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Barry S. Weinstock
Yale University

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by

Barry S. Weinstock

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ABSTRACT

INFLUENCE OF VERAPAMIL ON TOTAL AND REGIONAL INTRAVASCULAR VOLUME IN THE DOG

BARRY S. WEINSTOCK

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Verapamil's influence on intravascular volume (IV) in the total capacitance circulation was examined in anesthetized dogs after mecamylamine administration. Blood was drained from the vena cavae to an extracorporeal reservoir and returned to the right atrium at a constant rate so that IV changes could be measured as reciprocal changes in reservoir volume. In 10 dogs, verapamil (50 mcg/min, n=17) was associated with a prompt and sustained decrease in total IV of 80 +/- 10 ml (P<.0001) at 20 minutes and a decrease in systemic arterial pressure from 77 +/- 4 to 67 +/- 2 mmHg (P<.0001). After evisceration in 6 animals, extrasplanchnic (XSPL) IV decreased 87 +/- 23 ml (P<.001, n=16). In 11 animals with separate perfusion and drainage of the splanchnic and XSPL circulations, XSPL IV decreased 78 +/- 19 ml (P<.0001), and splanchnic IV increased 25 +/- 8 ml (P<.001, n=17). Since XSPL arterial pressure decreased while XSPL arterial flow and venous outflow pressure were maintained constant, it is likely that a decrease in the resistance to venous return mediated the XSPL volume decrement. In 4 animals on cardiopulmonary bypass, IV decreased 154 +/- 61 ml

$(P<.0001, n=8)$. In 6 animals in which the hind limb was separately perfused and drained, verapamil (25 mcg/min, $n=7$) was associated with a decrease in limb IV of 40 +/- 10 ml $(P<.0001)$. Thus, verapamil is associated with a decrease in total IV due entirely to a decrease in systemic XSPL IV. The IV decrement likely is mediated by a decrease in the resistance to venous return.

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INTRODUCTION

Verapamil, a calcium channel blocker, is used extensively for the clinical management of arrhythmias, hypertension, myocardial ischemia, and hypertrophic cardiomyopathy (1-9). While prior work has delineated the effect of this agent on overall circulatory hemodynamics (10-15), the influence of verapamil on the capacitance vasculature remains unclear. Since changes in intravascular volume in the peripheral capacitance vasculature would be expected to influence venous return and cardiac output, it is important to clearly define the effect of verapamil on the total capacitance vasculature. Thus, the present study was designed to delineate the direct effect of sustained verapamil administration on total intravascular volume, to identify the regional vasculature responsible for the total intravascular volume change, and to determine a possible hemodynamic mechanism responsible for the regional volume change.

METHODS

Forty-two mongrel dogs, weighing 14 +/- 1 kg, were anesthetized with sodium thymol (0.5 mg/kg iv), chloralose (60-80 mg/kg iv), and urethan (600-800 mg/kg iv). Each animal was intubated and ventilated with a mixture of room air and 100% oxygen. Ventilation was adjusted to maintain arterial oxygen tension greater than 100 torr, and carbon dioxide and pH in the physiologic range, (Micro-13 pH/blood gas analyzer; Instrumentation Laboratory; Lexington, MA). The arterial carbon dioxide tension, oxygen tension and pH recorded at the beginning of each experiment were not significantly different from the values recorded at the end of each experiment (pH 7.38 +/- .01 vs. 7.38 +/- .02; pCO_2 25 +/- 1 vs. 23 +/- 1; pO_2 239 +/- 8 vs. 221 +/- 10). Mecamylamine (Inversine; Merck, Sharpe & Dohme, West Point, PA), 100-200 mg iv, was administered to establish ganglionic blockade in all of the animals except those in which the limb vasculature was separately studied or in which radionuclide imaging of the abdominal vasculature was performed. These two groups of animals underwent sinoaortic baroreceptor denervation and bilateral cervical vagotomy. Blockade of autonomic reflexes was confirmed by administering phenylephrine (Neo-Synephrine Hydrochloride; Winthrop Laboratories, New York, NY), 25-100 mcg iv, before and

after the reflexes were eliminated and observing that the decrease in heart rate associated with the increase in systemic arterial pressure was abolished after pharmacologic blockade or surgical denervation. In all of the experimental groups, except the group in which the limb was separately studied, the perfusion pumps and reservoir were primed for each experiment with heparinized blood from 1-2 donor dogs.

Venous Bypass Preparation

To assess the influence of verapamil on total intravascular volume, 10 dogs were placed on venous bypass as previously described (16). Briefly, the azygos vein was ligated and the superior and inferior vena cavae were cannulated so that the entire venous return could be drained into an overflow column adjusted to a height of 5 cmH_2O relative to the level of the right atrium. This overflow column drained into a 2-liter graduated cylinder from which blood was returned by a roller pump (Travenol perfusion pump, Travenol Laboratories, Inc., Morton Grove, IL) at a constant rate of 877 +/- 82 ml/min to the right atrium. This preparation allowed changes in intravascular volume to be measured as reciprocal changes in reservoir volume.

Following a 20 minute pre-infusion control period, verapamil (Calan; Searle Laboratories, Chicago, IL) was infused on 17 occasions into the left atrium at a rate

of 50 mcg/min (1 ml/min) for 20 minutes, and a post-infusion control period of up to 20 minutes was observed. A minimum of 60 minutes, including the pre-infusion and post-infusion control periods, was allowed between successive infusions in each animal. Whether hemodynamic parameters returned to control after drug administration was further examined in 2 additional dogs by infusing verapamil for only 6 minutes at 50 mcg/min (n=2) or administering a 100-250 mcg bolus (n=4) and by recording hemodynamic measurements for up to 34 minutes after termination of drug administration.

Brachial arterial, left atrial, and central venous pressures were measured with Statham P23Db pressure transducers (Gould, Cleveland, OH). All pressures and the electrocardiogram were recorded continuously on an eight channel 7758A Hewlett-Packard recorder (Waltham, MA), and reservoir volume was recorded every 2 minutes.

Separate Perfusion and Drainage of the Splanchnic Vasculature

To delineate the contribution of the splanchnic and extrasplanchnic vasculatures to the change in total intravascular volume, the splanchnic and extrasplanchnic vasculatures were separately perfused and drained in 11 dogs on venous bypass as previously described (16). The celiac axis, and the superior and inferior mesenteric

arteries were isolated and perfused with blood from the femoral artery at a constant rate. A ligature was placed between the hepatic and renal veins so that the splanchnic venous return could be drained to the graduated cylinder via a cannula in the inferior vena cava. Heavy ligatures were placed around the gastroesophageal junction and the rectum and running sutures were placed in the diaphragm to eliminate all vascular communications between the splanchnic and extrasplanchnic circulations. The extrasplanchnic venous return was drained via cannulae in the femoral veins and the superior vena cava. Splanchnic volume changes were determined by integrating the changes in splanchnic venous outflow measured every 2 minutes, and changes in total intravascular volume were measured as before. Changes in extrasplanchnic volume were determined by calculating the difference between the total and splanchnic volume changes. Verapamil (50 mcg/min) was infused into the left atrium on 17 occasions in these animals.

Evisceration

To further examine the influence of verapamil on the extrasplanchnic vasculature, 8 dogs were studied under conditions of abdominal evisceration. In 3 of these animals, verapamil had been previously administered under conditions of separate perfusion and

drainage of the splanchnic and extrasplanchnic vasculatures. Evisceration in these 3 animals was accomplished by stopping the splanchnic perfusion pump and cross-clamping the splanchnic tubing. In the other 5 animals, (2 of which had been studied previously on venous bypass prior to evisceration), evisceration was accomplished by ligating the celiac, superior mesenteric, and inferior mesenteric vessels. Anastomoses in the regions of the gastroesophageal junction and the rectum were eliminated with heavy ligatures and visible collateral vessels in the diaphragm were ligated. Verapamil (50 mcg/min) was infused into the left atrium on 16 occasions in these animals.

Venous Bypass with Abdominal Imaging

The influence of verapamil on splanchnic intravascular volume was further assessed in 6 additional dogs on venous bypass. Each animal's erythrocytes were labelled with 3 mCi of Technetium-99m pertechnate and a gamma camera with an integrated computer (Ohio Nuclear Sigma 420; Solon, Ohio) was placed over the abdomen to obtain serial quantitative images every 2 minutes. Changes in total splanchnic intravascular volume were estimated from changes in total splanchnic counts, *in vivo* tissue attenuation, and blood radioactivity as described by Bell et. al. (17).

Verapamil (50 mcg/min) was infused in these 6 animals on 14 occasions.

Cardiopulmonary Bypass Preparation

To examine the influence of verapamil on total intravascular volume in the absence of the pulmonary circulation, 4 dogs were studied under conditions of cardiopulmonary bypass similar to that described previously (18). Under these conditions, changes in total systemic intravascular volume were measured as reciprocal changes in the blood volume of the oxygenator (Model S-070/S, Shiley, Inc., Irvine, CA). Verapamil (50 mcg/min) was administered on 8 occasions.

Separate Perfusion and Drainage of the Limb

In order to further assess the influence of verapamil on intravascular volume in the systemic extrasplanchnic circulation, volume changes were examined in the hind limbs of 6 animals studied under conditions of separate perfusion and drainage of the hind limb with an otherwise intact circulation. The left femoral artery was perfused by a pump (Cole-Parmer Instrument Co.; Chicago, IL) at a constant rate of 69 +/- 13 ml/min with blood drained from the right femoral artery. The left femoral vein was cannulated and left limb venous return was drained at a constant venous pressure of 5 cmH_2O into a 250 ml graduated cylinder. A second perfusion pump was used to return blood at a

constant rate from this extracorporeal reservoir to the systemic circulation via the right femoral vein so that changes in left hind limb intravascular volume could be measured as reciprocal changes in reservoir volume. A catheter was advanced through the left femoral artery cannula to monitor limb arterial pressure.

Because of extensive collateral blood flow through deep muscle groups, it was not possible to ligate each vessel separately. Thus, a ligature was tied securely around the entire limb just above the perfusion and drainage catheters. Adequate interruption of all collaterals was confirmed in 3 manners. After briefly stopping the perfusion pump prior to the start of each study in all animals, limb pressure decreased rapidly to a stable, non-pulsatile baseline. In addition, at the conclusion of all studies in each animal, venous outflow from the limb was noted to stop completely shortly after stopping the limb perfusion pump. Finally, colored latex was injected into the limb perfusion catheter after all studies were completed in each of 3 animals and surgical dissection above the ligature revealed that no latex reached the circulation above the ligature. Verapamil was administered at a dose of only 25 mcg/min (iv) since the total circulating blood volume was not increased by the use of blood from donor dogs.

The present study was designed so that each animal could serve as its own control since control data was recorded prior to and after each verapamil infusion. In addition, prior work from this laboratory has demonstrated that when a vehicle containing no hemodynamically active agent is administered, total intravascular volume, arterial pressure, and left atrial pressure do not change significantly, (personal communication: Leonard Bell, M.D.).

Statistics

To determine changes in intravascular volume, a line of best fit was determined by performing a linear regression on the reservoir volume data obtained during the pre-infusion control period. The difference between the observed volume and the volume predicted by linear regression analysis was determined for all points in time for each animal. Means and standard errors were calculated for all hemodynamic parameters within each experimental group. Analysis of variance was performed to test the proposition H_0: all control and experimental values are equal. Control means were then compared to experimental values obtained at 10 minute intervals and the Bonferroni correction for multiple comparisons was performed. Statistical significance was assumed as $P<0.05$.

RESULTS

For the 17 infusions in the 10 animals studied under conditions of venous bypass, verapamil administration was associated with a prompt and sustained decrease in total intravascular volume which was 80 +/- 10 ml (P<0.0001) at 20 minutes (Figure 1). Systemic arterial pressure decreased from 77 +/- 4 to 67 +/- 2 mmHg (P<0.0001) and left atrial pressure increased from 6.5 +/- 0.5 to 7.5 +/- 0.5 mmHg (P<0.002).

For one infusion in one animal studied prior to mecamylamine administration, total intravascular volume decreased 289 ml during verapamil administration. Systemic arterial pressure decreased from 120 to 90 mmHg and left atrial pressure remained stable at 5.0 mmHg.

The data associated with the 16 infusions in the 9 animals studied after evisceration are presented in Figure 2. Verapamil was associated with a decrease in total intravascular volume which was 87 +/- 23 ml (P<0.001) at the end of infusion. Systemic arterial pressure decreased from 75 +/- 4 to 61 +/- 2 mmHg (P<0.0001) and left atrial pressure increased from 6.0 +/- 0.5 to 7.0 +/- 1.0 mmHg (P<0.0001).

For the 17 infusions in the 11 animals in which the splanchnic and extrasplanchnic vasculatures were separately perfused and drained, verapamil was associated with a decrease in total intravascular volume

of 53 +/- 14 ml ($P<0.001$) at 20 minutes (Figure 3A). Splanchnic volume increased 25 +/- 8 ml ($P<0.001$) and extrasplanchnic volume decreased 78 +/- 19 ml ($P<0.0001$) (Figure 3B). Systemic arterial pressure decreased from 92 +/- 5 to 70 +/- 2 mmHg ($P<0.0001$) and left atrial pressure increased from 6.0 +/- 0.5 to 7.0 +/- 0.5 mmHg ($P<0.0001$).

For the 6 animals in which the radionuclide imaging technique was used to estimate splanchnic volume changes, splanchnic intravascular volume was not significantly changed (12 +/- 6 ml decrease) at 20 minutes although total intravascular volume decreased 49 +/- 9 ml ($P<0.0001$). Systemic arterial pressure decreased from 96 +/- 5 to 77 +/- 4 mmHg ($P<0.0001$) and left atrial pressure increased from 7.0 +/- 1.0 to 7.5 +/- 1.0 mmHg ($P<0.05$).

The data associated with the 8 infusions in the 4 animals on cardiopulmonary bypass are presented in Figure 4. Verapamil administration was associated with a decrease in systemic intravascular volume of 154 +/- 61 ml ($P<0.0001$) and a decrease in systemic arterial pressure from 78 +/- 3 to 71 +/- 3 mmHg ($P<0.01$). Since verapamil was administered for only 18 minutes in one animal, the mean pressure and volume decrements reported were those present at that time.

For the 6 animals in which the hind limb was separately perfused and drained, verapamil was associated with a decrease in limb intravascular volume of 40 +/- 10 ml ($P<0.0001$, n=7) at 20 minutes (Figure 5). Limb arterial pressure decreased from 145 +/- 22 to 126 +/- 19 mmHg ($P<0.001$), and systemic arterial pressure decreased from 76 +/- 5 to 69 +/- 7 mmHg ($P<0.05$). A direct correlation existed between baseline limb arterial pressure and the magnitude of the limb intravascular volume decrement ($r=0.77$, $P<0.05$). For the 4 infusions associated with the lowest baseline limb arterial pressures (mean 105 +/- 14 mmHg), limb intravascular volume decreased 21 +/- 8 ml ($P<0.01$), limb arterial pressure decreased to 87 +/- 7 mmHg ($P<0.01$), and systemic arterial pressure decreased from 70 +/- 3 to 60 +/- 8 mmHg ($P<0.01$).

In the 2 animals in which verapamil was administered for only 6 minutes or as a bolus, total intravascular volume decreased promptly (38 +/- 11 ml at 6 minutes, $P<0.025$) but did not return to baseline even when examined for up to 34 minutes after termination of drug administration.

In the 7 animals in which tachyphylaxis was assessed by comparing the intravascular volume change associated with the first infusion to the change associated with the second infusion, total intravascular

volume decreased 72 +/-18 ml during the initial infusion and decreased 51 +/-38 ml during the second infusion. These responses were not significantly different from each other.

DISCUSSION

The present study directly measured the effect of sustained verapamil administration on intravascular volume in the total capacitance vasculature. The region responsible for the total intravascular volume change was identified and the hemodynamic mechanism responsible for the regional volume change is suggested.

The data obtained utilizing the venous bypass preparation demonstrate a decrease in total intravascular volume associated with verapamil administration. Since neurogenic reflexes were eliminated by the presence of the ganglionic blocking agent, mecamylamine, or by sinoaortic baroreceptor denervation and cervical vagotomy, the observed volume decrement is not related to baroreceptor stimulation. Since arterial pH, carbon dioxide tension, and oxygen tension did not change significantly, the volume decrement is not related to a change in acid-base balance. Thus, the observed total intravascular volume decrement is due to the direct effect of verapamil on the capacitance vasculature.

The extrasplanchnic vasculature is responsible for the total volume decrement for the following reasons. First, the verapamil associated decrease in total intravascular volume was not attenuated by evisceration. Second, when the splanchnic and

extrasplanchnic circulations were simultaneously examined under conditions of separate perfusion at constant rates, the decrease in extrasplanchnic volume was entirely responsible for the decrease in total volume. Third, when splanchnic and extrasplanchnic arterial flows were not controlled and splanchnic volume changes were estimated with the radionuclide imaging technique, the total intravascular volume decrement was not associated with a significant change in splanchnic intravascular volume. Thus, the decrease in total intravascular volume with verapamil administration is due entirely to a decrease in extrasplanchnic intravascular volume.

Since the total intravascular volume decrement was not attenuated during verapamil administration under conditions of cardiopulmonary bypass, the pulmonary circulation did not contribute to the total intravascular volume decrement. Since the verapamil associated total volume decrement was larger in the absence of the pulmonary circulation, pulmonary intravascular volume may have increased during verapamil administration in the animals studied under conditions of venous bypass. This increase could be due to a direct vasodilating effect of verapamil on the pulmonary capacitance vessels or to a passive increase in pulmonary volume mediated by the increase in left atrial

pressure (19) associated with verapamil's negative inotropic effect.

The hemodynamic mechanism responsible for the decrease in systemic extrasplanchnic volume is suggested by examination of the hemodynamic data associated with the extrasplanchnic volume decrement. Redistribution of arterial inflow away from the extrasplanchnic vasculature with a subsequent passive loss of extrasplanchnic volume could not occur, since extrasplanchnic arterial flow was maintained constant and extrasplanchnic volume still decreased after evisceration or under conditions of separate perfusion of the extrasplanchnic circulation. Vasoconstriction of the extrasplanchnic capacitance vasculature was unlikely to have caused the volume decrement since systemic arterial pressure decreased and verapamil is not known to constrict arteries or veins (20). A decrease in right atrial pressure could not have caused a subsequent passive loss of systemic capacitance volume, since central venous pressure was maintained constant. Thus, the decrease in extrasplanchnic intravascular volume likely is mediated by a decrease in the resistance to extrasplanchnic venous return and a subsequent passive loss of blood volume from the vasculature proximal to the site of the resistance decrease.

The mechanism by which the volume decrement is mediated as well as the identification of the region responsible for the total volume decrement is supported by the work of other investigators. Ito and Hirakawa (21) examined the influence of verapamil on the resistance to venous return and mean circulatory pressure by intermittently arresting the heart and rapidly pumping blood from the systemic arteries to the systemic veins until arterial and venous pressures were equal. Since mean circulatory pressure did not increase, verapamil was not thought to be associated with vasoconstriction of the capacitance vasculature. However, the resistance to venous return decreased. Work by Altura et. al. (22) is consistent with the possibility that the decrease in the resistance to venous return occurs in the systemic extrasplanchnic vasculature, since perivascular application of verapamil in vivo was associated with vasodilation of terminal arterioles and muscular venules of the skeletal muscle microvasculature but not of the mesenteric microvasculature. Thus, this prior work supports the present conclusions that the extrasplanchnic volume decrement is responsible for the decrease in total intravascular volume and a decrease in extrasplanchnic venous resistance mediates the volume decrement.

Observations in the isolated limb in the present study further support the conclusion that systemic extrasplanchnic volume decreases and the decrease is mediated by a decrease in the resistance to venous return. When the limb circulation, a major constituent of the systemic extrasplanchnic circulation, was studied under conditions of separate perfusion and drainage, verapamil was associated with a decrease in limb intravascular volume. Since the arterial inflow and the venous outflow pressure were maintained constant, the volume loss was not due to changes in these hemodynamic parameters. Furthermore, since limb arterial pressure decreased and since verapamil is known to dilate skeletal muscle arteries and veins (22), vasoconstriction was unlikely to have been responsible for the decrease in limb volume. Thus, a decrease in the resistance to venous return with a subsequent passive loss of blood volume from the limb vasculature proximal to the site of resistance likely is responsible for the verapamil associated decrease in limb intravascular volume.

Limb arterial inflow in the isolated limb studies was maintained at a level comparable to that reported by other investigators who assessed hemodynamic changes in isolated limbs (23,24). As a result, baseline hind limb perfusion pressure was greater than the baseline

systemic arterial pressure in all of the other experimental groups in the present study. It is clear that baseline limb perfusion pressure influenced the magnitude of the limb volume decrement since the two parameters were correlated directly. When limb volume decrements were examined in the animals with limb perfusion pressures more comparable to the systemic arterial pressures observed in the other experimental groups, a smaller but still significant decrease in limb intravascular volume was observed.

Other investigators have assessed the influence of verapamil on venous return or cardiac output in animals with intact circulations (11,21,25,26). However, these studies do not allow determination of the influence of verapamil on intravascular volume in the peripheral capacitance circulation since associated hemodynamic changes also would have been expected to influence venous return or cardiac output.

Taira et. al. (27) assessed the influence of verapamil on the capacitance vasculature using a venous bypass preparation similar to that employed in the present study. They noted that bolus administration of verapamil (10-100 mcg/kg) resulted in a transient decrease in total intravascular volume. However, since systemic arterial pressure decreased and neurogenic reflex mechanisms were intact, decreased carotid sinus

baroreceptor stimulation could have mediated the entire decrease in total intravascular volume (28,29). Indeed, the present study demonstrates that reflex mediated volume changes could have been substantial in Taira's study since the largest volume decrement in the present study was observed during the single infusion of verapamil in an animal with intact autonomic reflexes. Thus, it is impossible to ascertain from their work whether this effect is due to the direct action of verapamil on the capacitance vasculature or due to baroreceptor stimulation.

Intravascular volume did not return to baseline in any of the experimental groups in the present study including the group given only a small dose of verapamil either as a brief infusion or as a bolus. A prolonged effect of verapamil has been observed by others: systemic blood pressure failed to return to baseline in the studies of Kokubun et. al. and Taira et. al. and required one hour to return to baseline in the studies of Salles et. al. It is possible that this prolonged effect of verapamil following the first infusion of verapamil was responsible for the small statistically insignificant attenuation of the intravascular volume response associated with the second infusion of the drug.

The present study demonstrates that verapamil administration results in a sustained decrease in total intravascular volume in the capacitance circulation which occurs independent of autonomic reflex phenomena. The total intravascular volume decrement is due entirely to a decrease in systemic extrasplanchnic intravascular volume. A decrease in the resistance to venous return appears to be the mechanism responsible for the decrease in intravascular volume. In the intact circulation, one would expect that the decrease in resistance would result in the transport of blood from the peripheral capacitance circulation to the central circulation. Furthermore, this shift in intravascular volume would be expected to be associated with an increase in ventricular end diastolic volume which would act to augment cardiac output via the Starling mechanism.

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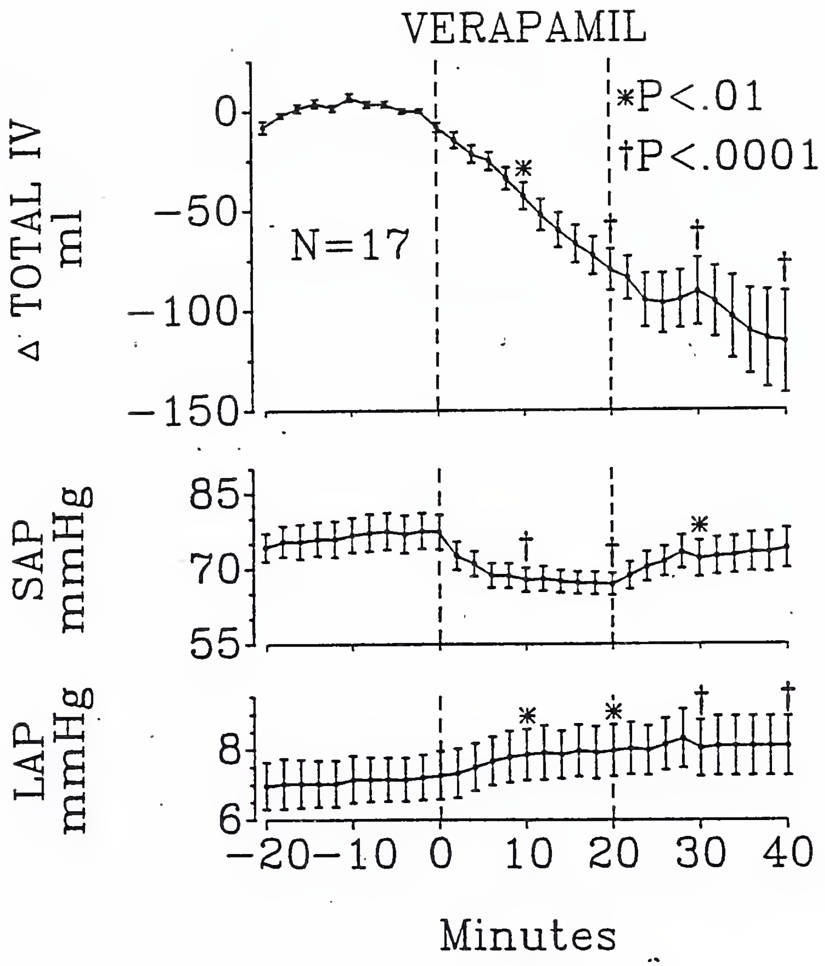

Figure 1. Venous Bypass. Effect of verapamil administration at 50 mcg/min on total intravascular volume (IV), systemic arterial pressure (SAP), and left atrial pressure (LAP). Note the prompt and sustained decrease in total intravascular volume. Each bar represents +/- 1 standard error of the mean.

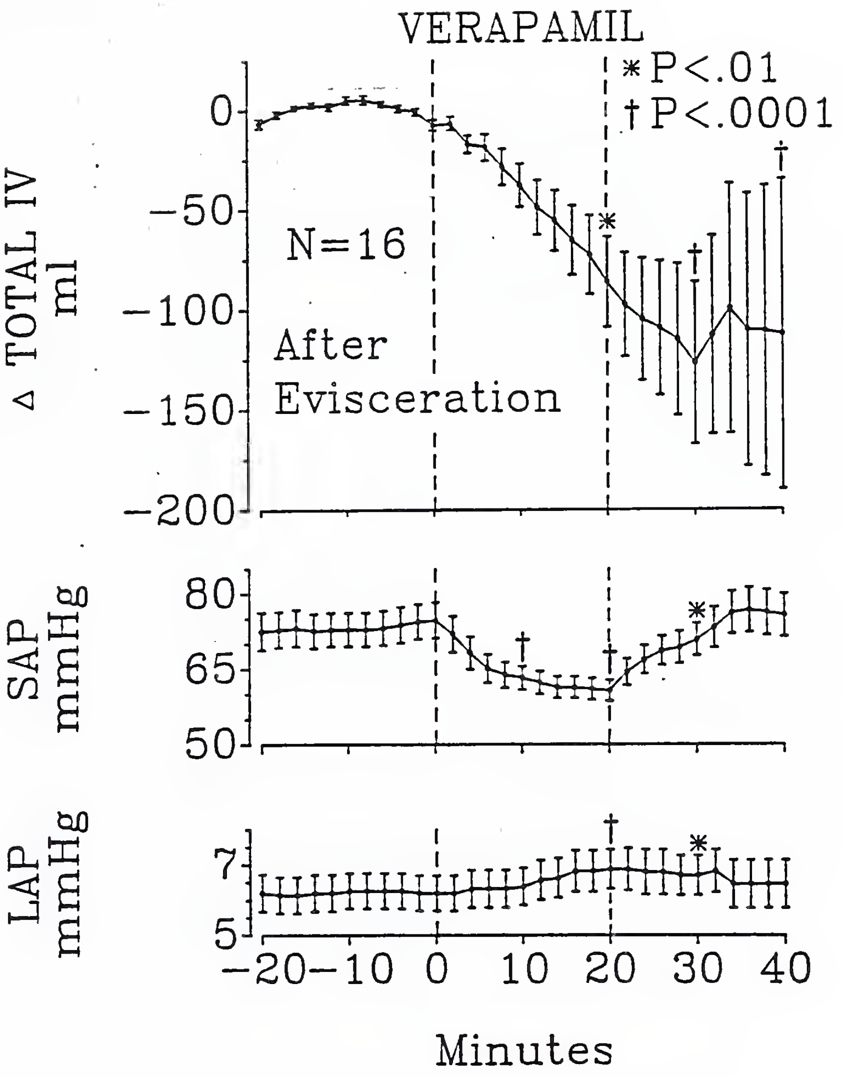

Figure 2. Venous Bypass after Evisceration. Effect of verapamil on total intravascular volume, systemic arterial pressure, and left atrial pressure. Note that the decrease in total intravascular volume illustrated in Figure 1 was not attenuated by evisceration. Standard errors associated with the change in intravascular volume increased substantially during the post-infusion period since 20 minutes of post-infusion data was recorded during only 9 of the 16 experiments.

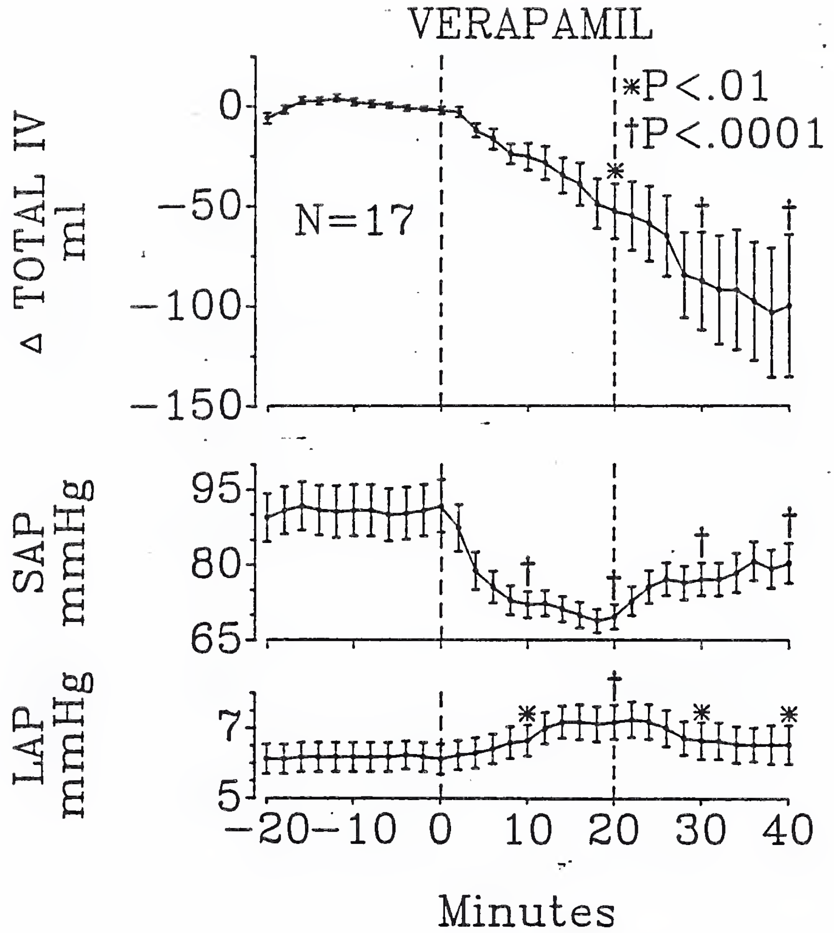

Figure 3A. Separate Perfusion and Drainage of the Extrasplanchnic and Splanchnic Circulations. Effect of verapamil on total intravascular volume, systemic arterial pressure, and left atrial pressure.

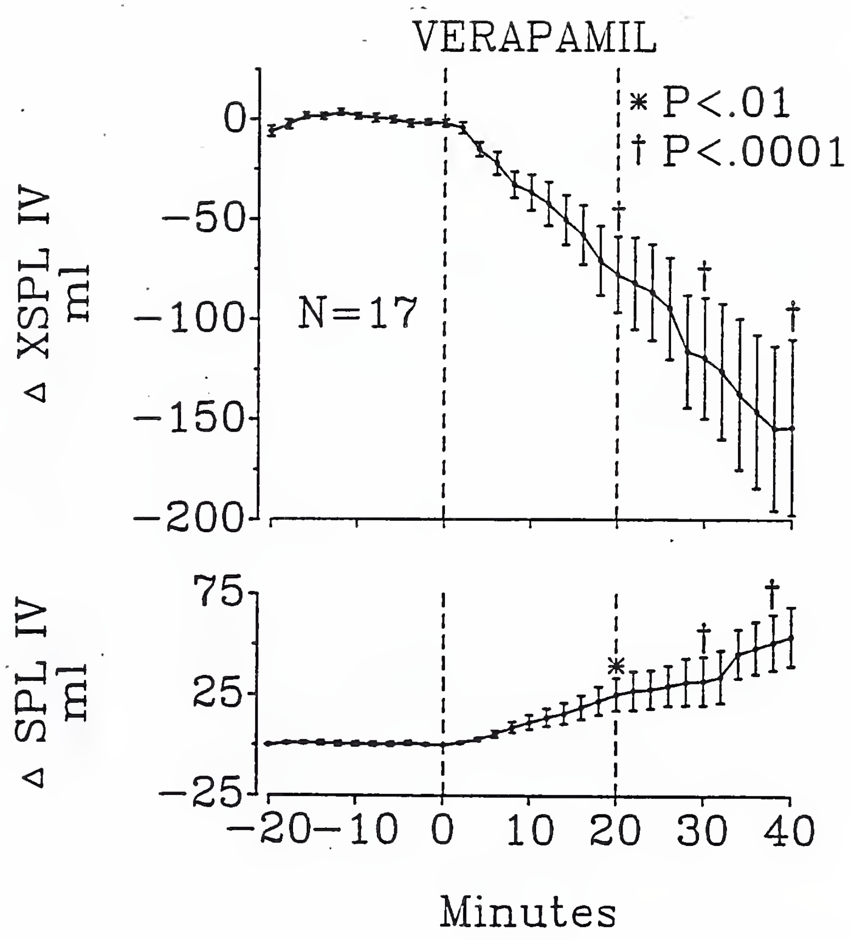

Figure 3B. Separate Perfusion and Drainage of the Extrasplanchnic and Splanchnic Circulations. Extrasplanchnic (XSPL) and splanchnic (SPL) intravascular volume changes associated with the total intravascular volume changes presented in Figure 3A. Note that the decrease in total intravascular volume was due entirely to a decrease in extrasplanchnic intravascular volume.

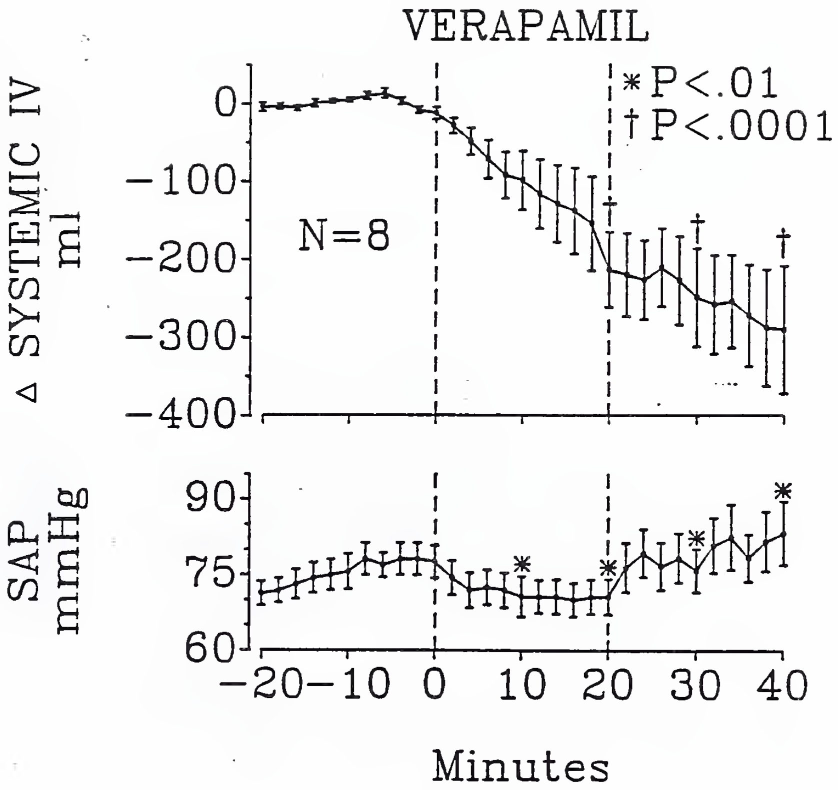

Figure 4. Cardiopulmonary Bypass. Effect of verapamil on systemic intravascular volume and systemic arterial pressure. Note that the intravascular volume scale is different in this figure and the decrease in intravascular volume is not attenuated compared to the decrease observed in animals studied under conditions of venous bypass.

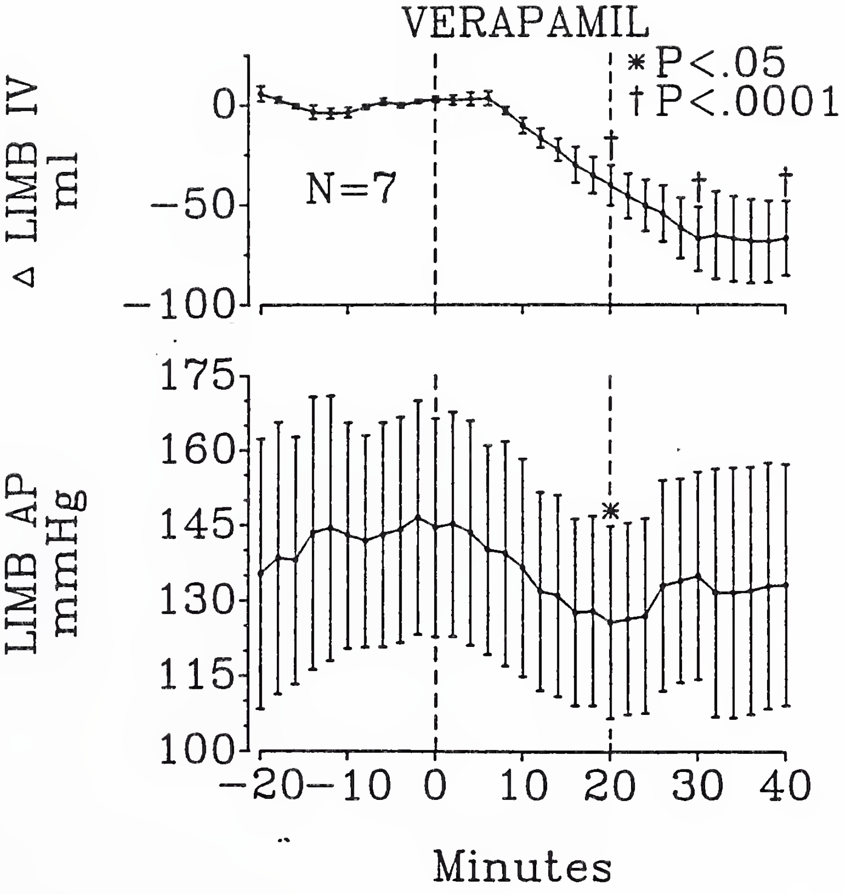

Figure 5. Separate Perfusion and Drainage of the Hind Limb. Effect of intravenous verapamil (25 mcg/min) on limb intravascular volume and limb arterial pressure (AP). Note the decrease in limb intravascular volume.

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