Blood Volume Determination, A Nuclear Medicine Test in Evolution

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Abstract: The method for determining blood volume has evolved substantially since first attempts were made in the beginning of the nineteenth century with the exsanguination of animals. The now accepted methods are based on indicator dilution methodologies. First attempts utilized inert dyes such as Evans Blue and Cardiogreen. These were found to be impractical due, primarily, to their rapid clearance from the blood. For many years, the most accepted method for blood volume determination was the dual isotope technique. This procedure utilizes chromium 51 to label autologous red cells and radiiodine 125 or 131 or ⁹⁹mTc to label human serum albumin (HSA). Plasma and red cell volumes are measured separately and the results “combined”. The procedure requires on-site labeling of autologous red cells and HSA, and meticulous preparation of standards and doses. The complexity of this method leads to performance times of 6 to 8 hours. An FDA-approved single isotope method is now employed in over 60 major institutions. HSA is labeled with ¹³¹I in an off-site pharmaceutical manufacturing facility, and test doses and standards are provided to laboratories in kit form. The red cell volume is derived by a calculation utilizing the measured plasma volume and the value for the average whole-body hematocrit. All calculations are carried out by a dedicated microprocessor, and a final report is generated and printed. The results are compared with predicted normal values for males and female patients based on percentage deviation from normal weight. Preliminary results are available in 30 minutes and complete calculations in 90 minutes.

Key Words: blood volume, heart failure, renal failure, syncope, occult anemia, hypertension, shock

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Methods for blood volume measurement have evolved since the latter part of the nineteenth century when experiments involved the exsanguination of animals. Indicator dilution methods were first proposed over 60 years ago. Initial dye dilution techniques with Evans Blue and Indocyanine green have been largely replaced by radioactive indicator dilution methods. Human serum albumin (HSA) labeled iodine-131 or iodine-125 have been used to measure plasma volume and Cr-51-labeled autologous red cells to measure red cell volume.¹–⁵

The dual isotope method requires that both red cell and plasma volumes be separately determined and the results “combined” to yield values for total blood volume. This method requires preparation on site of both standards and doses for injection and may take as long as 6 to 8 hours total to yield a result. Many hospital laboratories no longer offer this test because of technologist time considerations.

A single isotope method of blood volume determination is now available. It utilizes an FDA-approved instrument (BVA-100 Analyzer; DAXOR Corporation, New York, NY, USA), with matched standards and injectates in volumetric flow chambers prepared in a licensed radiopharmaceutical manufacturing facility. An intrinsic microprocessor calculates and prints final reports that incorporate red cell and plasma volumes, transfusion rates (reflecting the state of capillary permeability), the mean and normalized whole-body hematocrit, and an interpretation of the test results. In critical situations, preliminary results can be obtained in under 30 minutes.

A major challenge in the development of an accurate means of evaluating blood volume test results was the establishment of accurate norms for individual subjects. Initially, a fixed ratio of blood volume to body weight (milliliters per kilogram) was proposed. It was soon discovered that differences in blood volume per kilogram body weight differ in men and women and range widely in lean and obese individuals.

In 1977, Feldschuh and Eason² performed isotope studies on 128 healthy individuals and combined their data with the result of studies undertaken by Keys et al³ involving 32 individuals who participated in a weight loss study. The results demonstrated that blood volumes in healthy individuals span a range from approximately 40 mL/kg in extremely obese individuals to 105 mL/kg in extremely underweight individuals.

Further, it was shown that accurate normal blood volumes could be predicted for males and females of all weights and heights by utilizing a formula based on a determination of their deviation from ideal weight for healthy individuals found in a “Table of Ideal Weights” of more than 100,000 men and women compiled by the Metropolitan Life Insurance Company.⁴ A major advantage of this method for calculating normal blood volume values is that, unlike methods with normal values based on height, weight, and body surface area (normal range of ±25%), the variance from ideal weight method was improved with a normal range of only ±5%. Values outside this range could be accurately classified in 8% increments as mild, moderate, severe, and extreme excess or deficiency. Subsequent research has substantiated the clinical utility of this method of classification.⁵

A major advance in blood volume measurement was the demonstration that the single isotope method was as accurate as the dual isotope method. Fairbanks¹¹ and Dworkin¹² in separate studies, with patients blood volumes measured by both dual-tracer and single-tracer techniques, confirmed that the results of both methods were practically identical. In Dworkin’s study, the difference in red cell volumes by the 2 methods was 0.9%,¹³–²¹

METHODOLOGY

The indicator dilution technique for blood volume determination is based on the principle that when a radiotracer of known volume and activity is injected intravenously, its dilution can be compared to a matching standard and a volume calculated.

For the dual isotope method, chromium-51-labeled red cell dilution is used to measure red cell volume and radiiodine-labeled human serum albumin is used to measure plasma volume. Injectate and standards are prepared on site by the technical staff. The dual isotope technique requires that the volumes of interest, red cell and plasma volumes, must be measured individually and the results “combined.”

The single-isotope method involves the intravenous injection of 5-25 μCi of iodine-131-labeled human serum albumin and collection of 6 blood samples. In adults, this dose results in minimal
thyroid exposure and thyroid blocking with stable iodine is optional. A written directive is not required. The first sample, collected prior to tracer administration, is utilized to determine background activity. The next 5 samples are collected at approximately 6-minute intervals beginning 12 minutes following injection. Exact times of collection are carefully recorded. The 10 samples are split into equal aliquots. Five duplicate plasma volumes are derived from this data and utilizing the mean or average whole-body hematocrit, 10 separate blood volumes are calculated. The blood volume pairs are averaged and the 5 averaged volumes are electronically plotted on a semi-log graph. A regression line fitted to the data points is extrapolated to time zero (the time of injection) to yield the true blood volume. Potential errors due to incomplete mixing of the tracer in the blood pool and transudation of the tracer through the capillary walls are eliminated.

The albumin transudation rate can be determined. In normal subjects, it is approximately 0.25% of the injected dose per minute. High rates of transudation occur in sepsis and shock.

To calculate the blood volume, an average or mean whole-body hematocrit value is required. The hematocrit in the capillary beds of tissues and organs is considerably lower than that of the larger blood vessels; accordingly, the peripheral hematocrit must be multiplied by a correction factor f to determine the correct mean whole-body hematocrit value. Many investigators have reported determinations of f. The average of the reported values is 0.91. Utilization of larger or smaller f values in the physiologic range of those reported has been shown to have only a small impact on the final blood volume results. A very small correction is made for the trapping of plasma between the red cells when the hematocrit is determined by microcentrifugation.

Clinical Application of Blood Volume Measurement

Congestive Heart Failure

In the United States, there are approximately 5 million individuals in congestive heart failure (CHF). Annually, approximately 550,000 new CHF cases are diagnosed. Eleven million office visits and 875,000 hospitalizations are CHF-related, and annually, 287,000 deaths are attributed to this condition.

At diagnosis, CHF is most frequently characterized by hypervolemia due, primarily, to an expansion of plasma volume. However, CHF is also seen secondary to severe anemia, excessive diuresis, or myocardial damage. In this setting, the blood volume may be normal or subnormal. The American College of Cardiology/American Heart Association guidelines recommend assessing volume status in all heart failure patients with the goal of restoring patients to normovolemia (euvolemic).

A recent report, based on blood volume measurement, revealed “hidden” polycythemia in a group of CHF patients. If diureased, polycythemic patients are at risk of thrombotic events.

In 2004, Androne et al. reported on the Relation of Unrecognized Hypervolemia in Chronic Heart Failure to Clinical Status, Hemodynamics, and Patient Outcomes. In a cohort of 43 patients whose blood volume was measured, the clinical assessment of blood volume was correct in only 51%. In a 2-year follow-up of these patients, a dramatic Kaplan-Meier plot of the outcomes revealed that 39% of the hypervolemic patients were dead or had undergone emergent heart transplant within 1 year. At 2 years, a total of 57% of the hypervolemics had expired or been transplanted. In contrast, all the normovolemic or slightly hypovolemic patients survived.

In 2004, Katz reported on the unrecognized volume overload in congestive heart failure.

In 2004, Androne et al. reported on the Treatment of Anemia in Patients with Chronic Heart Failure and Concomitant Kidney disease. It was shown that the severity of anemia could not be determined utilizing only the hematocrit and that a subnormal hematocrit could reflect a combination of hemodilution and anemia. A significant improvement in the New York Heart Association (NYHA) classification occurred when both anemia and hypervolemia were corrected.

In 2007, Katz reported on “Blood Volume measurement in the Diagnosis and Treatment of Congestive Heart Failure”. Significant inaccuracies utilizing surrogate methods of blood volume assessment in diagnosing CHF were described. In this study of 43 CHF patients, there were no physical signs typical of congestive heart failure in 18 who were found to have an abnormal elevation of their pulmonary capillary wedge pressure (PCWP) greater than or equal to 22 mm Hg. Clinicians have depended on serum B-type natriuretic peptide (BNP) levels to diagnose and manage CHF.

In a presentation at the Valley Hospital, Strobeck reported on the poor correlation of 131-I-labeled albumin measurements of blood volume and BNP levels in hypervolemic heart failure patients.

In 2010, Bogaes reported on “Cost Considerations in the Treatment of Heart Failure”. They demonstrated that the current 30-day readmission rate for patients hospitalized with CHF is approximately 25%. Under new CMS regulations, hospitals will not be reimbursed for the care of patients readmitted in CHF within 30 days of discharge following treatment for this condition. A blood volume determination prior to discharge would confirm that a patient is normovolemic or euvolemic and ready to be released from hospital.

The BVA-100 Analyzer also provides a benchmark “normalized” hematocrit. The “normalized” hematocrit is a theoretical hematocrit value. It is obtained when the directly measured red cell mass and a predicted normal plasma volume are combined to equal the predicted normal whole-blood volume.

During follow-up, to prevent the need for readmission, a peripheral hematocrit close to the normalized hematocrit assures that the patient is euvolemic and is not relapsing into failure.

Renal Failure

Approximately 500,000 individuals in the United States are classified as being in “End Stage Renal Disease” (ESRD). Half are on renal dialysis. Dialysis patients have very significant fluctuations in both red cell and total blood volume, and sometimes become dangerously hypotensive during treatment.

Anemia, due to a significant erythropoietin deficiency, is common in ESRD. Patients require erythropoietin administration and/or blood transfusions to maintain an adequate red cell volume. An accurate determination of the red cell volume can guide selection of the appropriate dose of erythropoietin (EpoGen or Procrit) for each patient.

A direct blood volume measurement can establish the normal intravascular volume of dialysis patients. Knowing the “normal” intravascular volume prior to dialysis can lead to a better estimate of the optimal amount of fluid to be extracted during the procedure. It will help reduce excessive fluid withdrawal and decrease the frequency of hypotensive episodes.

In 1998, Bleyer et al. reported on sudden and cardiac death rates in hemodialysis patients. They noted that the rate was highest on Mondays and Tuesdays, when patients had experienced the longest time intervals between dialyzes that are commonly carried out 3 times weekly.

Hypotension in this setting is associated, particularly in diabetics, with an increase in the rate of stroke and myocardial infarction. First heart attacks in dialysis patients carry a mortality rate of 41%.

Syncope

The underlying cause of syncope is a drop in blood pressure leading to loss of consciousness. The 2 major causes are hypovolemia and autonomic dysfunction. Tilt table testing to demonstrate a drop in blood pressure when patients are moved from the supine to erect posture merely confirms that a rapid change in position from horizontal to vertical results in an abnormal drop in blood pressure. Tilt
table results document the condition but do not provide an etiology.
In 2007, Fouda-Tarzi et al. reported on blood volume measurements in syncope. They found that syncopal patients have a wide variation in
blood volumes. The blood volumes of 539 symptomatic patients
were determined. Many of the patients were already on treatment.
Some were receiving mineralocorticoids to increase blood volume.
Others were on midodrine, an alpha agonist to increase vascular
wall tone. Some were on both medications. They found that many
patients were receiving either inappropriate or inadequate treatment.
Of the patients taking mineralocorticoids, 48% were still hypovolemic.
Ninety percent of the patients taking a combination of midodrine and
mineralocorticoids had subnormal volumes. The investigators indicated
that a blood volume determination should be included in the diagnostic
workup of all syncope patients.

Postural Orthostatic Tachycardia Syndrome

Postural orthostatic tachycardia syndrome (POTS) is a condition
often associated with chronic fatigue syndrome. Changes in position,
going from the supine to erect posture, can trigger tachycardia. Even
raising the arms above the head can cause paroxysms in afflicted
individuals. This condition, like syncope, is most frequently related to
either or both a decrease in blood volume or to autonomic dysfunction.
Raj et al. reported on the “Blood Volume Perturbations in the
Postural Tachycardia Syndrome” in 2007. Mineralocorticoids to
increase salt and water retention and the alpha agonist midodrine to
increase vascular tone may alleviate POTS symptoms. A direct
measurement of blood volume can facilitate an accurate assessment
of the patient’s status and guide treatment.

Hyponatremia

Hyponatremia is a common complication in CHF and neuro-
logic trauma patients. In these conditions, there may be a significant
increase in the production of vasopressin (antidiuretic hormone)
leading to retention of water and dilutional hyponatremia. A rapid
decrease in serum sodium levels can lead to acute brain swelling,
fatal in some cases. Treatment includes water restriction and the ad-
ministration of the vasopressin blocker tolvaptan (Samsa). However,
the EVEREST study on clinical effectiveness of this drug revealed a
short-term benefit but no long-term survival benefit.
Renal tubular salt wasting causes hyponatremia by a different
mechanism. Salt wasters are both hyponatremic and hypovolemic.
Treatment with water restriction and anti-ADH are inappropriate.
These individuals may be identified if a direct blood volume mea-
surement is carried out.

Preoperative and Postoperative Screening for
Occult Anemia

During surgery, a stable blood pressure is essential to assure
adequate blood flow to vital organs. Blood volume and vascular tone
are 2 of the key determinants in the maintenance of blood pressure.
The current standard of care for the preoperative and intra-
operative estimation of blood volume relies on hematocrit and
hemoglobin determinations. However, the hematocrit and hemoglo-
bin may be deceptive and values may be “normal” even when a
patient is significantly hypovolemic.
The term “Hidden Anemia” has been used to describe the vol-
ume status of patients with normal hematocrit and hemoglobin values
who have a significant deficiency of the red cell volume. In major
surgery, where a significant blood loss is anticipated, a preoperative
direct measurement of blood volume can unmask this condition and
permit appropriate patient preparation.
Because patients receive large volumes of crystalloids prior to
some surgical procedures, low postoperative hematocrit values are
common, reflecting both hemodilution and/or a significant decrease
in red cell volume. Patients may enter or leave surgery with a critical
deficiency in red cell volume. Such patients are subject to sudden
postoperative collapse, delayed recovery, and the need for emergent
blood transfusion.

A correct assessment of blood volume in patients undergoing
major surgery is critical. Van et al. pointed out that blood volume
measurement can prevent unnecessary blood transfusions. They
emphasized the need to differentiate hemodilution with a normal red
cell volume from true anemia. In hemodilated patients, the peripheral
hematocrit can actually overestimate anemia and lead to an unnec-
essary transfusion. Women’s red cell volume is normally 18% lower
than that of males of equal height and weight. Blood loss during
surgical procedures is similar for both genders. Women are more
likely than men to require blood transfusions during major surgery.
Shevde et al. reported that female patients undergoing coronary
artery bypass graft surgery needed 4 times as many blood trans-
fusions as male patients.

Hypertension

Only 34% of the 50 million hypertensive individuals in the
United States are adequately treated. Initial treatment is usually trial
and error administration of one or more of the 50 FDA-approved
antihypertensives. Frequently, there is no effort to establish the un-
derlying physiologic abnormality.
Renal artery stenosis is a well-known but uncommon cause of
hypertension. The two most common mechanisms leading to hyper-
tension are volume overload and/or vasoconstriction. Patients whose
hypertension is related to hypervolemia are most appropriately
treated with diuretics. Vasoconstricted patients may have a normal or
even decreased blood volume. They respond best to drugs that relax
the smooth muscle in the blood vessel walls. These include beta
blockers, ACE inhibitors, and calcium channel blockers.
Treatment of normovolemic patients with diuretics can lead to
hypovolemia and can induce dizziness or syncope. In addition, in this
clinical setting, the administration of diuretics may cause decreased
renal perfusion, putting patients at risk for the development of renal
failure and the need for dialysis. A blood volume measurement can
distinguish volume overload versus vasoconstriction and guide for
evidence-based treatment.

Shock

More than 100,000 patients die in septic shock every year. The
reported mortality rate for septic shock is 20%–60%. A study by Yu
et al. described the use of blood volume measurement in addition to
pulmonary artery catheter (PAC) values to guide resuscitation of
critically ill surgical patients with septic shock, severe respiratory
failure, and/or cardiovascular collapse. A group of 100 critically ill
patients underwent both a blood volume and PAC determinations.
The combined test results were used in the management of the first
subgroup and only PAC in the matched controls. The mortality rate in
the group where both results were available was 8% compared to
24% using PAC alone (P = 0.03).
Van reported that blood volume analysis can distinguish true
anemia from hemodilution in critically ill patients. He pointed out
that the peripheral hematocrit overdiagnosed anemia in 46.7% of
ychypovolemic patients.

In 2000, Alnami presented a paper entitled “Would Hy-
poolemic be an Advantage or Disadvantage in the Management of
Critically Ill Patients With Septic Shock?” He reported on the out-
comes of 40 septic patients, all of whom underwent direct measure-
ment of blood volume. Mean age of the patients was 75.5 years. There
were 28 males and 12 females. Twenty-five were found to be hypo-
olemic, 7 were hypervolemic, and 8 were normovolemic. There
were 4 deaths, all in the hypovolemic group.
Burns involving large areas of the skin are often fatal. With large burns, there are marked disturbances in fluid and electrolyte balance. A significant loss of albumin through damaged skin may lead to hypovolemia and hypotension.

When there is an increased capillary transudation rate, serum albumin levels may be misleading and the total body albumin deficit may be significantly underestimated. Hematocrit and hemoglobin levels may be “normal” even when, due to hypofibrinogenemia, the total blood volume is significantly decreased.

Blood volume measurement can be extremely useful in the burn unit to gauge the effectiveness of the replacement of blood, albumin, and fluids. Direct measurement of the transudation rate can lead to more rational treatment planning as regards albumin replacement.

SUMMARY

The methods for measurement of blood volume have undergone a significant evolution since the first reports of the dye dilution technique over 60 years ago. Combined dual isotope dilution methods were favored for many years. The availability of a rapid single-tracer method as described here simplified blood volume measurement, significantly decreasing the time of performance and making it more applicable in emergency situations. The interpretation of results is based on a well-documented method for prediction of norms for individuals of both genders of the entire spectrum of heights and weights.

REFERENCES