

## Postural Pseudoanemia: Posture-Dependent Change in Hematocrit

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**OBJECTIVE:** To determine the magnitude of posture-related changes in blood components.

**SUBJECTS AND METHODS:** Twenty-eight healthy subjects were studied between 1995 and 2004 at the Vanderbilt Autonomic Dysfunction Center, Nashville, Tenn. Lying and standing plasma volume (PV) and hematocrit (Hct) values were determined for each subject.

**RESULTS:** Individual PV decreases on standing ranged from 6% to 25%. The absolute mean  $\pm$  SD PV shift was  $417 \pm 137$  mL (range, 149-717 mL). The mean  $\pm$  SD change in Hct was from  $37.7 \pm 2.8\%$  while supine to  $41.8 \pm 3.2\%$  within 30 minutes of standing. This absolute increase in Hct of  $4.1 \pm 1.3\%$  represents a relative increase of  $11.0 \pm 3.6\%$  from lying to standing.

**CONCLUSIONS:** Changes in posture can lead to substantial changes in Hct, which may be attributed mistakenly to blood loss or acute anemia and result in a cascade of unnecessary diagnostic costs. In reality, these changes represent *postural pseudoanemia*, a normal physiological response to a change in position from standing to lying (and vice versa).

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BV = blood volume; Hct = hematocrit; PV = plasma volume

Assessment of the cellular component of blood has been a cornerstone of patient evaluation for more than a century. Determination of hematocrit (Hct [packed red blood cell volume]) and hemoglobin levels has become the mainstay of monitoring anemia and an important indicator of blood loss. Because of the simplicity of Hct determination, this test is used widely in many clinical settings to track anemia of iron deficiency, chronic disease, vitamin B<sub>12</sub> deficiency, folate deficiency, and many other conditions. Although determination of Hct seems reproducible and straightforward under controlled laboratory conditions, it is a far more complicated index of erythrocyte status than is commonly appreciated. Many factors can influence the value obtained for Hct in a clinical setting. These factors are usually pathological, although some may be due to normal physiological circumstances.

Simply standing upright increases hydrostatic pressure in dependent regions (such as the lower extremities), and this shift in balance between hydrostatic and oncotic pressures leads to a net movement of fluid from intravascular to interstitial spaces.<sup>1</sup> The resulting filtration is halted eventually by a combination of tissue pressure and increased intravascular oncotic pressure.<sup>2</sup> Thompson et al<sup>3</sup> first

showed a loss of plasma volume (PV) on standing in 1928. Tombridge<sup>4</sup> and Nunnally<sup>5</sup> addressed this effect in typical hospital conditions, suggesting that the hemoconcentration that results from plasma loss to the interstitium may alter Hct in a clinically important manner.

Therefore, posture can cause wide fluctuations in Hct levels. These fluctuations are often substantial enough to shift the Hct out of the "normal" range for a particular patient and may lead to an inaccurate diagnosis of anemia, which we refer to as *postural pseudoanemia*. Clinically, the initial Hct level on hospital admission often is measured when the patient is upright or was recently upright. After admission, Hct levels measured when the patient is supine may be remarkably lower, which may alarm the physician. It is important to know whether the change in Hct is a result of acute bleeding or can be explained simply by postural influences on the blood cell concentration (ie, pseudoanemia). Thus, the purpose of this study was to determine the magnitude and variability of the changes in PV shifts and consequently on obtained Hct values resulting from changes in posture from lying to standing.

### SUBJECTS AND METHODS

Twenty-eight healthy subjects (21 female) were studied at the Vanderbilt Autonomic Dysfunction Center in Nash-

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ville, Tenn, between 1995 and 2004. All subjects were medication free for at least 5 days before determination of PV. Study protocols were approved by the Vanderbilt University Institutional Review Board, and each participant gave written informed consent to participate in the study.

#### PROTOCOL

Subjects were admitted to the Elliot V. Newman General Clinical Research Center at Vanderbilt University and given a diet that contained 150 mEq of sodium per day and 70 mEq of potassium per day for at least 3 days before the study. After remaining supine overnight, subjects underwent assessment of PV and Hct, and then posture-induced dynamic changes in PV and Hct were evaluated. A subset of the patients (n=10) also underwent total protein determinations while supine and while upright. For upright assessments, a tilt table test (60° for up to 30 minutes) was used in 18 subjects or unsupported standing (for up to 60 minutes) in 10 subjects. During upright posture, Hct measurements were made at 2.5, 5, 7.5, 10, 15, 20, 30, 45, and 60 minutes (when applicable).

Plasma volume was determined by using the indicator dye-dilution technique with radiolabeled albumin (n=18; October 2002-May 2004) or Evans blue dye (n=10; before 2000). Two different techniques were used because of changes in the methods approved by the Food and Drug Administration for PV determination. In both cases, a 20-gauge intravenous catheter was placed in an antecubital vein, and blood samples were obtained without stasis. When the technique was performed with radiolabeled albumin, a prefilled 1-mL syringe of up to 25  $\mu$ Ci of iodine 131-labeled human serum albumin (Volumex, DAXOR Corp, New York, NY) was injected into the antecubital vein and flushed with 30 mL of normal saline. Venous blood samples were collected before injection and at 12, 18, 24, and 30 minutes after injection. Plasma radioactivity was measured in duplicate and averaged (for each sample and for a reference standard) using an automated counter (BVA-100 Blood Volume Analyzer, DAXOR Corp). A least squares regression of the volume of distribution at each time point was performed automatically to determine the volume of distribution at the time of injection. Plasma volume was determined as the volume of distribution of albumin. In the remaining subjects (n=10), PVs were determined with Evans blue dye by using a modification of the technique of Campbell et al.<sup>6-8</sup> Sephadex columns (PD-10, Pharmacia, Uppsala, Sweden) were used in place of hand-packed cellulose columns. Baseline measurements were performed on plasma obtained 10 minutes after dye injection.

Total blood volume (BV) was calculated from measured PV and microcapillary venous Hct corrected for trapped plasma (0.96) and whole body Hct (0.91).<sup>8</sup> Subsequent relative dynamic percent changes in PV were calculated from Hct from free-flowing blood samples, in which Hct<sub>1</sub> was the control and Hct<sub>2</sub> was the test as follows<sup>9</sup>: Dynamic  $\Delta$ PV (%) =  $100 \times [(Hct_1 - Hct_2)/Hct_2] \times [1/(1 - Hct_1)]$ ; Hct was measured in quadruplicate.<sup>7</sup> Total protein was measured in triplicate by refractometry in 10 subjects (TS meter, Leica, Buffalo, NY).

The percentage difference in BV was calculated from the ratio between the measured total BV and the estimated total BV. Estimated BV values for each subject were calculated from the height (Ht [m]) and weight (Wt [kg]) as follows<sup>10</sup>: Estimated BV (liters) =  $(0.414 \times Ht^3) + (0.0328 \times Wt) - 0.03$  (with gender correction).

#### STATISTICAL ANALYSES

Results are presented as mean  $\pm$  SD;  $P < .05$  was considered statistically significant. Multiple measurements were taken while subjects were upright, but only the final upright value was used for statistical analysis. Thus, 2-tailed paired *t* tests were used to compare mean values obtained while subjects were supine and upright. Linear regression analysis was used to assess the relationship between changes in PV and plasma total proteins. Nonlinear regression analysis was used to assess dynamic changes in PV (1-phase exponential decay). A 1-phase exponential association model was used to assess the changes in plasma total proteins. These modeled values were used in the linear regression analysis. Data were analyzed with Quattro Pro (Borland Software Corp, Scotts Valley, Calif) and Prism 4.02 (GraphPad Software, Inc, San Diego, Calif).

#### RESULTS

The general characteristics of the study population are shown in Table 1. In response to a change in posture from supine to standing, there was a significant mean  $\pm$  SD increase in Hct ( $37.7\% \pm 2.8\%$  vs  $41.8\% \pm 3.2\%$ ;  $P < .001$ ) and a significant decrease in PV ( $2770 \pm 460$  mL vs  $2350 \pm 390$  mL;  $P < .001$ ). The absolute increase in Hct of  $4.1\% \pm 1.3\%$  represents a relative increase of  $11.0\% \pm 3.6\%$  from lying to standing. The maximal individual PV changes with posture ranged from 6% to 25%. These changes translate into absolute changes in PV that ranged from 149 to 717 mL, with a mean PV change of  $417 \pm 137$  mL.

Of note, the changes in PV occurred briskly, most within the first 10 to 15 minutes of the new posture (Figure 1, left). The hemoconcentration was essentially complete within 20 minutes of standing, with no further significant changes thereafter. The dynamic PV shifts, as assessed by

TABLE 1. General Characteristics and Baseline Measurements\*

Parameters	Baseline values
Age (y)	33.6±8.0
Sex (F/M)	21/7
Weight (kg)	70.9±11.9
Height (m)	1.69±0.08
BMI (kg/m <sup>2</sup> )†	24.9±3.5
Blood pressure (mm Hg)	
Systolic	113±12
Diastolic	68±8
Heart rate (beats/min)	64±11
Measured (upright) Hct (%)	
Overall	41.8±3.2
Male	45.3±2.3
Female	40.5±2.3
Corrected (supine) Hct (%)	
Overall	37.7±2.8
Male	41.3±1.9
Female	36.3±1.6
Total blood volume (L)	4.20±0.78
Plasma volume (mL)	2770±460

\*Data presented as mean ± SD. BMI = body mass index; Hct = hematocrit.  
†BMI = weight (kg)/[height (m)]<sup>2</sup>.

Hct measurements, were reciprocal to the changes in total plasma protein concentrations and were perfectly correlated ( $r^2=0.96$ ;  $P<.001$ ) (Figure 1, right).

## DISCUSSION

Blood volume regulation is challenged seriously by assumption of upright posture. Standing leads to rapid and persistent hemoconcentration, which may result in conspicuous intravascular PV loss. Assumption of upright posture leads to rapid pooling of blood in the lower extremities due to gravity and causes a shift of plasma fluid into

surrounding tissues. This study clearly shows that Hct is affected by postural manipulation. We also have found that Hct, when cautiously measured, often provides a reliable estimate of PV changes, as confirmed by simultaneous direct measurement of total plasma protein changes.

Our results illustrate the importance of posture in Hct measurement. Plasma volume shifts that may contribute to aberrant Hct values have been observed by many researchers using various techniques, including Evans blue dye, carbon monoxide dilution, and the mechanical oscillator technique. These various studies have shown that PV may shift from 10% up to 18%<sup>11-14</sup> in response to a person changing from a supine to an upright posture. Seated posture also has resulted in significant but smaller PV shifts (4%-6%).<sup>15-17</sup> The time required to attain near-maximal PV shift varies among studies, ranging between 15 and 20 minutes.<sup>8,14</sup> Restoration of PV on resumption of supine posture occurs within a similar period. Generally, PV is restored within 20 minutes,<sup>3,18</sup> with little further change, even with measurements taken at 35 minutes.<sup>19</sup>

Several authors have investigated whether PV shifts result from fluid movement into the interstitium or into the erythrocyte. Simultaneous measurements of Hct, mean corpuscular volume, and mean corpuscular hemoglobin concentration have shown that Hct changes are unaccompanied by changes in mean corpuscular volume and mean corpuscular hemoglobin concentration.<sup>16,17,19,20</sup> Some authors have claimed that small protein molecules (eg, albumin) may shift into the interstitium along with the plasma and cause an underestimation of the PV shift.<sup>13,21</sup> However, our results show similar PV shifts whether inferred from total protein or Hct values.

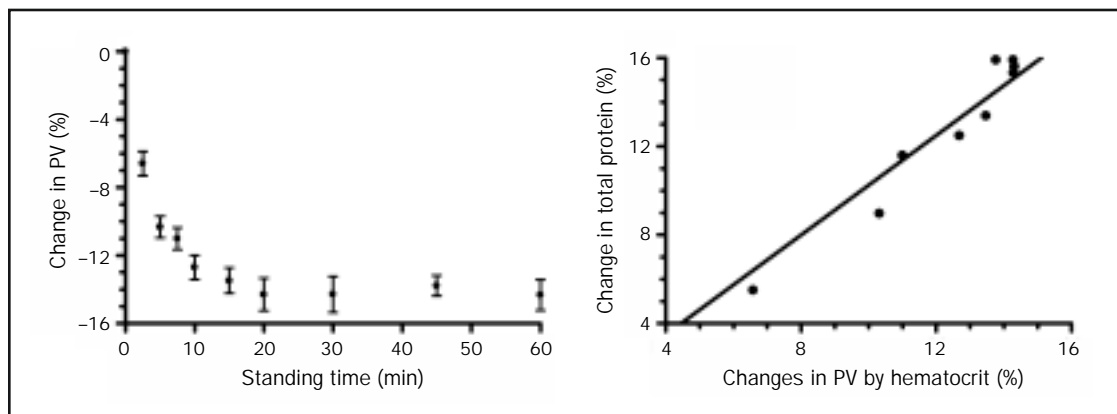


FIGURE 1. Left, The time course of dynamic plasma volume (PV) changes (as a percentage of baseline) during standing. Data are taken from the Evans blue dye PV assessment, with 10 subjects at each time point except the last 2 time points with 9 subjects. Error bars represent  $\pm 1$  SEM. Right, Linear relationship between the absolute values of the percent change in total plasma protein vs the percent change in PV as determined by hematocrit. The correlation was highly significant ( $r^2=0.96$ ;  $P<.001$ ).

## CONCLUSIONS

Hematocrit change is a reliable estimate of PV shift. Clearly, assumption of different postures significantly affects PV homeostasis and results in changes in blood component concentration. The magnitude of PV shift is time dependent and varies among individuals.

Most previously published data on this topic were driven by a desire to elucidate physiology and did not focus on the clinical importance of these findings. Our data reveal the extreme degree to which PV can shift during the assumption of upright posture. In the clinical setting, this shift can be attributed erroneously to acute anemia if measurement of Hct in supine patients follows measurement in upright patients. Because the change occurs merely in the fluid fraction and not a change in red cell mass, the term *pseudoanemia* is appropriate. Therefore, we have termed this phenomenon *postural pseudoanemia*. From these data, it is clear that we must treat a patient's posture as an important variable in our assessment of Hct. We suspect that a prospective clinical study would find that such misinterpretation of Hct occurs commonly in our hospitals. Attention to this phenomenon should allow the clinician to avoid mistaken clinical interpretation that may result in costly, invasive, and unnecessary clinical procedures aimed at discovering a source of acute bleeding.

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