Volume-Pressure Analysis of Reflex Changes in Forearm Venous Function

A Method by Mental Arithmetic Stress and Radionuclide Plethysmography

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Mental arithmetic stress is known to cause forearm arterial dilation, but the venous responses, including possible changes in the volume-pressure relation, have not been defined. Hence, 10 apparently normal subjects, eight men and two women, mean age 46.9 years, were studied before and during mental arithmetic stress. Changes in forearm venous volume were estimated with 99mTc blood pool scintigrapy. Group variability of this measurement technique was 1.8±2.5%. A brachial blood pressure cuff was used to obtain venous occluding pressures of 0, 10, 20, and 30 mm Hg. Mental arithmetic stress increased group systolic and diastolic blood pressure from 126±12 to 152±20 mm Hg and from 83±8 to 93±15 mm Hg, respectively (p<0.001). Heart rate increased from a mean of 75±15 to 85±17 beats/min (p<0.01). There was no evidence of interaction between or nonlinearity of the volume-pressure plots. Linear regression then yielded the equations V=99.8±0.96P before and V=86.3±0.96P during mental arithmetic stress, which represents a 13.5±1.6% decrease in forearm vascular volume (p<0.001). We conclude that 1) a linear relation exists between forearm venous volume and pressure at physiologic pressures before and during mental arithmetic stress; 2) mental arithmetic stress causes forearm venoconstriction; and 3) such venoconstriction takes place by a parallel shift in the volume-pressure relation (i.e., a shift in unstressed venous volume).

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Athough mental stress may induce profound cardiovascular changes,1-4 studies of its effects on the forearm venous system have been limited and have not included descriptions of the volume-pressure relations.5-8 Early studies7,8 showed venoconstriction of the isolated superficial veins of the forearm. Only two studies5,6 have examined the effect, with volume displacement plethysmography, of mental arithmetic stress on forearm venous volume (limb volume). Neither study produced conclusive results, but both tended to show an increase in forearm venous volume. This was unexpected in view of the fact that mental arithmetic is a pressor stimulus,9,10 and Delius et al16 also showed the expected increase in venous tone. Neither study attempted to plot volume-pressure relations; hence, changes in forearm blood volume observed could not be attributed to either a passive or active venous response in the forearm.

Recently, 99mTc blood pool scintigraphy was used by us11,12 and others13,14 as a sensitive method of serially assessing changes in peripheral intravascular volume (changes in venous volume). Thus, we used this technique to assess changes in forearm venous volume in response to a common psychologic stressor, mental arithmetic. We plotted the forearm volume-pressure relation before and during mental stress to characterize the venous response. This method not only provides the opportunity to determine whether forearm venous volume changes with mental stress, but it also allows clarification of the situation when venous tone and volume are concurrently increased.6 If the pressure-volume coordinates fall on a different curve during mental stress, an intrinsic change in forearm venous properties is implied (active venous response), whereas
movement along the same pressure-volume curve represents no change in these intrinsic venous properties (passive venous response).

**Methods**

**Study Population**

The study population (Table 1) consisted of 10 patients, eight men and two women, 33–62 years of age (mean ± SD, 46 ± 9 years), with no clinical evidence of organic cardiovascular or other disease. Nine of these patients had atypical chest pain (with a pretest likelihood of significant coronary disease <10%), and one had asymptomatic premature ventricular beats. These patients were all unmedicated, and none had a history of previous vasovagal syncope or presyncope. Informed consent was obtained from all patients before participation in the study.

**Mental Arithmetic Stress**

We used a standard mental arithmetic test administered by one of two individuals, neither of whom was well known to the subject. Serial 17s were subtracted from a four-digit number or serial 7s and 3s from a three-digit number. Beginning the arithmetic test with serial subtraction of 7s, the difficulty was adjusted to obtain optimal effort without causing the patient to stop due to frustration. The only interaction with the subjects during the administration of the test was frequent prompting to concentrate or to speed up if they appeared to be relaxing at the task. Although we believe most patients operated close to their optimum, the individual’s perception of the stress varied widely and did not relate to how well or how poorly he performed.

**Radionuclide Plethysmography**

Relative changes in forearm venous volume were assessed by measuring changes in regional forearm blood volume with blood pool imaging. This technique has been described and validated previously. Briefly, after in vivo labeling of the red blood cells with 740 mBq (20 MCl) of $^{99m}$Tc, 30-second static images were acquired with a standard gamma camera (Picker dyna camera - 4, Northford, Connecticut) equipped with a high-sensitivity parallel-hole collimator and interfaced to a dedicated nuclear medicine computer system (ADAC model 3000, San Jose, California). Imaging was performed at least 30 minutes after initial labeling to minimize measurement error due to unbound $^{99m}$Tc. Images were recorded 30 seconds after inflation of the blood pressure cuff to allow for hemodynamic stabilization.

A segment of the forearm, excluding the distal and proximal 3–4 cm, was outlined by metal markers taped to the skin. The count rate in this region of interest obtained with no occluding pressure or mental arithmetic stress was arbitrarily taken to represent 100% forearm blood volume. All subsequent readings were expressed as a percentage of this value. Background was not taken into account because it is quantitatively small and remained constant throughout this short study. All counts were corrected for physical decay. A technician was responsible for sphygmomanometer cuff inflation and activation of successive scintigrams. This person maintained close attention to ensure stable occluding pressures throughout the study. Measures of scintigraphic vascular volume (in percent units) at occluding cuff pressures of 0, 10, 20, and 30 mm Hg were used to construct venous volume-pressure plots as described previously.

**Study Design**

The study was performed in the postabsorptive state. In a few patients, the study was performed after exercise radionuclide ventriculography, but in these patients, we ensured that more than 2 hours...
had elapsed after completion of exercise. The subjects were allowed to relax for at least 30 minutes after the study was explained. Then, with the subject seated, the forearm was placed prone on the horizontal collimator of the gamma camera. The middle of the forearm was maintained at a level 4 cm below the sternal angle.

The laboratory was quiet and cool (20–22°C). Thirty-second scintigrams (control stage) were taken at 0, 10, 20, and 30 mm Hg arm occluding pressures, starting at zero and increasing stepwise at 1-minute intervals until 30 mm Hg. After data at 30 mm Hg occluding pressure, cuff pressure was decreased to zero. Mental arithmetic stress was begun 2–4 minutes later. Scintigrams were again recorded (stress stage) 2 minutes after initiation of mental arithmetic stress, at identical successive occluding pressures. Heart rate (by 30-second electrocardiogram rhythm strip recording) and blood pressure (by sphygmomanometer cuff on the opposite arm) were recorded during both control and mental stress. This experiment had a factorial structure, with two levels of stress and four levels of congesting pressure applied to individual subjects.15

To test the variability of the radionuclide technique to measure regional forearm blood volume, duplicate scintigrams were recorded during both control and mental arithmetic stress in eight of the 10 patients. In these eight patients, pairs of data (forearm regional blood volume determinations at each level of cuff congesting pressure) were obtained during the following successive stages: control 1, control 2, mental stress 1, and mental stress 2, with a 1-minute free interval (zero cuff occluding pressure) between stages and with cuff congesting pressures (0, 10, 20, and 30 mm Hg) always applied in the same order.

In five patients, we continued recording volume-pressure plots immediately on cessation of mental arithmetic stress. Although we presumed that the time course of recovery from induced emotional stress would show marked individual variability, we felt it worthwhile to identify any directional trends that may be evident in the volume-pressure plots in the immediate poststress period.

Statistical Analysis

Analysis of the relative forearm regional blood volume changes produced by mental arithmetic stress was performed with analysis of variance with an orthogonal polynomial decomposition.15 Possible effects of stress and occluding pressure on venous volume were examined with a within-patients comparison. The Student’s t test for paired data was used to analyze the significance of the changes in blood pressure and heart rates produced by mental stress (maximal response). Statistical significance was accepted at the 95% confidence level (p<0.05). Data are presented as mean±SD.

Results

The clinical characteristics of participant subjects are presented in Table 1. Also included are the blood pressure and heart rate responses to mental arithmetic stress. Systolic blood pressure increased from a mean of 126±12 to 152±20 mm Hg (p<0.001) and diastolic blood pressure from 83±8 to 93±15 mm Hg (p<0.001). There was also a significant increase in heart rate, from 75±15 to 87±17 beats/ min (p<0.01).

Figure 1 shows the individual plots of forearm relative blood volume versus occluding pressure at control and during mental arithmetic stress. There was a consistent downward shift in the volume-pressure relation in response to mental arithmetic stress. Only one patient (patient number 3), noted to be obviously tense throughout the study participation, showed no appreciable change in forearm blood volume from mental arithmetic stress. Of note, although individual volume-pressure plots vary in slope (compliance), within individuals there was little change in slope between control and mental arithmetic states. Thus, shifts in the curves induced by mental arithmetic were parallel.

Orthogonal contrasts were used for curve fitting and to examine for evidence of interaction (i.e., lack of parallelism) between the curves at control and during mental arithmetic. Values of F obtained for nonlinear fits and interaction were insignificant (p>0.2). The corresponding F value for linearity was highly significant (p<0.001). We therefore adopted a parallel straight line model. Analysis of variance showed significant effects of mental arith-
venous volume-pressure relations in apparently normal individuals, who were medication-free. The results of this study indicate that mental arithmetic stress causes venoconstriction by a parallel shift in the volume-pressure relation and that this relation is linear both at baseline and during mental arithmetic stress.

In the present investigation, the changes in blood pressure and heart rate found during mental arithmetic stress are consistent with results of previous studies.\(^\text{3,9,10}\)

### Radionuclide Plethysmography

Radionuclide plethysmography was well described recently\(^\text{11-14}\) and has several advantages over other techniques currently in use.\(^\text{12}\) In particular, because it is relatively noninvasive and less susceptible to motion artifact, it lends itself to widespread use for assessing reflex changes and dysfunctional peripheral venous responses in humans who undergo diagnostic procedures for which the blood pool has been already labeled. We previously used this technique in our laboratory to successfully evaluate the capacitance effects of nitroglycerin\(^\text{11}\) and showed a good correlation with strain gauge plethysmography.\(^\text{12}\) It is a more direct measure of intravascular capacity than are the volumetric methods that measure total limb volume or circumference. It largely obviates the inherent assumptions associated with limb volumetric methods (strain gauge plethysmography): incompressibility of all intraforearm structures, absence of fluid extravasation, and constancy of limb geometry during volume changes.\(^\text{10}\) Subtle external pressure on forearm veins is also removed as a potential confounding factor.\(^\text{14}\) The absolute variability of approximately 6% is small enough to allow detection of the venous responses to mental stress demonstrable in our study.

Total regional blood volume by blood pool scintigraphy was used as an index of actual venous volume because 80% of the systemic blood volume is contained in the veins,\(^\text{17}\) and changes in intravascular volume can be assumed to occur predominantly in the compliant venous capacitance vessels.\(^\text{18}\)

### Venous Physiology

In the apparently normal subjects studied in this investigation, we have shown a reduction in forearm venous volume that averages 13.5% at all occluding pressures. We excluded all subjects with a history suggestive of vasovagal episodes who may theoretically develop a “fainting reaction” to stress.\(^\text{19}\) Our results showed homogeneity of individual responses and a highly statistically significant \((p<0.001)\) whole forearm venoconstriction in response to mental arithmetic stress. This would be the expected response to a pressor stimulus\(^\text{4,10}\) despite the fact that earlier studies failed to show this.\(^\text{5,6}\) These former studies used only 50 seconds or less of mental arithmetic stress, which may not be long enough to obtain maximal or steady-state

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**Discussion**

The present study was designed to determine the effect of mental arithmetic stress on the forearm volume-pressure relation at control (C) and during mental arithmetic stress (MS) obtained by analysis of variance after testing revealed no lack of linearity or parallelism. At cuff pressures of 0 and 30 mm Hg, the standard error of the estimate (SEE) was 1.52%; at 10 and 20 mm Hg, 1.16%.

Hence, these data from apparently normal subjects show that mental arithmetic caused a parallel downward shift in the volume-pressure relation that represented a 13.5% decrease in forearm blood volume at all levels of pressure used.

The variability of the radionuclide method to measure forearm venous volume was assessed by duplicate measurements in eight patients. During 32 repeated measures of forearm blood volume at 0–30 mm Hg of cuff occluding pressure during control (control 1 vs. control 2), the average absolute variability (absolute difference between readings) was 5.8±4.0%. The group variability (considering that the second reading of forearm regional blood volume was greater in five patients and smaller in three, relative to the first reading) was 1.6±2.1%. Similarly, during 32 pairs of readings during mental stress (mental stress 1 vs. mental stress 2), the absolute variability (no sign considered) was 5.8±4.0%, and the group variability (considering a + or − sign) was 1.8±2.3%.

Data on five patients immediately after stress showed that the volume-pressure relation had similar slope and shifted toward the control curve in a parallel manner.
effects of the applied stress. We delayed data collection until subjects were at least 2 minutes into arithmetic calculations. In addition, two earlier studies used volume displacement plethysmography, which may be less sensitive in the forearm. One such study, which used exogenous catecholamine infusion, did not detect an increase in forearm volume until occluding pressures were in the 10–20 mm Hg range. In our study, we regularly obtained an increase in forearm blood volume for each 10-mm Hg increment in congesting pressure (see Figure 1).

A similar measurement technique has been applied in anesthetized instrumented dogs to examine the response of limb blood volume. Maximal stimulation of the sympathetic outflow to the limb caused only half the decrease in limb blood volume seen in our study. Apart from obvious species and preparation differences, mental stress releases adrenomedullary catecholamines that can augment the constriction of uninnervated smooth muscle. The same group of workers showed a higher estimate for the decrease in whole-dog vascular capacitance with infused norepinephrine. Other studies with volume displacement plethysmography have shown higher estimates of muscle bed vеноconstriction in the cat. Thus, we believe that the degree of reduction in forearm venous volume to a pressor stimulus (mental arithmetic) shown in our study is consistent with available animal data.

One human study concluded that the veins in muscles of the forearm do not react to mental arithmetic stress. Epinephrine iontophoresis was used to eliminate the cutaneous circulation. Despite efforts to only eliminate the cutaneous circulation, it is possible that unwanted constriction of muscle veins by iontophoresis took place before mental stress because none of the stimuli subsequently used elicited a response. Systemic reactions to iontophoresis have been noted previously. With radionuclide plethysmography, we were unable to localize where in the forearm the observed venoconstriction took place. Although muscle veins are sparsely innervated by sympathetic nerves, the pressor stimulus of mental arithmetic releases plasma catecholamines and could indeed constrict noninnervated veins in the forearm. We therefore cannot exclude the participation of muscle veins in the response to mental arithmetic stress.

Although earlier studies tended to show curvilinearity of the forearm venous volume-pressure relation, linearity at physiologic pressures has been shown recently in the splanchnic veins and in plots of whole body vascular capacitance in animals. In the cat liver, Greenway et al showed not only a linear resting venous volume-pressure relation but also a parallel shift during norepinephrine administration, which led to a decreased unstressed volume (i.e., volume extrapolated to zero pressure). In the present study, a similar shift in the human forearm veins was observed during mental arithmetic stress. In comparison with a simple change in compliance (slope), a parallel shift in the volume-pressure curve is of obvious advantage in that venoconstriction is not attenuated in cases where prevailing venous pressures are low, such as during hemorrhage. Our demonstration of a parallel shift in the forearm venous volume-pressure relation in response to reflex-induced changes provides human data to support the hypotheses of Greenway et al and Shoukas and Sagawa that changes in venous capacitance occur in this manner. Mental arithmetic stress induced a shift in the volume-pressure relation of the forearm veins, which suggests a change in some intrinsic property of these veins. How this active venous change occurs without altering venous compliance is unknown.

By far, the largest component of the human forearm is muscle, which constitutes approximately 60% of its volume. However, the reactivity of the muscle venous bed is probably not as pronounced as that of other beds in response to sympathetic stimuli, although, given the size of the human muscular bed, it may have significant systemic hemodynamic effects. Although any extrapolation of our results to the entire human systemic venous bed must be made with caution, the increase in cardiac output that occurs with emotional stress may be, in part, assisted by translocation of blood from the limbs.

**Possible Limitations of the Present Study**

In our efforts to minimize instrumentation, we did not measure intravenous pressures. Data from our laboratory suggests that in persons without elevated venous pressures, occluding cuff pressures of 10–30 mm Hg are within 1–2 mm Hg of intravenous pressure. Obviously, the difference is most marked at zero occluding pressure, where intravenous pressures are about 4 mm Hg. No patients had evidence of elevated jugular venous pressure at the time of this study.

We did not attempt to show in all patients a return of the venous volume-pressure plot to control values. In four of five patients in whom we did postmental arithmetic stress recordings, we obtained clear evidence of partial or complete recovery of forearm venous volume.

The most important drawback of our study is that we did not measure forearm blood flow. If blood flow changed during mental stress, the observed shift in the venous volume-pressure curve could have been due to a change in blood flow or a change in venous smooth muscle activity or both. Rothe and others have pointed out that distending pressure in the small, more compliant veins is directly related to blood flow (because of a flow-dependent pressure gradient between large and small veins and venules). Thus, some of the decrease in forearm blood volume during mental arithmetic stress may have resulted from arterial vasoconstric-
tion, less blood flow, and less distending pressure in the small veins and venules (even though the large-vein [cuff] pressure was the same during measurements). However, mental stress has caused an increase in blood flow in every study in which it has been measured. Increased blood flow from arterial dilatation will result in augmentation of the distending small vein and venular pressure and will thereby increase forearm regional blood volume. If such a sequence of events did take place, the venoconstriction measured in the present study during mental stress was underestimated. Our qualitative results should remain valid; our quantitative results remain to be confirmed. Moreover, in recent animal experiments performed by A.A. Shoukas (personal communication), directly measured pressures in large veins were similar to those in small veins and venules of the splanchnic circulation. Dr. Shoukas’s data appear to be similar to those reported by H.G. Bohlen et al., who, in a series of experiments, found insignificant pressure differences between large and small veins and venules of intestinal and cremasteric regions of normotensive and hypertensive rats. If this is confirmed in other venous beds, such as in the human forearm, our qualitative and quantitative results will be validated.

Summary

The results of this study demonstrate that mental arithmetic stress causes whole forearm venoconstriction, which results in a 13.5% decrease in volume and takes place without detectable change in venous compliance. This study provides human data to support recent animal studies that show linearity of the venous volume-pressure relation at physiological pressures. The findings that pharmacologic and baroreceptor-mediated shifts in systemic venous volume involve changes only in unstrained volume in animals now are extended to include reflex mechanisms that alter sympathetic activity in noninnervated conscious humans in whom the regional forearm veins were studied. We believe that radionuclide plethysmography offers significant potential to assess peripheral venous responses in humans.

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