**Rapid Nuclear Medicine Blood Volume Analysis for Emergency Assessment**

David Sadowsky*, Abel Suarez-Mazon*, Charles Lugo, Tariq Rashid, Jennifer Wu, Perry Gerard, Matty Mozzor

Department of Radiology, Westchester Medical Center, Valhalla, NY, USA

*David Sadowsky and Abel Suarez-Mazon are co-first authors/contributed equally

**Abstract**

Assessment of fluid status can play a critical role in the diagnosis and management of emergent conditions such as trauma, shock, decompensated heart failure, syncope, and hypertension. Unfortunately, common methods are all qualitative and/or indirect, and often inaccurate. With the recent introduction of a modernized method of nuclear medicine blood volume analysis (NM-BVA), offering results in 90 min or less as well as improved precision and ease of performance, this decade-old technique is for the first time a viable tool in the emergent setting. In this review, we discuss the history of NM-BVA, the modern method, and our institution’s experience implementing this method.

**Keywords:** Blood volume, fluid status, indicator dilution, nuclear medicine, rapid

**History of Nuclear Medicine Blood Volume Analysis**

Various methods of BVA have been used since its introduction, most based on the principle of indicator dilution. This technique involves the injection of a known amount of an indicator into an unknown volume. Subsequently, after allowing for mixing, a sample is taken and the new concentration of the indicator is measured. From these concentrations, the unknown volume can be calculated based on the simple dilution relationship:

$$V = \frac{C_1 V_1}{C_2}$$

where $V$ is the unknown volume, $C_1$ is the initial concentration, $V_1$ is the initial volume, and $C_2$ is the final concentration.

For over half a century, nuclear medicine blood volume analysis (NM-BVA) has been the gold standard for directly, accurately, and quantitatively measuring intravascular blood volume through several well-studied techniques. Despite these advantages, its use in clinical practice has been historically limited by a long exam time of 4–6 h. Additional limiting factors have been a lack of universally accepted reference values and a time-consuming process that is prone to errors. Now, however, with the recent introduction of a modernized method offering results in 90 min or less, as well as improved precision and ease of performance, NM-BVA is for the first time a viable tool in the emergent setting. In this review, we discuss the history of NM-BVA, the modern method, and our institution’s experience implementing this method.
### Table 1: Comparison of Blood Volume Assessment Methods

| Description of technique | Nuclear Medicine Blood Volume Analysis | Pulmonary artery/Swan-Ganz catheter | BUN/creatinine | Hematocrit | Urine output monitoring | Physical examination | Urine sodium concentration |
|--------------------------|----------------------------------------|-------------------------------------|----------------|------------|-------------------------|---------------------|---------------------------|
|             | Direct assessment of blood volume utilizing a variety of techniques described herein | A catheter is inserted into the pulmonary arterial system, which can then measure different pressures (central venous, pulmonary artery capillary wedge) and cardiac output that can be correlated with volume | Increased urea reabsorption in cases of hypovolemia, combined with unaffected creatinine production or reabsorption, leads to an elevation in this ratio in patients without complicated renal disease | Since red blood cells are limited to the vascular space, hematocrit is affected by changes in fluid volume | Urine output (measured noninvasively or through an indwelling catheter), compared with an accepted range of normal intake and patient weight | Assessment of indicators such as skin turgor, dryness of mucous membranes, postural dizziness or pulse increments, arterial blood pressure, and jugular venous pressure | Decreased in hypovolemic patients unless they have certain pathologies |
| Advantages | Direct | Modern technique is automated, fast, and only requires minimum radiation dose | Quantitative Real-time results Commonly used in shock and during procedures | Quantitative Low-cost Typically included in routine laboratory testing | Quantitative Low-cost Typically included in routine laboratory testing | Quantitative Low-cost Can be noninvasive | Noninvasive, bedside maneuver No cost |
| Disadvantages | Radiation to patient requires specialized equipment and staff | Indirect Invasive procedure with potential for life-threatening complications | Indirect Affected by several confounding variables unrelated to blood volume, such as renal function and urea production rate | Indirect Affected by several confounding variables unrelated to blood volume, such as renal function, urea excretion Collection and measurement often performed inaccurately Risk of infection (when invasive) | Indirect Many metrics are subjective | Indirect | Indirect |
| Accuracy metrics | Gold standard for blood volume assessment | Central venous and pulmonary capillary wedge pressures do not correlate with direct measurements of blood volume | In the setting of pediatric dehydration, BUN/creatinine $\geq 40$ has sensitivity of 0.23 and specificity of 0.89 | In the setting of pediatric dehydration, capillary refill time has LR 4.1, skin turgor 2.5, and respiratory pattern 2.0\(^{[5]}\) In adults, capillary refill time and skin turgor have no proven diagnostic value\(^{[4]}\) Severe postural dizziness and postural pulse increments have sensitivity of 22% for moderate blood loss and 97% for severe blood loss, with specificity 98%\(^{[6]}\) | In the setting of pediatric dehydration, capillary refill time has LR 4.1, skin turgor 2.5, and respiratory pattern 2.0\(^{[5]}\) In adults, capillary refill time and skin turgor have no proven diagnostic value\(^{[4]}\) Severe postural dizziness and postural pulse increments have sensitivity of 22% for moderate blood loss and 97% for severe blood loss, with specificity 98%\(^{[6]}\) | In the setting of pediatric dehydration, capillary refill time has LR 4.1, skin turgor 2.5, and respiratory pattern 2.0\(^{[5]}\) In adults, capillary refill time and skin turgor have no proven diagnostic value\(^{[4]}\) Severe postural dizziness and postural pulse increments have sensitivity of 22% for moderate blood loss and 97% for severe blood loss, with specificity 98%\(^{[6]}\) |

All methods except for Nuclear Medicine Blood Volume Analysis are indirect and have additional disadvantages. BUN: blood urea nitrogen

\[ C_1 V_1 = C_2 V_2, \] rearranged to \( V_2 = \frac{(C_1 V_1)}{C_2}, \) where \( C_1 \) is the concentration of tracer injected, \( V_1 \) is the volume of tracer injected, \( C_2 \) is the concentration of tracer in the sample obtained after mixing, and \( V_2 \) is the unknown volume.

---

Sadowsky, et al.: Rapid nuclear medicine blood volume analysis for emergency assessment
In the traditional method, both red blood cells and plasma are labeled (red blood cells with $^{51}$Cr and plasma with $^{125}$I). Combined, these components account for over 99% of blood volume. Theoretically, only measurement of a single component is needed, as the other can then be estimated based on the patient’s hematocrit. In practice, the use of dual tracers has been preferred as a more accurate method. This method remains the gold standard for NM-BVA, but is not practical in the emergent setting due to the length of testing (4–6 h) and lack of automation resulting in decreased precision when not performed by properly trained technologists.

While the dose to the patient in the traditional method is low, other NM techniques have been attempted in the past in an effort to further minimize radiation exposure. In one example of this, neutron activation analysis was used in conjunction with the indicator dilution to assess red blood cells labeled with $^{51}$Cr and plasma labeled with $^{125}$I-human serum albumin (HSA). After mixing, a sample irradiated with a thermal neutron flux to produce $^{51}$Cr and $^{59}$Fe is analyzed with a Ge (Li) gamma-ray detector system. Exposure is eliminated with fluorescence excitation analysis, in which red blood cells were labeled with nonradioactive cesium. After mixing, the analysis performed with an Americium source and Si (Li) detector proved to be close in precision to the traditional method.

In addition to eliminating radiation exposure, alternative BVA methods have also been developed in an attempt to avoid blood sampling. In pulse dye densitometry, a pulse spectrophotometer measured arterial indocyanine green concentration through the nose or finger. When compared to a modified standard method in which plasma was labeled with $^{131}$I-HAS and red blood cells were not labeled, pulse spectrophotometry measurements agreed to within approximately 10% in patients with normal oxygenation but errors significantly increased in patients with decreased oxygen saturation, doubling 20% with SaO2 decreasing from 95% to 90%. This method is also susceptible to error from probe dislodgement caused by body motion.

A more recent alternative method noninvolving radiation or repeat sampling is ultrasound dilution, which tracks the change in ultrasound velocity of blood after injection of isotonic saline to extrapolate a measure known as active circulation blood volume index. This method has been shown to agree strongly with NM-BVA results, but suffers from several significant sources of error including: decreased precision, marked background noise in low flow states, patient motion and precision, and air bubbles affecting measurements.

**Modern Nuclear Medicine Blood Volume Analysis**

In 2007, a modernized version of NM-BVA was introduced offering comparable accuracy to the traditional method, but in an automated system that can provide results in 90 min or less. Only plasma is labeled in this method, with $^{131}$I-HSA. Starting 12 min after injection, five measurements are taken over a period of 24 min. Taking advantage of the decrease in apparent blood volume over time due to transudation of the label, the Daxor BV-100 system calculates a regression line to interpolate the blood volume at time 0. The system output values of total blood volume, plasma volume, and red blood cell volume in comparison to estimated normal values for the patient’s height, weight, and gender, facilitating interpretation of results. A sample output is provided in Figure 1.

Unlike the traditional method, the modern method is applicable in the emergent setting due to decreased exam time and increased automation, without sacrificing accuracy. Additional benefits include reduced radiation dose and avoiding reinjection of the patient’s own blood. The Daxor system, seen in Figure 2, is compact and can easily fit on a standard desk or laboratory bench. A comparison of the traditional and modern NM-BVA methods is made in Table 2.

**Discussion**

**Our experience with rapid nuclear medicine blood volume analysis**

At our institution, a 652-bed tertiary care facility, including 76 adults and 67 pediatric intensive care unit (ICU) beds, NM physicians, and medical physicists, actively seek to inform both inpatient and outpatient ordering providers about all available NM diagnostic examinations, including NM-BVA. In recent years, we average approximately 1 NM-BVA examination per month, most of which are for cases of suspected polycythemia. The second most common indication

**Figure 1:** Sample output from the Daxor blood volume-100
is orthostasis. Continuing outreach to ICUs and cardiology is ongoing in an effort to increase knowledge of this service for heart failure patients.

Discussions with the emergency room (ER) have not yet yielded many orders, which we suspect is in large part due to our department only offering NM examinations during daytime hours on weekdays. Departments offering 24/7 NM services may find greater success increasing adoption in the emergency setting. In at least one institution, we are aware of, rapid NM-BVA has become part of the standard workup and treatment protocols for heart failure patients. In the setting of acute heart failure admissions, rapid NM-BVA has resulted in reduced readmission and mortality rates.[13]

**I-131 dissociation concerns**

Although not recommended by the FDA, we utilize thyroid protection due to concerns about possible dissociation of I-131 from albumin. For a typical examination, the expected dose to the thyroid is minimal; however, theoretically could reach higher levels in cases of dissociation and/or thyroid pathology resulting in increased uptake. This dose is avoidable and can be reduced with potassium iodide (KI) to almost 0.

For outpatient exams, our thyroid protection premedication protocol is KI administered 2 days before, the day of, and the day after the examination, with doses of 130 mg per day for adults, 75 mg for pediatric patients aged 1–18 years, and 35 mg for ages 0–1 years. In the inpatient and emergent setting, we do not delay the examination and instead instruct the ordering service to administer a dose of KI, as soon as possible, as stable KI will protect the thyroid if given within 4 h of the examination.

Our concerns are supported by the case of an asymptomatic volunteer who underwent rapid BVA testing as we were preparing to implement this technology. As part of our safety testing, we scanned the volunteer’s thyroid to confirm the manufacturer’s claims that there is no dissociation of I-131 and instead saw diffuse uptake [Figure 3]. The volunteer’s blood volume results were normal. He was referred to an endocrinologist, who, after a full work-up, diagnosed him with Hashimoto’s thyroiditis.

**Table 2: Comparison of traditional and modern blood volume analysis methods**

| Description of technique | Traditional | Modern |
|--------------------------|-------------|--------|
| Red blood cells are tagged with $^{51}$Cr to calculate red blood cell volume, albumin is tagged with $^{125}$I to calculate plasma volume (includes reinfusion of patient’s own blood) | Albumin is tagged with $^{131}$I to calculate plasma volume, this result and the patient’s hematocrit are then used to calculate total blood volume (no reinfusion) |
| 4-6 h | 90 min or less |
| 2 isotopes, standards, and injections | Single injection |
| $^{51}$Cr, ~1 mBq (30 uCi) | ~1 mBq (25 uCi) $^{131}$I-HSA |
| $^{125}$I-HSA, 0.3 mBq (8 mCi) | 0.2 mSv effective dose |
| 100 mSv effective dose (almost entirely from $^{125}$I-HSA) | |
| Manual- difficult to perform with precision and prone to error | Automated- highly precise and reproducible (sampling technique and standard preparation must be precisely done) |

The modern method is faster and simpler to perform, without sacrificing accuracy. HSA: Human serum albumin

**Figure 2:** The Daxor blood volume-100 system is compact and can easily fit on a standard desk or laboratory bench

**Figure 3:** Thyroid scan showing diffuse I-131 uptake after rapid blood volume analysis testing (external midline marker also present). The patient was asymptomatic and blood volume results were normal. Based on this result, the patient was referred to an endocrinologist who diagnosed him with Hashimoto’s thyroiditis
**Conclusion**

Modern NM-BVA can be performed in a short amount of time with high accuracy and precision and should be considered for use in the emergent setting where the accurate interpretation of blood volume affects both diagnosis and treatment. Compared to traditional BVA, the modern method offers increased speed and ease of use while maintaining accuracy and reducing radiation exposure. As with other innovative imaging modalities and techniques, radiologists can work with referring providers to increase awareness in an effort to reach patients who will likely benefit from the rapid assessment of fluid status that modern NM-BVA can provide.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Alrawi SJ, Miranda LS, Cunningham JN Jr, Acinapura AJ, Raju R. Correlation of blood volume values and pulmonary artery catheter measurements. Saudi Med J 2002;23:1367-72.
2. Ohashi S, Endoh H. Does central venous pressure or pulmonary capillary wedge pressure reflect the status of circulating blood volume in patients after extended transthoracic esophagectomy? J Anesth 2005;19:21-5.
3. Steiner MJ, DeWalt DA, Byerly JS. Is this child dehydrated? JAMA 2004;291:2746-54.
4. McGee S, Abernethy WB 3rd, Simel DL. The rational clinical examination. Is this patient hypovolemic? JAMA 1999;281:1022-9.
5. United States Department of Defense (2018) Direct Blood Volume Analyzer for Improvement of Combat Casualty Care. Solicitation DoD 2019.2 SBIR, Topic Number A18-22. Available from: https://www.sbir.gov/sbirsearch/detail/1482227. [Last accessed on 2019 Dec 26].
6. Berman I, Carr R, Malone E. Determination of total blood volume from measurements of total red blood cell mass and plasma volume, using simultaneously injected isotopes. Nature 1964;202:1013-5.
7. Manzone TA, Dam HQ, Soltis D, Sagar VV. Blood volume analysis: A new technique and new clinical interest reinvigorate a classic study. J Nucl Med Technol 2007;35:55-63.
8. Wright RR, Tono M, Pollycove M. Blood volume. Semin Nucl Med 1975;5:63-78.
9. Yamabayashi H, Izumo M, Motoki R, Yamamoto T, Nishida H, Shin S, et al. Blood volume measurement of newborn using stable isotope 50Cr. Radioisotopes 1985;34:144-50.
10. Price DC, Swann SJ, Hung ST, Kaufman L, Huberty JP, Shohet SB. The measurement of circulating red cell volume using nonradioactive cesium and fluorescent excitation analysis. J Lab Clin Med 1976;87:535-43.
11. Haruna M, Kumon K, Yahagi N, Watanabe Y, Ishida Y, Kobayashi N, et al. Blood volume measurement at the bedside using ICG pulse spectrophotometry. Anesthesiology 1998;89:1322-8.
12. Furuta S, Inouye DS, Hayashi MS, Takanishi DM Jr, Yu M. Blood volume measured by ultrasound and radioisotope dilution in critically ill subjects. J Surg Res 2017;207:77-84.
13. Strobeck JE, Feldschuh J, Miller WL. Heart failure outcomes with volume-guided management. JACC Heart Fail 2018;6:940-8.