAP), mean and phasic RBF, mean and phasic IBF, and pressure in intravisceral balloon (BP).
The present study showed that the efferent pathways of PRA response to gallbladder distension involved the renal nerves. Previously, we showed that such a distension can cause a widespread sympathetic activation. The present results showed that the latter has included activation of the RAS through β-adrenergic mechanisms. We prevented this reflex response by blockade of β-adrenergic receptors with propranolol at a dose that has previously been shown in the same experimental model to prevent the reflex HR response to gallbladder distension and has been used to block vascular β-adrenergic receptors.

Significance of Findings
Angiotensin II receptor blockade with losartan significantly reduced the pressor and regional vasoconstriction responses to gallbladder distension, indicating a contribution to these responses from concomitant RAS activation. Given that sympathoexcitation and liberation of angiotensin may each result in increases in resistance and ABP, our findings indicated that ~44% of the pressor response to gallbladder distension could be attributed to the RAS. This contribution amounted to ~54%, 46%, and 51% with regard to the vasoconstriction in the coronary, mesenteric, and iliac regions, respectively. It is possible, however, that a coronary vasoconstrictor effect of angiotensin could have enhanced the sympathetic vasoconstrictor responses in the pig, a species known to have few coronary α-adrenergic receptors.

These considerations have important implications with regard to gallbladder distension and pathology in relation to coronary artery disease. The observed responses may be argued to provide a mechanism for the association between gallbladder and coronary artery disease or angina pectoris in that gallbladder distension, with its vasoconstrictor effect, may aggravate myocardial ischemia. This is possible because such an effect was elicited by innocuous distension of the vissus and also because the responses of PRA and CBF were related to increases in the distension. However, we did not examine the effect of chronic gallbladder distension, but chronic liberation of the hormone angiotensin may result in structural changes in the coronary blood vessels or other regions of the circulation.

Conclusions
The present study has shown that gallbladder distension primarily caused a reflex increase in PRA, with the afferent limb in the vagus nerves and the efferent pathways involving the renal nerves and β-adrenergic mechanisms. This activation of the RAS contributed significantly to the pressor and regional vasoconstriction responses to gallbladder distension.

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References
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