Assessment of the Human Splanchnic Venous Volume–Pressure Relation Using Radionuclide Plethysmography

Effect of Nitroglycerin

Dante E. Manyari, MD; Zhi Wang, MD; James Cohen, MD; and John V. Tyberg, MD, PhD

Background. No method exists to assess human splanchnic venous function, the most important region in terms of vascular capacity.

Methods and Results. We studied 25 stable patients without heart failure or hypertension to develop a method to assess the splanchnic venous volume–pressure (V–P) relation and to determine the effect of nitroglycerin (GTN). We used blood pool scintigraphy to assess changes in regional splanchnic vascular volume (SVV) and low levels of continuous positive airway pressure (CPAP) to passively alter venous pressure and thus, SVV. We postulated that the relation between SVV and the CPAP used would reflect the capacitance of the splanchnic venous bed and that changes in the position of this relation would provide a relative measurement of any change in capacitance. In 12 patients (group 1), the splanchnic vascular V–P curves were recorded before and 2, 9, and 20 minutes after 0.6 mg sublingual GTN; in eight patients (group 2), recordings were made at similar times before and after sublingual administration of placebo; in five patients (group 3), the hemodynamic effects of CPAP were assessed by means of right and left cardiac catheterization. Right atrial and femoral venous pressures increased (p<0.001) and cardiac output fell (p<0.05) during CPAP. There was an apparently linear relation between CPAP and SVV (r=0.74–0.98); SVV increased an average of 7.4±2.2% (p<0.001) by 12 cm H2O CPAP. The splanchnic vascular V–P curves were reproducible with minimal variability in SVV (±2%, p>0.2) in group 2. After administration of GTN, the splanchnic vascular V–P curve shifted away from the pressure axis in a parallel fashion by an average of 9.4±5.4% (p<0.001).

Conclusions. We have developed a reproducible noninvasive technique that may be used to assess human splanchnic venous V–P relations. We have demonstrated for the first time in humans that GTN exerts its dilatory effect by increasing the unstressed splanchnic venous volume. (Circulation 1993;87:1142–1151)

Key Words • vein • venodilation • venoconstriction • blood pool • positive airway pressure

The splanchnic venous bed is the largest and most important region in terms of vascular capacitance in animals1–4 and probably in humans.5–11 Current understanding of splanchnic venous physiology, pathophysiology, and pharmacology is based on data from animal experiments,1–4,12–18 and limited number of human studies.5–7 Those human studies were performed using invasive techniques and indicator–dilution methods to assess splanchnic blood flow and/or splanchnic vascular volume (SVV) changes,5–8 but splanchnic vascular volume–pressure (V–P) relations were not determined. Since venous volume (so-called capacitance25) may be altered by changes in distending pressure (passively, up or down the same V–P curve) or by active changes in venous distensibility or tone (different V–P curves), venous responses to physiological, pathological, or pharmacological alterations are best understood by defining venous V–P relations. Techniques have been developed to assess acute changes of the V–P relation of capacitance vessels in liver and splanchnic regions of experimental animals.3,4,15–18,24,25 These techniques, however, are invasive, cumbersome, and not applicable to humans. The V–P relation of the capacitance vessels in the splanchnic region has never been assessed in humans because of the lack of a suitable technique.

Quantitative radionuclide blood pool scintigraphy has been used to measure acute changes of regional vascular volume in the liver, lungs, spleen, and splanchnic and forearm regions in humans during physiological and pharmacological interventions.25–37 More recently, this method has been used to assess the venous V–P relation in the human forearm, i.e., radionuclide plethysmography.38,39 Forearm venous V–P curves obtained with radionuclide plethysmography were remarkably similar to those obtained with standard mercury-in-rubber strain gauge plethysmography, with both techniques
Having similar variability.\textsuperscript{38} Radionuclide plethysmography has been used successfully to study the effects of vasoactive drugs\textsuperscript{38} and mental stress\textsuperscript{39} on forearm veins. Furthermore, the radionuclide method has been used to assess acute changes in splanchnic vascular \( V-P \) relations in animal experiments.\textsuperscript{25} Therefore, we designed this study to test the hypothesis that quantitative blood pool scintigraphy can be used to assess human splanchnic venous \( V-P \) relations. We used continuous positive airway pressure (CPAP) to alter right atrial pressure,\textsuperscript{40} which could passively change splanchnic venous distending pressure and thus, SVV, allowing us to define the splanchnic vascular \( V-P \) relation to characterize a given state of venous tone. A secondary goal of this study was to use this method to investigate the effect of nitroglycerin (GTN) on human splanchnic vascular capacitance.

\section*{Methods}

\subsection*{Patient Population}

Patients undergoing diagnostic radionuclide ventriculography were enrolled in the study (groups 1 and 2) if they met the following criteria: 1) apart from atypical chest pain, they had no history of cardiorespiratory symptoms and physical examination was normal; 2) normal ECG; 3) the postrule likelihood of coronary artery disease was \(<10\%\); 4) there was no history or clinical evidence of hypertension, diabetes mellitus, or hepatic or respiratory disease; 5) they were not taking medications except for GTN; 6) they were able to tolerate a CPAP mask comfortably; and 7) they were willing to participate. Patients undergoing cardiac catheterization for the evaluation of chest pain were included in group 3 to assess the hemodynamic effects of CPAP if they had no evidence of heart failure, hypertension, or pulmonary disease, they were willing to participate, and tolerated CPAP breathing. Informed consent was obtained from each patient before participation in this study, which was approved by our institutional ethics committee.

\subsection*{Radionuclide Studies}

Radionuclide blood pool imaging was performed after labeling the red blood cells with \( ^{99m}\text{Tc} \).\textsuperscript{42} To assess regional SVV changes, successive 30-second static images of the abdomen were recorded. To minimize the amount of free circulating \( ^{99m}\text{Tc} \), images were recorded at least 30 minutes after initial labeling.\textsuperscript{25} Scintigrams were recorded using a conventional Anger type gamma camera equipped with a high-sensitivity parallel-hole collimator interfaced to a dedicated nuclear medicine computer system. With patients in the supine position, the gamma camera was positioned horizontally, facing down, with the collimator parallel to and approximately 2.5 cm from the patient's anterior abdominal wall. Patients were instructed not to move, and care was taken to maintain a constant patient-camera position throughout the experiment. Lead markers were taped to the abdominal wall.

A "splanchnic" region of interest was drawn as large as possible (usually 20\( \times \)20 pixels) taking care to avoid liver, spleen, kidneys, stomach, urinary bladder, and large abdominal blood vessels. Since the total counts in a region is proportional to the amount of blood in that region, changes in count rate in successive scintigrams (corrected for physical and biological decay) are proportional to changes in regional intravascular blood volume.\textsuperscript{3,4,25,39} Successive scintigrams were used to obtain successive regional SVV changes. To compare volume changes between patients, we used percentage changes from baseline count rate (count rate at zero CPAP during control 1 was defined as 100\%). Using the lead markers helped to ascertain that we had defined the same region of interest in successive images.

\subsection*{Study Design}

Studies were performed in the postabsorptive state before their clinical radionuclide ventilulograms. The laboratory was cool (20–22\(^\circ\)C) and devoid of visual or auditory stimuli. Patients were first taught to relax while breathing with various levels of CPAP. After a 15-minute training period, patients were allowed to rest in the supine position for 30 minutes.

\subsection*{Volume–pressure relation.}

To define the \( V-P \) relation of the splanchnic venous bed, 30-second abdominal scintigrams were recorded successively at CPAPs of 0, 5, 8, 10, and 12 cm \( \text{H}_2\text{O} \), with stepwise increases at 1-minute intervals; the images were recorded during the second half of each minute. In this way, the regional SVV was measured at each of the above noted CPAPs; these five pairs of data were used to describe the splanchnic venous \( V-P \) relation.

A dedicated technician was responsible for adjustment of the CPAP levels and for training the patients before the experiment. Changing the level of CPAP required between 5 and 15 seconds. A second technician was responsible for positioning and control of the gamma camera, activating the automated blood pressure and heart rate recordings, timing each step of the protocol, and coordinating the changes in CPAP with the radionuclide acquisitions.

\subsection*{Effect of nitroglycerin.}

The effect of GTN on the human splanchnic venous \( V-P \) relation was investigated in patients of group 1. Two sets of control data to construct two \( V-P \) curves (control 1 and control 2) were obtained 5–8 minutes apart before any intervention, after which patients received 0.6 mg sublingual GTN. Serial abdominal scintigrams at increasing CPAPs, as noted above, were recorded during the control period and 2, 9, and 20 minutes after GTN had dissolved. Thus, we obtained data to plot five splanchnic vascular \( V-P \) curves, two controls, and three after GTN. Blood pressure and heart rate were recorded every minute using an automated blood pressure cuff and an ECG, respectively.

\subsection*{Spontaneous variability.}

The variability of this method to define the splanchnic vascular \( V-P \) relation was studied in patients of group 2. Two sets of control data to construct two \( V-P \) curves (control 1 and control 2) were obtained 5–8 minutes apart before any intervention, after which patients received a placebo (a small sugar tablet). Abdominal scintigrams were then recorded at increasing CPAPs beginning at 2, 9, and 20 minutes after the placebo had dissolved. Thus, we obtained data to construct five splanchnic vascular \( V-P \) curves over a 35–40-minute period at identical times to those in patients of group 1. Blood pressure and heart rate were monitored and recorded every minute.
Hemodynamic effects of low levels of CPAP. The cardiac and circulatory effects of CPAP at levels used in this investigation were studied in five patients of group 3 by means of right and left cardiac catheterization. Measurements were performed 30 minutes after completion of their clinical studies, which included left ventricular and coronary cineangiography. The modulations cardiac output and aortic, pulmonary, pulmonary capillary wedge, right atrial, and femoral venous pressures were recorded at CPAPs of 0, 5, 8, 10, and 12 cm H2O and again at 0 cm H2O.

Statistical Analysis

Since individual SVVs were collected at the same CPAPs, individual SVVs were averaged at each CPAP to obtain the group splanchnic vascular V-P curves. ANOVA with an orthogonal polynomial decomposition was used to assess the changes of the relative regional SVV produced by CPAP, GTN, and placebo. Orthogonal contrasts were used for curve fitting and to examine for evidence of interaction or lack of parallelism between the curves at control and during each intervention. Two-way ANOVA followed by the Tukey procedure when appropriate was used to analyze the significance of the blood pressure and heart rate changes as well as the hemodynamic effects of CPAP. Statistical significance was accepted at the 95% confidence level (p<0.05). Unless otherwise noted, group data are presented as mean±SD.

Results

Twenty-six patients were recruited to participate in the study (groups 1 and 2). Despite the “CPAP training session,” complete data were not available in six patients. Five patients did not complete the study protocol because they were somewhat restless during the investigation and did not follow instructions. These patients frequently breathed through their mouths, took frequent deep inspirations, or coughed repeatedly. Another patient moved frequently because of back pain, preventing imaging of identical abdominal regions and preventing application of a constant level of CPAP. Thus, 20 patients completed the investigation. Twelve patients, seven men and five women aged 51±21 years (range, 23–74 years), were in group 1, and eight patients, five men and three women aged 59±13 years (range, 31–77 years), were in group 2. Four patients had been taking calcium antagonists, but these drugs were discontinued at least 72 hours before the study session. Six patients had taken GTN in the past, but no one had taken this drug within 24 hours before the study session.

Control Studies

Splanchnic vascular volume increased by an average of 7.4±2.2% when CPAP was increased from zero to 12 cm H2O. The best fit between these two variables was a linear relation when results were analyzed in individual patients (r values from 0.74 to 0.98) or as a group (r values from 0.93 to 0.97, p<0.001).

There were no significant differences (p>0.5) between the group splanchnic vascular V-P curves recorded during the control stages (control 1 and control 2) in the entire patient population (Figure 1) or in the two groups of patients analyzed separately (Figure 2).

Effect of Nitroglycerin (Group 1)

Group splanchnic vascular V-P curves before and after administration of GTN are shown in Figure 4.
Compared with control (average of control 1 and control 2), the splanchnic vascular V–P curves at 2–6, 9–13, and 20–24 minutes after GTN were significantly shifted to the right, implying active splanchnic venodilation. Regional SVVs increased at all levels of CPAP by an average of 8.4% (p<0.001), 9.4% (p<0.001), and 5.7% (p<0.01) at 2–6, 9–13, and 20–24 minutes after GTN, respectively, compared with the average volume of the control curve. Analyses of lack of parallelism showed insignificant probability values (p>0.2) between these four V–P curves, implying that the differences in slopes were not statistically significant.

**TABLE 1. Hemodynamic Data Before and After Sublingual Nitroglycerin in 12 Patients (Group 1)**

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>HR (bpm)</th>
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</thead>
<tbody>
<tr>
<td>Control: Average values of control 1 and control 2 stages</td>
<td></td>
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<tr>
<td>CPAP 0</td>
<td>128±14</td>
<td>83±7</td>
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<tr>
<td>CPAP 5</td>
<td>125±11</td>
<td>82±7</td>
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<tr>
<td>CPAP 0</td>
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<td>70±10*</td>
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<td>113±17*</td>
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</tr>
<tr>
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<td>107±23*</td>
<td>64±15*</td>
</tr>
<tr>
<td>CPAP 10</td>
<td>106±12*</td>
<td>64±12*</td>
</tr>
<tr>
<td>CPAP 12</td>
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<tr>
<td>GTN 2: 9–13 minutes after GTN</td>
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<td></td>
</tr>
<tr>
<td>CPAP 0</td>
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<td>68±10*</td>
</tr>
<tr>
<td>CPAP 5</td>
<td>112±22*</td>
<td>66±8*</td>
</tr>
<tr>
<td>CPAP 8</td>
<td>106±22*</td>
<td>65±11*</td>
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<tr>
<td>CPAP 10</td>
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<td>CPAP 12</td>
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<td>GTN 3: 20–24 minutes after GTN</td>
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<td>CPAP 10</td>
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<tr>
<td>CPAP 12</td>
<td>119±13</td>
<td>79±11</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; CPAP, continuous positive airway pressure expressed in cm H2O; GTN, nitroglycerin.

*p<0.001 vs. control.

**TABLE 2. Hemodynamic Data Before and After Sublingual Placebo in Eight Patients (Group 2)**

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>HR (bpm)</th>
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</thead>
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<td>Control: Average values of control 1 and control 2 stages</td>
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<tr>
<td>CPAP 0</td>
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<td>71±10</td>
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<tr>
<td>CPAP 5</td>
<td>113±14</td>
<td>71±11</td>
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<tr>
<td>CPAP 8</td>
<td>114±14</td>
<td>71±10</td>
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<tr>
<td>CPAP 10</td>
<td>113±12</td>
<td>71±10</td>
</tr>
<tr>
<td>CPAP 12</td>
<td>113±12</td>
<td>72±10</td>
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<tr>
<td>PLB 1: 2–6 minutes after PLB</td>
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<tr>
<td>CPAP 0</td>
<td>111±12</td>
<td>69±10</td>
</tr>
<tr>
<td>CPAP 5</td>
<td>113±13</td>
<td>69±10</td>
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<tr>
<td>CPAP 8</td>
<td>112±11</td>
<td>71±10</td>
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<tr>
<td>CPAP 10</td>
<td>111±10</td>
<td>68±10</td>
</tr>
<tr>
<td>CPAP 12</td>
<td>117±12</td>
<td>70±9</td>
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<tr>
<td>PLB 2: 9–13 minutes after PLB</td>
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<td>CPAP 0</td>
<td>115±11</td>
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<td>71±8</td>
</tr>
<tr>
<td>CPAP 12</td>
<td>116±11</td>
<td>72±8</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; CPAP, continuous positive airway pressure expressed in cm H2O; PLB, placebo.

**FIGURE 3. Line plots of human splanchnic venous volume–pressure (V–P) relation: Individual data of control 1 and control 2 stages in all 20 patients are shown. Splanchnic vascular volume data are presented as mean±SEM. Reproducible individual V–P curves were obtained. CPAP, continuous positive airway pressure.**

**FIGURE 4. Line plot: Group effects of nitroglycerin (GTN) on the human splanchnic venous volume–pressure (V–P) relation in 12 stable patients (group 1). The control (C) curve is the average of control 1 and control 2 data. There was a significant parallel shift of the splanchnic vascular V–P curve to the right 2–6 minutes (GTN-1), 9–13 minutes (GTN-2), and 20–24 minutes (GTN-3) after sublingual GTN (p<0.001, p<0.001, and p<0.01, respectively). CPAP, continuous positive airway pressure.**
SPLANCHNIC VASCULAR VOLUME(%)

Figure 5. Line plots of effect of nitroglycerin (GTN) on the individual splanchic vascular volume–pressure (V–P) relation in patients of group 1. The control curve (open symbols) is the average of control 1 and control 2 data. In each of the 12 patients, there was a significant (parallel in most cases) rightward shift of the V–P curve after GTN. Maximal displacement of the V–P curves after GTN are depicted (closed symbols). CPAP, continuous positive airway pressure.

As illustrated in Figure 5, after GTN the splanchic vascular V–P relation (maximal displacement) shifted to the right in all 12 subjects. Maximal displacement at zero CPAP occurred 2–7 minutes after GTN in five patients and at 9–13 minutes after GTN in seven patients. Compared with control values, regional SVV at CPAP of zero cm H2O increased by >20% in one patient (patient 11), by 10–20% in two patients (patients 2 and 8), by 6–10% in seven patients (patients 3, 4, 5, 6, 7, 9, and 12), and by <6% in the remaining two patients (patients 1 and 10). The slopes of the individual splanchic vascular V–P curves after GTN administration were similar to those of control in most patients.

After GTN, mean heart rate increased by 14±5 (p<0.001), 10±6 (p<0.001), and 1±4 beats per minute (p>0.2), and group systolic blood pressure decreased by 17±10 (p<0.001), 16±9 (p<0.001), and 8±9 mm Hg (p>0.05) at 2–6, 9–13, and 20–24 minutes after GTN, respectively, compared with control values (Table 1).

Spontaneous Variability (Group 2)

The group splanchic vascular V–P curves before and after administration of placebo are shown in Figure 6. Compared with the control curve, the curves at 2–6, 9–13, and 20–24 minutes after placebo were not significantly different in terms of magnitude or slope (p>0.5). Splanchic vascular volumes at CPAP of zero cm H2O were 100.1%, 100.2%, and 99.2% at 2–6, 9–13, and 20–24 minutes after placebo, respectively, compared with the control value of 100% (p>0.5).

The splanchic vascular V–P curves before and after administration of placebo were also similar in terms of magnitude and slope in individual patients as shown in Figure 7 (maximal displacement after placebo). Maximal displacement at zero CPAP occurred at 2–6 minutes in one patient, at 9–13 minutes in three patients, and at 20–24 minutes after placebo in four patients. Compared with control values, regional SVV at CPAP of zero cm H2O increased or decreased by 0–0.9% in four patients, by 1.0–1.9% in three patients, and by ≥2.0% in the remaining patient. Splanchic vascular capacity did not vary by >2.2% from the initial control value at CPAP of zero or by >7.6% from the initial control value at CPAP of 12 cm H2O.

After placebo, mean heart rate and systolic and diastolic blood pressures were not significantly different from those during the control stage (Table 2).

Hemodynamic Effects of Low Levels of CPAP (Group 3)

Eight patients consented to participate in the hemodynamic study, but the protocol could not be completed in three because of difficulty in placing the pulmonary artery catheter, back pain, and equipment failure. Therefore, five patients were included in group 3: four men and one woman, mean age, 54±18 years. They had chronic coronary disease without left ventricular dysfunction, hypertension, or heart failure. One patient had insignificant aortic stenosis (peak systolic gradient, 20 mm Hg). The hemodynamic changes produced by CPAP are noted in Table 3. Only the right atrial and femoral vein pressures changed significantly at all levels.

Figure 6. Line plot of repeated measures of the human splanchic venous volume–pressure (V–P) relation before and after administration of placebo (PLB) in eight stable patients (group 2). No significant differences were noted between the control (C) splanchic vascular V–P curve (average of control 1 and control 2 data) and those recorded 2–6 minutes (PLB-1), 9–13 minutes (PLB-2), and 20–24 minutes (PLB-3) after sublingual administration of PLB (p>0.5). CPAP, continuous positive airway pressure.

Figure 7. Individual splanchic venous volume–pressure (V–P) relation during control (average of control 1 and control 2 data, open symbols) and after placebo (closed symbols). Maximal displacement of the V–P curves after placebo are depicted. No significant changes were noted. CPAP, continuous positive airway pressure.
of CPAP used. Minor but significant changes of cardiac output were noted only at the higher levels of CPAP used (10 and 12 cm H2O). We do not know if increasing the number of patients would result in significant cardiac output changes at CPAP of 5 and 8 cm H2O as well. There were no significant changes in aortic or pulmonary pressures or heart rate.

**Discussion**

The importance of the venous system in overall cardiovascular homeostasis has been emphasized.2-4,8-11,17,23,44-47 The splanchnic vessels, the largest and most important capacitance region,1-1,17,23,44-47 however, has not been studied systematically in humans. The scarcity of knowledge regarding the physiology, pathophysiology, and pharmacology of human splanchnic capacitance may be attributed to the absence of a suitable technique to study this vascular bed. The results of the present investigation, which used blood pool scintigraphy and CPAP, detected the expected changes in SVV produced by GTN and placebo in a reproducible manner, thus providing evidence that quantitative blood pool scintigraphy can be used to assess changes of the splanchnic vascular capacity and, for the first time in humans, changes of the splanchnic vascular (venous) V–P relation.

Only a few studies have assessed human SVV changes as a result of acute blood volume changes (hemorrhage) and exercise,5-7 using indicator–dilution methods with 131I-labeled serum albumin and sampling from a systemic artery and hepatic vein. These first “blood pool” methods were abandoned once the unwanted effects of 131I were fully appreciated.

Blood pool scintigraphy using red blood cells tagged with 99mTc has been used recently in our laboratory25,33,38,39 and by others26-32,34-37,48 to assess regional venous volume changes in humans. After blood pool labeling,42 radioactivity emanating from a given region is proportional to the blood volume in that region. Changes in radioactivity reflect changes in blood volume in that region. This principle has been used for the past 15 years to routinely measure intracardiac volume changes which, when synchronized with the ECG, provide information to assess right and left ventricular function and volumes.49 When the same principle is applied to the hepatic,26-28 pulmonary,27-31 splenic,27,28,32,36,37 and splanchnic25,28,33,36,37 regions, changes in radioactivity reflect changes in intravascular blood volume in these organs. Because approximately 70–80% of the total blood volume is contained in the veins,2-4,10,19,23,44-46,50 changes in regional intravascular volume must primarily reflect changes in regional venous volume.

Regional venous volume changes may occur passively, as a result of changes in venous distending pressure (stressed venous volume), or actively, as a result of changes in venous smooth muscle contractile characteristics (unstressed venous volume), or both. Changes in venous capacitance, therefore, are best defined by changes in venous pressure–volume relations.2,23,13,15-17,19,23,24,44-46,50,51 We recently validated a blood pool scintigraphic method to assess forearm vascular V–P relations.38 A good correlation was found between radionuclide plethysmography and standard plethysmography (mercury-in-rubber strain gauge). Moreover, qualitatively similar and quantitatively proportional forearm venous V–P curves were obtained before and after administration of vasoactive drugs, both techniques having similar degrees of variability.38 Forearm radionuclide plethysmography has since been used successfully to study reflex changes in venous function in normal subjects39 and in patients with neuromediated syncope.52 The few studies of the human splanchnic veins5-7,25,28,33,36,37 have assessed changes in SVV during acute interventions, but venous V–P relations have never been defined.

The present study describes a method to assess the splanchnic venous V–P relation using blood pool scintigraphy to quantitate changes in SVV. To alter splanchnic venous distending pressure passively, we used low levels of CPAP. CPAP breathing results in increased right atrial pressure directly proportional to the level of CPAP caused by elevation of the intrathoracic pressure and thus external constraint, which opposes right atrial filling. Thus, a given level of CPAP decreases the gradient between thoracic and extrathoracic venous pressure and, since splanchnic flow presumably continues, splanchnic venous pressure must increase and cause a degree of passive distension, i.e., a new equilibrium point in the splanchnic venous V–P curve is reached passively. This mechanism is supported by our hemodynamic study (see below). By recording the SVVs at different levels of CPAP, we were able to describe splanchnic vascular V–P curves.

### Table 3. Hemodynamic Changes Produced by Low Levels of Continuous Positive Airway Pressure (Group 3)

<table>
<thead>
<tr>
<th>CPAP (cm H2O)</th>
<th>Aortic pressure (mm Hg)</th>
<th>PA pressure (mm Hg)</th>
<th>RA pressure (mm Hg)</th>
<th>FV pressure (mm Hg)</th>
<th>PCW pressure (mm Hg)</th>
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<th>HR (bpm)</th>
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CPAP, continuous positive airway pressure; PA, pulmonary artery; RA, right atrial; FV, femoral vein; PCW, pulmonary capillary wedge; CO, cardiac output; HR, heart rate; S, systolic; D, diastolic; M, mean; bpm, beats per minute.

*p<0.01 vs. initial 0 CPAP.

*p<0.001 vs. initial 0 CPAP.

*p<0.05 vs. initial 0 CPAP.
How accurately does quantitative blood pool scintigraphy reflect splanchnic vascular volume? As noted above, blood pool scintigraphy has been shown to accurately reflect regional vascular (venous) volume changes in limbs,38 and it has been accepted to be a valid measurement of regional intravascular volume changes in liver, lungs, spleen, and kidneys.26-32,36,37 When blood pool scintigraphy is used to measure count-rate changes in an abdominal region away from large vessels (aorta, inferior vena cava, femoral, and iliac veins), liver, spleen, urinary bladder, and kidneys, the count-rate changes reflect changes in intravascular volume of intestines, stomach, and the richly vascularized mesenteric region. This concept has not only been accepted and used to study the effects of exercise and vasoactive drugs in human25,27,28,33,36,37 and animal3,4,18,25,53,54 experiments, but it has been validated in dog experiments in which absolute splanchnic blood volume changes were measured directly and by the radionuclide method in preparations with isolated and controlled perfusion and drainage of the splanchnic vasculature. Bell et al.14,36 concluded that blood pool scintigraphy can be used to determine the changes in relative and absolute SVV and have applied this method to study absolute SVV changes in humans. In the present study, we have used the same method as that described by Bell et al but have not attempted to calculate absolute volume measurements.

How accurately does CPAP reflect splanchnic distending venous pressure? Although no direct measurements of the effect of CPAP on splanchnic venous pressure have been performed, certain observations suggest that increasing levels of CPAP produces increasing levels of splanchnic venous distending pressure passively. First, in agreement with our results (group 3), it has been shown that increasing levels of intrathoracic pressure using CPAP or positive end-expiratory pressure (PEEP) produce elevation of right atrial or central venous pressure.40,55-58 Second, an increased right atrial pressure must raise the pressure in the peripheral veins to maintain flow, tending to increase the volume of blood they contain in a passive manner. Our results in group 3 confirmed this by documenting that CPAP was associated with a proportional increase of the femoral venous pressure. Third, Risöe et al.59 reported recently that 10 cm H2O PEEP increased portal venous pressure by 3.1±0.3 mm Hg and hepatic venous pressure by 4.9±0.4 mm Hg, indicating that an elevation of venous pressure probably occurs in all extrathoracic veins including those in the splanchnic region. In fact, CPAP or PEEP have been shown to induce an elevation of the mean circulatory filling pressure.60-62 Fourth, an elevated pressure in the extrathoracic veins associated with a passive increase of the volume of this vascular bed is suggested by the decrease of the pressure gradient between the femoral vein and right atrium with CPAP (from 4.2 to 2.7 mm Hg, Table 3) and by the reported passive increase in hepatic blood volume induced by 10 cm H2O PEEP.59 Concordant to our results, Chihara et al.62 also showed that elevation of the intrathoracic pressure induced a decrease of the pressure gradient for venous return (mean circulatory pressure minus right atrial pressure), which in turn produced a passive increase of volume in the extrathoracic veins. Fifth, diminished cardiac and thoracic blood volumes have in fact been documented during CPAP or PEEP,40,56-58 caused presumably by an increased blood volume in the extrathoracic capacitance vessels. We conclude, therefore, that the new equilibrium in total blood volume distribution for each level of CPAP occurs passively when low levels of CPAP are used and that low levels of CPAP reflect proportional changes of splanchnic venous distending pressure.

Our results (Table 3) are in agreement with previous publications on the hemodynamic effects of increased intrathoracic pressure. First, in our study and in previous studies, there was an increase in right atrial pressure55-58,60-63 and a tendency to decrease in cardiac output.40,55-63 Quantitatively, these changes were proportional to the levels of positive pressure ventilation, with low levels of positive pressure breathing (similar to those used in the present investigation) producing no change or only mild changes in cardiac output.63 Second, significant decreases in cardiac output and systolic aortic pressure and increases in heart rate were seen only in studies using higher levels (>15 cm H2O) of positive-pressure ventilation.40,55-57,60 Studies using ≤15 cm H2O positive airway pressure documented no changes in heart rate.57-59,63,64 In studies such as those by Bjurstedt et al67 and others68 who used various levels of positive pressure ventilation, significant changes in heart rate were noted at pressures of 30 cm H2O but not at pressures of 15 cm H2O. These previous studies support our findings that low levels of CPAP (≤12 cm H2O) produce slight but significant changes in intrathoracic and extrathoracic venous volume distribution passively, without significant activation of cardiovascular reflexes or sympathetic stimulation. Low levels of CPAP reflect proportional changes in splanchnic venous distending pressure. A slight decrease in blood flow (cardiac output) during low levels of CPAP may change (unmeasured) pressure in upstream venules; however, this will cause a decrease in the venous volume and, as such, will cause us to underestimate the increase in splanchnic venous volume measured during CPAP. Radionuclide-measured SVV changes at the corresponding CPAPs should, therefore, be useful to estimate the splanchnic venous V-P relations.

Radionuclide Plethysmography to Assess the Splanchnic Venous V-P Relation

Individual and group splanchnic venous V-P curves were highly reproducible and shifted as expected after administration of GTN. Spontaneous variability of the technique was <2% at zero CPAP and <6% at CPAP of 12 cm H2O. The variability of SVV was slightly greater (<2.5% at zero CPAP and <8.0% at CPAP of 12 cm of H2O) when observations were made for longer periods after administration of placebo, reflecting a greater degree of spontaneous (real) change in venous tone. This degree of variability is similar to or smaller than what is generally seen with other measures of cardiovascular function.

Although the venous V-P relation over a large range of pressures must be curvilinear, recent animal studies have demonstrated linearity over a similar range of pressures as explored here in the splanchnic capacitance vessels.13,15-17,25 The present study, which is the first to assess the splanchnic venous V-P relation in humans, showed that the relation was linear in agree-
ment with previous animal data presented by Shoukas et al.\textsuperscript{17,65} and Greenway et al.\textsuperscript{15} Moreover, the dilatory effect of GTN was shown to take place by a parallel shift of the splanchnic vascular V–P relation resulting from an increased unstressed venous volume similar to that found in the human forearm\textsuperscript{21,38} and the canine splanchnic veins.\textsuperscript{25}

Potential Limitations

The major limitation of this investigation is also what makes it most meritorious. Our results could not be validated by comparing them with other methods because no other method to assess the splanchnic venous V–P relation in humans exists. However, the usefulness of the radionuclide method for assessing regional venous volume changes has been validated in the human forearm\textsuperscript{38} and the canine splanchnic\textsuperscript{4,23} and pulmonary\textsuperscript{66} circulations.

The region of interest used to define the splanchnic region included both anterior and posterior abdominal walls in addition to the target mesenteric and intestinal regions. Preliminary data at our laboratory suggest that this is not a significant problem.\textsuperscript{67} In dog experiments in which the abdominal walls were isolated, the posterior abdominal wall contributed <2% to total regional counts, and although approximately 25–30% of total counts originated in the ventral abdominal wall, the change in the V–P curves was not significantly different when using total counts or total counts minus counts from the abdominal wall.\textsuperscript{67}

The SVV changes are expressed as a percentage of baseline values. Using the methods described here, quantitative measures of splanchnic vascular V–P curves can be accurately assessed during acute interventions. However, when studies are performed on different days, absolute volumes are desirable. Bell et al.\textsuperscript{66,68} recently described a method in which radionuclide units were used to estimate absolute volume units using attenuation correction methods. Therefore, slight modifications of the method described here might be used to obtain the human splanchnic vascular V–P relations in absolute volume units, which might then be used during chronic experiments.

Common to most plethysmographic methods used in humans, various levels of CPAP reflect well the directional and quantitative changes in right atrial pressure and probably in large splanchnic veins, but we do not know how well changes in CPAP reflect pressure changes in small splanchnic veins and venules. Concerns that large pressure differences exist between small- and medium-sized veins have not been confirmed in recent studies by Shoukas and Bohlen.\textsuperscript{17} Insignificant differences were found between distending pressures in first-, second-, and fourth-order intestinal venules in rats.\textsuperscript{17} They also found that first-, second-, and fourth-order venules all behaved similarly in response to interventions that produced venoconstriction or venodilation.

We have shown that incremental increases in CPAP produce incremental increases in SVV, presumably by increasing splanchnic venous volume passively as portal pressure increases. However, elevating portal venous pressure may not be the only hemodynamic effect of CPAP that affects SVV. A change in splanchnic blood flow might change venous blood volume, and although the relation between changes in splanchnic blood flow and changes in cardiac output is not clear, cardiac output may have decreased minimally in our study, even at pressures of 5 and 8 cm H\textsubscript{2}O. The effect of any CPAP-induced decrease of splanchnic blood flow on splanchnic venous volume would, however, be opposite to that of the CPAP-induced increase of venous pressure, and the fact that SVV did increase with increasing CPAP indicates that the latter effect predominates. Furthermore, any flow-related effect of CPAP on venous volume can only affect the slope of the V–P relation. We conclude that it is unlikely that flow-related changes in venous volume might have influenced our observations to any significant degree and thereby undermined the validity of our technique. The effects of CPAP on cardiac output may be different in other clinical settings such as in some patients with heart failure.\textsuperscript{68} Therefore, it cannot be assumed that this method will also be useful in subjects with heart failure or significant pulmonary or hepatic disease.

Summary

The study of the splanchnic veins in humans has remained elusive because of lack of a suitable technique, and until now, the V–P relation of human splanchnic veins has never been recorded. The results of this study showed that quantitative abdominal blood pool scintigraphy and low levels of CPAP can be used to define the human splanchnic venous V–P relation in a reproducible manner. Using this novel method, we have shown that GTN exerted its venodilatory effect by increasing the unstressed splanchnic venous volume. The radionuclide and CPAP method described here appears to be promising for the study of the human splanchnic venous system in health and disease.

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References

58. Sewell JE, Abendschein DR, Carlson CJ, Rapaport E, Murray JF: Mechanism of decreased right and left ventricular end-diastolic
volumes during continuous positive pressure ventilation in dogs.
_Circ Res_ 1980;47:467–472


Assessment of the human splanchnic venous volume-pressure relation using radionuclide plethysmography. Effect of nitroglycerin.
D E Manyari, Z Wang, J Cohen and J V Tyberg

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