

# Blood Volume Measurement as a Tool in Diagnosing Syncope

FETNAT FOUAD-TARAZI, MD; J. CALCATTI, MD; R. CHRISTIAN, MD;  
R. ARMSTRONG, MD; M. DEPAUL, MD

**ABSTRACT:** *Background:* The cause of syncope remains unknown in 24% to 37% of cases even after standard diagnostic tests. Measuring blood volume may elucidate the mechanisms of syncope in the individual patient and prove helpful in determining optimal therapy. This report includes the largest set of blood volume measurements performed in syncope patients to date. *Methods:* We performed radioisotopic blood volume measurement (Daxor BVA-100) on 539 patients who presented to our center with syncope/presyncope of unclear etiology. There were 202 men and 337 women, ages 16 to 88 years; many were receiving treatment at the time they were referred to our center. We also measured blood pressure, heart rate, and cardiac index before and during tilt, with complete data available for 411 patients. *Results:* Blood

volume derangements ranged from -32% to +116% deviation from normal. Hematocrit could not be used to predict volume status. Volume depletion was found in 241 (44.7%) patients and volume expansion was found in 63 (11.7%). Blood pressure, heart rate, and cardiac index before and during tilt did not correlate with any component of blood volume and could not be used to predict volume status. *Conclusions:* Syncope patients are heterogeneous with respect to blood volume, and blood volume derangements are common and are not identified through tilt table testing. Empirically prescribed pharmacological treatment for syncope is frequently inappropriate. Blood volume measurement should be included in syncope diagnosis. **KEY INDEXING TERMS:** Blood volume; Measurement; Syncope. [*Am J Med Sci* 2007;334(1):53-56.]

The underlying cause of syncope remains unknown in 24% to 37% of cases even after diagnostic workups.<sup>1,2</sup> In idiopathic syncope, treatment is often chosen on a trial-and-error basis. Pharmacological treatment may involve the use of medications that increase blood volume (Fludrocortisone) or increase vasomotor tone (Midodrine).

Determining a patient's blood volume status can allow a physician to confirm or rule out hypovolemia as a contributing factor in syncope and to choose appropriate medication. However, clinical assessment of blood volume, using physical symptoms or surrogate tests such as hematocrit and hemoglobin, has been found to be inaccurate in a number of conditions.<sup>7-10</sup>

In recent years, tilt table testing has been found to be instrumental in detecting and evaluating many characteristics of neurally mediated syncope.<sup>3-6</sup> However, it is not known how effective Tilt test response is for evaluating the presence of hypovolemia or other volume abnormalities.

Multisample radioisotopic blood volume measurement is the gold standard for blood volume measurement.<sup>11</sup> Recent technology (BVA-100, Daxor Corporation, NY) enables accurate, semiautomated blood volume measurement to be completed in 1.5 hours or less and compares favorably with lengthier standard methods.<sup>12,13</sup> This allows blood volume measurement to be routinely used in a clinical setting.

In this report, we examine the relations between radioisotopically measured blood volume, hematocrit, blood pressure, cardiac index, and response to tilt table testing in syncope patients referred to the Cleveland Clinic syncope section. Blood volume results are reported for 539 patients, and results of blood volume, blood pressure, and cardiac index are reported for 411 of those patients. This is, to date, the largest cohort of syncope patients in whom blood volume has been directly measured and compared to tilt test response.

## Methods

### *Patient Population*

Patients were referred to the Cleveland Clinic for a history of syncope or symptoms suggestive of increased susceptibility to syncope, such as orthostatic hypotension.

The length and severity of syncope varied, as did medications and comorbid conditions. Some of these medications, such as diuretics and antihypertensives, and comorbid conditions are known to cause alterations in blood volume and autonomic func-

---

*From the Department of Cardiovascular Medicine, Hemodynamic and Neuroregulation Laboratory, Syncope Clinic, The Cleveland Clinic Foundation, Cleveland, Ohio.*

*Correspondence: Dr. Fetnat M. Fouad-Tarazi, Hemodynamic and Neuroregulation Lab, Syncope Clinic, Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*

## Blood Volume and Diagnosing Syncope

tion. All patients underwent physical examination, tilt table testing, hematocrit measurement, and blood volume measurement as part of their syncope evaluation.

No patient had a history of acute myocardial infarction, acute stroke, active congestive heart failure, severe valvular heart disease, or critical arrhythmias at the time of the evaluation. There were no patients receiving dialysis. Treatment varied from no medications to several medications, according to comorbid conditions and previous patient evaluations by the primary physician. Medications included  $\beta$ -blockers, Fludrocortisone, Midodrine, antidepressants, hematinics, nitrates, anticholesterolemics, antihypertensive agents, antidiabetic medications, and antacids and were given according to previous clinical prescriptions.

Of the 539 patients tested, 337 were female and 202 were male. The average age was  $46 \pm 24$  years, ranging from 16 to 88. Of the 411 patients for whom complete blood volume, blood pressure, and cardiac index data were available, 263 were female and 148 were male. The average age was  $46 \pm 17$  years, ranging from 16 to 85. Blood pressure and cardiac index were measured in the supine position and at a 70 degree tilt.

### Blood Volume Determination

Blood volume was measured with the Daxor BVA-100, a semi-automated system for radioisotopically measuring blood volume approved by the FDA in 1998. This system is used in conjunction with a kit that contains a flow-chamber Albumin I-131 (Volumex) injectate supplied with matching standards. A multisample collection kit eliminates repeat venipunctures.

The BVA-100 compares a patient's absolute blood volume (measured in milliliters) against norms based on his or her gender and deviation from ideal body weight. This method of determining norms was reported to be more accurate than any other method available and eliminates systematic errors related to use of fixed-ratio norms.<sup>14</sup> Whole blood volume, plasma volume, and red cell volume are each expressed as an absolute value and as a percent deficit or excess from the individual's calculated norm.

The normal range for whole blood volume is defined as  $\pm 8\%$  from the individual patient's predicted normal blood volume. Normal range for red cell volume is  $\pm 10\%$ .

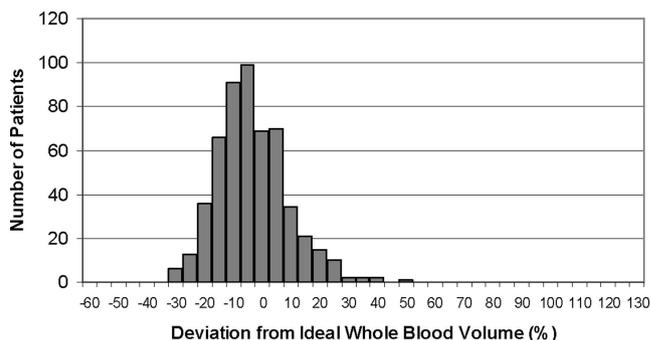
A systemic hemodynamic evaluation was done in some patients by using a computerized <sup>99m</sup>Tc-Technetium-RBC radionuclide imaging technique. (Stewart Hamilton).<sup>15,16</sup> Measurements of cardiac output and pulmonary mean transit time were obtained in duplicate in the supine position and once in the head-up sitting posture. Cardiac output was normalized for body surface area (cardiac index).

## Results

From the cohort of 539 patients, 241 (44.7%) patients were hypovolemic, 235 (43.6%) were normovolemic, and 63 (11.7%) were hypervolemic (Figure 1). Red cell volume was depleted in 306 (56.8%) patients, normal in 192 (35.6%) patients, and expanded in 41 (7.6%) patients (Figure 2).

The correlation between whole blood volume and hematocrit was very low ( $r^2 = 0.028$ ,  $P < 0.0001$ ). The correlation between red cell volume and hematocrit was higher ( $r^2 = 0.325$ ,  $P < 0.0001$ ), but the scatter was too wide to use hematocrit as a clinical indicator of red cell volume (see Figure 3). For example, at a hematocrit of 39%, the red cell volume ranged from a depletion of  $-29.1\%$  to an expansion of  $+21.5\%$ .

**Distribution of Deviation from Ideal Whole Blood Volume in 539 Syncope Patients**



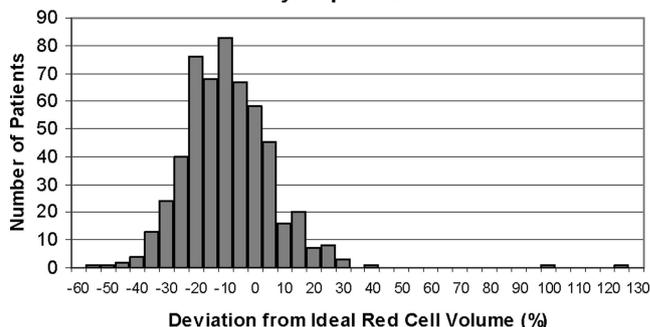
**Figure 1.** Histogram of percent deviation from ideal whole blood volume in 539 syncope patients: 45% of patients had a normal whole blood volume; 55% had blood volume derangements, mostly hypovolemia.

Of particular note was that 102 (18.9%) patients had a red cell depletion with a normal or high hematocrit (38% or higher for women, 41% or higher for men). These patients' anemia could not be detected with hematocrit testing alone.

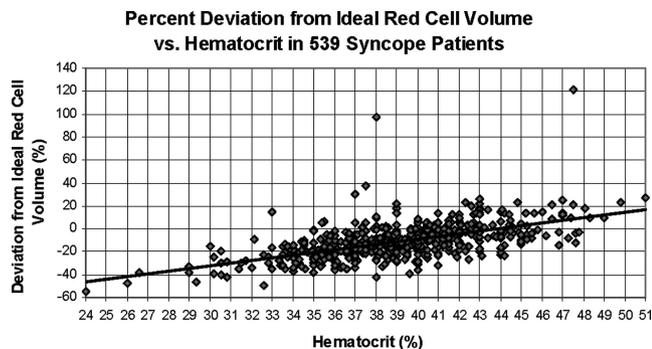
A subset of 46 patients were already being treated with Fludrocortisone or Midodrine when they were referred to the syncope clinic; 21 were taking Fludrocortisone, 15 were taking Midodrine, and 10 were taking both Fludrocortisone and Midodrine (see Table 1.)

Of the 15 patients taking Midodrine (without Fludrocortisone), 5 (33%) were volume-depleted. Vasoconstriction in conjunction with hypovolemia may decrease perfusion rather than improve it. Among the 21 patients taking Fludrocortisone (without Midodrine), 10 (48%) had a depleted blood volume. In these cases, Fludrocortisone was an appropriate type of treatment, but the persistence of volume depletion indicates that the dosage was insufficient to achieve a normal blood volume. Of the 10 patients

**Distribution of Deviation from Ideal Red Cell Volume in 539 Syncope Patients**



**Figure 2.** Histogram of percent deviation from ideal red cell volume in 539 syncope patients: 36% of patients had a normal whole blood volume; 64% had blood volume derangements, predominantly anemia.



**Figure 3.** Scatterplot of percent deviation from ideal red cell volume versus peripheral hematocrit. Although hematocrit tends to decrease with decreasing red cell volume, individual hematocrit measurements do not provide an accurate assessment of red cell volume.

taking both Fludrocortisone and Midodrine, 9 (90%) had a depleted blood volume. It is possible that the rise in blood pressure as a result of the combined effect of the 2 medications overrides the volume retention effects of Fludrocortisone alone.

There were 411 patients in whom blood pressure and cardiac index data (mean ± SD) were available. In the supine position, patients tended to be normotensive (125/71 ± 25/11), with a normal heart rate (67 ± 11) and a normal cardiac index (2.9 ± 0.7). Systolic blood pressure dropped slightly at maximum head-up sitting posture (122 ± 22, *P* < 0.001), but there was no significant change in diastolic blood pressure. Heart rate increased (74 ± 13, *P* < 0.001), and cardiac index decreased to below normal (2.4 ± 0.6, *P* < 0.001).

There was no correlation between any compartment of blood volume and blood pressure, heart rate, or cardiac index (supine, inclined, or the change from supine to inclined). The 3 patients with the greatest drops in systolic blood pressure were hypovolemic, but the distinction was not statistically significant.

### Discussion

Blood volume in syncope patients was heterogeneous. Patients exhibited a wide range of volume abnormalities. A large number of patients were hypovolemic and/or had a depleted red cell mass, but these and other volume abnormalities could not be

**Table 1.** Blood Volume Status Among 46 Patients Taking Fludrocortisone and/or Midodrine

	Midodrine	Fludrocortisone	Both
Depleted BV	5	10	9
Normal BV	9	11	1
Expanded BV	1	0	0

BV, Blood volume.

correctly identified with hematocrit testing. In addition, blood pressure, heart rate, and cardiac index before and during tilt table testing did not correlate with volume abnormalities.

On average, patients responded to tilt testing with an increase in heart rate and a decrease in systolic blood pressure and cardiac index. The increase in heart rate was insufficient to maintain normal blood flow at maximum tilt. Blood volume status was not a predictor of hemodynamic changes during tilt testing.

While tilt table testing provides essential information about the progression of syncope, a patient's response to tilt testing cannot be used to accurately estimate blood volume or vice versa.

The drop in blood pressure and perfusion that occurs in syncope may be related to an inappropriate vasomotor response and/or to hypovolemia. Accurately identifying volume status can help a physician choose pharmacological treatments that are more likely to address the underlying causes of an individual patient's syncope. In patients who are hypovolemic or anemic, treatment of the volume abnormality may help resolve the syncope. Because volume abnormalities may involve the red cell volume, plasma volume or both, optimal treatment depends on correctly identifying and treating the specific volume abnormality. In patients who are normovolemic or hypervolemic, inappropriate vasomotor response is more likely to underlie the syncope, and patients are more likely to respond to medications aimed at improving vasomotor response.

Almost all of the patients who were evaluated were receiving empiric therapy before referral, and the patients were still symptomatic, as evidenced by their referral to the Cleveland Clinic. Among patients who were already taking Midodrine and/or Fludrocortisone, several were receiving inappropriate or inadequate treatment, indicating previous inaccurate clinical assessment of volume status. Of the patients taking Midodrine, 33% were hypovolemic, putting them at risk for decreased perfusion in response to vasoconstriction. Of the patients taking Fludrocortisone, 48% were volume-depleted, indicating a possible insufficient dosage or lack of response to Fludrocortisone. Of particular note were the 10 patients taking both medications; 90% of these patients were hypovolemic. These patients were not able to maintain a normal blood volume with their current dosage of Fludrocortisone, and they were at risk for decreased perfusion from the combination of Midodrine and hypovolemia.

Blood volume measurement in these instances could be used to identify clearly inappropriate treatment or to help a physician determine how best to alter treatment, such as choosing between increasing a dosage of Fludrocortisone or adding a different medication such as Midodrine.

The results from this study strongly suggest that blood volume measurement should be added to tilt table testing for comprehensive evaluation of syncope patients. Further studies should be performed to determine if using blood volume measurement to guide treatment decisions results in improved outcomes.

### References

1. **Soteriades ES, Evans JC, Larson MG, et al.** Incidence and prognosis of syncope. *N Engl J Med* 2002;347:878–85.
2. **Sarasin FP, Louis-Simonet M, Carballo D, et al.** How often does a standard evaluation of syncope identify an underlying etiology? *Am J Med* 2001;11:177–84.
3. **Bloomfield DM.** Strategy for the management of vasovagal syncope. *Drugs Aging* 2002;19:179–202.
4. **McLeod KA.** Dysautonomia and neurocardiogenic syncope. *Curr Opin Cardiol* 2001;16:92–6.
5. **Bloomfield DM, Sheldon R, Grubb BP, et al.** Putting it together: a new treatment algorithm for vasovagal syncope and related disorders. *Am J Cardiol* 1999;84:33Q–9Q.
6. **Garcia-Civera R, Ruiz-Granell R, Morell-Cabedo S, et al.** selective use of diagnostic tests in patients with syncope of unknown cause. *J Am Coll Cardiol* 2003;41:787–90.
7. **McGee S, Abernethy WB, Simel DL.** Is this patient hypovolemic? *JAMA* 1999;281:11.
8. **Androne AS, Hryniewicz K, Hudaihed A, et al.** Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. *Am J Cardiol* 2004;93:1254–9.
9. **Androne AS, Katz SD, Lund L, et al.** Hemodilution is common in patients with advanced heart failure. *Circulation* 2003;107:226–9.
10. **Shevde K, Pagala M, Tyagaraj C, et al.** Preoperative blood volume deficit influences blood transfusion requirements in females and males undergoing coronary bypass graft surgery. *J Clin Anesth* 2002;14:000.
11. Recommended methods for measurement of red-cell and plasma volume: International Committee for Standardization in Haematology. *J Nucl Med* 1980;21:793–800.
12. **Dworkin H, Premo M, Dees S.** Comparison of Red Cell and Whole Blood Volume as Performed Using Both Chromium-51 Tagged Red Cells and Iodine-125 Tagged Albumin and Using I-131 Tagged Albumin and Extrapolated Red Cell Volume. Presented at the June 2005 Annual Meeting of the Society of Nuclear Medicine, Toronto, Canada, June 2005. (Poster Presentation).
13. **Alrawi SJ, Miranda LS, Cunningham JN Jr, et al.** Correlation of blood volume values and pulmonary artery catheter measurements. *Saudi Med J* 2002;23:1367–72.
14. **Feldschuh J, Enson Y.** Prediction of the normal blood volume. *Circulation* 1977;56:605–11.
15. **Fouad FM, Houser T, MacIntyre WJ, et al.** Automated computer program for radionuclide cardiac output determination. *J Nucl Med* 1979;20:1301–7.
16. **Fouad FM, MacIntyre WJ, Tarazi RC.** Noninvasive measurement of cardiopulmonary blood volume: evaluation of the centroid method. *J Nucl Med* 1981;22:205–11.