Brain-type natriuretic peptide and right ventricular end-diastolic volume index measurements are imprecise estimates of circulating blood volume in critically ill subjects

Edwin A. Takahashi, BA, Sharon E. Moran, MD, Michael S. Hayashi, MD, David S. Inouye, MD, Danny M. Takanishi, Jr., MD, and Mihae Yu, MD, Honolulu, Hawaii

BACKGROUND: Surrogate indicators have often been used to estimate intravascular volume to guide fluid management. Brain-type natriuretic peptide (BNP) has been used as a noninvasive adjunct in the diagnosis of fluid overload and as a marker of response to therapy, especially in individuals with congestive heart failure. Similarly, right ventricular end-diastolic volume index (RVEDVI) measurements represent another parameter used to guide fluid resuscitation. The aim of this study was to evaluate whether BNP and RVEDVI are clinically valuable parameters that can distinguish among hypovolemia, euvoeemia, and hypervolemia, as measured by blood volume (BV) analysis in critically ill surgical subjects.

METHODS: This observational study was part of a prospective, randomized controlled trial. Subjects with pulmonary artery catheters for the treatment of traumatic injuries, severe sepsis/septic shock, cardiovascular collapse, adult respiratory distress syndrome, and postsurgical care were studied. Circulating BV was measured by a radioisotope dilution technique using the BVA-100 Analyzer (Daxor Corporation, New York, NY) within the first 24 hours of acute resuscitation. BV results were reported as percent deviation from the patient’s ideal BV based on height and percent deviation from optimum weight. Hypovolemia was defined as less than 0%, euvoeemia was defined as 0% to +16%, and hypervolemia was defined as greater than +16% deviation from ideal BV. RVEDVI was measured by continuous cardiac output pulmonary artery catheters (Edwards Lifesciences, Irvine, CA). BNP and RVEDVI measurements obtained with BV analysis were evaluated with Fisher’s exact test and regression analysis.

RESULTS: In 81 subjects, there was no difference in BV status between those with BNP of 500 pg/mL or greater and BNP of less than 500 pg/mL (p = 0.82) or in those with RVEDVI of 140 mL/m² or greater and RVEDVI of less than 140 mL/m² (p = 0.43). No linear relationship existed between BV and these parameters.

CONCLUSION: In critically ill surgical patients, BNP and RVEDVI were not associated with intravascular volume status, although they may be useful as indices that reflect increased cardiac preload. (J Trauma Acute Care Surg, 2013;75: 813–818. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Diagnostic study, level III.

KEY WORDS: BNP; RVEDVI; blood volume.

The maintenance of euvoeemia in intensive care unit (ICU) patients is fundamental to the optimization of cardiac output, tissue perfusion, and ultimately, the delivery of oxygen to tissues. Directly measuring circulating blood volume (BV) may provide valuable insight into intravascular volume status, while at the same time furnishing a practical means to judiciously guide fluid management. Assessing and monitoring the dynamic changes that occur in intravascular volume in this patient cohort are challenging because of the paucity of existing methodology that takes into account the extravascular fluid shifts that attend active fluid resuscitation.1–6 In this context, the combined double-radioisotope dilution technique using radiolabeled albumin and chromium 51–tagged red blood cells has traditionally been the reference method for BV measurement. The clinical applicability of this modality had been extremely limited in the ICU setting owing to both arduous methodology and an inordinate delay in obtaining timely results.7 Technologic innovations have made BV measurements in real time more feasible and useful with the development of the semiautomated, Food and Drug Administration–approved BVA-100 Blood Volume Analyzer (Daxor Corporation, Inc., New York, NY). Several studies have demonstrated that the BVA-100 Analyzer significantly reduces the duration and complexity of BV measurements with preliminary results available within 40 minutes.2,6–8 This enhancement provides point-of-care testing that is now practical and generalizable to the ICU sector.

Conventional surrogate markers often used to collectively estimate the intravascular volume status of a patient include laboratory values (hematocrit [Hct], electrolytes, blood urea nitrogen, and creatinine) and bedside clinical parameters (heart rate [HR], blood pressure, urine output, and the presence or absence of peripheral edema) that may or may not be integrated with hemodynamic and volumetric data obtained from pulmonary artery catheters (PACs), and pulse-contour continuous cardiac output monitoring.2,9–11 Because of their availability and ease of use, these systems have been, with the
relatively recent exception of PAC, widely used in the ICU to guide fluid management.12–15 Vincent et al.14,15 provided a thoughtful summary on possible causes for the lack of benefit of PAC and stressed the importance of correct measurement, correct interpretation, and correct application. They concluded that PAC are still a valuable tool for hemodynamic monitoring when used in selected patients and by physicians adequately trained to correctly interpret and apply the data provided. Our group has used PAC-guided goals of oxygen delivery to an end point of adequate tissue oxygenation parameters and have demonstrated improved survival in a prospective randomized trial.1 There are, however, conflicting perspectives in the scientific literature. Rajaram et al.13 in a 2013 Cochrane Review concluded that the use of PAC did not alter the outcomes of adult patients in the ICU but that these investigators nonetheless recommended that newer, less invasive, hemodynamic monitoring tools should be validated against PAC before clinical use in critically ill patients.

Within this framework, existing literature that has built upon previous attempts to clinically estimate a patient’s intravascular volume status reports on several, more recently used surrogate markers that may provide improved estimation of a patient’s BV. Two of these markers include serum brain-type natriuretic peptide (BNP) and right ventricular end-diastolic volume index (RVEDVI).8,16

BNP is a neurohormone produced by the ventricles of the heart in response to myocardial stretch (as may occur with intravascular volume expansion and increased wall tension), proinflammatory cytokines, norepinephrine, glucocorticoids, elevated angiotensin II concentration, myocardial ischemia, and inotropic agents.17–20 Its physiologic role is to stimulate vasodilation, natriuresis, diuresis, and inhibition of renin release in response to myocardial distension.20–23 Serum BNP may have value in the clinical setting, as an indirect estimate of intravascular volume status.17–23 Friese et al.17 showed that serum BNP levels after injury increase with volume resuscitation and that this measure may serve as a biomarker for preload status during resuscitation in trauma patients. Chiricop and Jelinek24 found that a BNP level of 500 pg/mL retains its diagnostic ability with a positive predictive value of 90% in ruling in heart failure. In contrast, Omland21 in a review of BNP in the evaluation of acute heart failure points out that the correlation between BNP and pulmonary artery occlusion pressure (PAOP) or left ventricular end-diastolic pressures are only moderately strong, not permitting reliable information to be obtained regarding filling pressures.

The RVEDVI is calculated from the right ventricular ejection fraction and cardiac index (CI) by dividing the stroke volume index (CI divided by HR) by the right ventricular ejection fraction. It is an accurate indicator of preload volume in the right ventricle. Notably, this cardiac parameter has already been described elsewhere.10,25,26 Diebel et al.27 have shown that trauma patients with RVEDVI of less than 90 mL/m2 had a positive hemodynamic response to fluid resuscitation with an increase in CI, whereas those with values greater than 140 mL/m2 did not. Other investigators have reported similar findings.25

Despite the widespread use of BNP and RVEDVI as indirect measures of cardiac preload, there is limited research on the value of these markers in predicting true circulating BV in the ICU population. The specific aim of this study was to determine whether BNP and RVEDVI are accurate surrogate predictors of intravascular volume, as directly measured by the BVA-100 Analyzer.

**PATIENTS AND METHODS**

The Research and Institutional Review Committee (Institutional Review Board equivalent) of The Queen’s Medical Center, a university-affiliated, tertiary care, teaching hospital, reviewed and approved this study before implementation. Written informed consent to participate in the study was obtained from all subjects or from a legal surrogate. This observational study was a planned side arm of a prospective, randomized controlled trial using PAC values compared with PAC + BV values to guide fluid and blood component transfusion management.2 Study subjects were recruited from consecutive patients admitted to the ICU, who were randomized to either a control group (fluid management guided by PAC parameters) or a BV group (fluid management guided by BV results in addition to PAC parameters).1 Subjects were excluded if they had surrogates who were unable or unwilling to provide consent, if they were younger than 18 years, were pregnant, or had brain injury documented on computed tomography with a Glasgow Coma Scale (GCS) score of 12 or less, quadriplegia, do-not-resuscitate status, height less than 122 cm or greater than 218 cm, and weight less than 21.3 kg or greater than 379 kg in men and greater than 351 kg in women. Subjects were excluded at these extremes of height and weight given that the accuracy of the BVA-100 Analyzer has not been validated in these ranges, based on the manufacturer’s guidelines. Subjects with traumatic brain injury were excluded because this cohort of ICU admissions is comanaged with our neurointensivists, and a different resuscitation protocol is applied to this group of subjects.

Patients with the following diagnoses were enrolled: (1) traumatic injuries and (2) postsurgical conditions requiring ICU care for fluid resuscitation and hemodynamic monitoring—low blood pressure (systolic blood pressure < 90 mm Hg despite adequate fluid resuscitation to a PAOP of 15–18 mm Hg), persistent tachycardia (defined as HR > 100 beats/min), low urine output (<0.5 mL/kg/h despite volume infusion), worsening renal function (serum creatinine increase of >20% of baseline), low CI (<2.5 L/min/m2 with PAOPs of 15–18 mm Hg), poor oxygenation (PaO2/FIO2 ratio <200 or Qs/Qt ratio >20%), persistent requirement for vasopressors or nonnormalization of lactate levels, (3) septic shock, (4) severe sepsis, (5) cardiovascular collapse, and (6) ARDS. The criteria for these diagnoses have already been described elsewhere.1,2,28

Baseline and demographic data were collected, which included HR, arterial blood pressure, urinary output, PAC data (including RVEDVI), chest radiograph interpretation, arterial blood gas analysis, BNP, lactic acid, blood urea nitrogen, creatinine, and hemoglobin/Hct concentrations as previously...
Extreme deviation

Severe deviation

Moderate deviation

Mild deviation

Normal

mize any impact that rapidly shifting intravascular volumes, 12 hours to 24 hours of resuscitation was performed to mini-
tation. More specifically, exclusion of subjects during the first
12 hours to 24 hours after acute resuscitation was completed, to
avoid confounding of data during BV analysis that may result
with the BV analysis. The BNP data were obtained within
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svO2 of 70% or greater. 1 After these end points of resuscitation
lactate to normal values, oxygen delivery adequate to achieve
100 beats/min, urinary output of greater than 0.5 mL/kg/h,
or within 40 mm Hg from known baseline, HR of less than
resuscitation for all subjects have been described previously
PAC that had been inserted in the operating room. The goals of
insertion or the time of ICU arrival if the subject came with a

TABLE 1. Categorization of Deviations From Ideal BV Components as Determined by the BVA-100 Analyzer

<table>
<thead>
<tr>
<th>Component</th>
<th>Whole BV</th>
<th>RBCV</th>
<th>PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>±8%</td>
<td>±10%</td>
<td>±8%</td>
</tr>
<tr>
<td>Mild deviation</td>
<td>±9–16%</td>
<td>±11–20%</td>
<td>±9–16%</td>
</tr>
<tr>
<td>Moderate deviation</td>
<td>±17–24%</td>
<td>±21–30%</td>
<td>±17–24%</td>
</tr>
<tr>
<td>Severe deviation</td>
<td>±25–32%</td>
<td>±31–40%</td>
<td>±25–32%</td>
</tr>
<tr>
<td>Extreme deviation</td>
<td>&gt;32%</td>
<td>&gt;41%</td>
<td>&gt;32%</td>
</tr>
</tbody>
</table>

TABLE 2. Demographics of the Study Population

<table>
<thead>
<tr>
<th>Category</th>
<th>n = 81, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>62 ± 16</td>
</tr>
<tr>
<td>No. patients ≥75 y</td>
<td>21/81 (26)</td>
</tr>
<tr>
<td>Female/male</td>
<td>33/48</td>
</tr>
<tr>
<td>Acute Physiology and Chronic Health Evaluation II, mean ± SD</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>14/81 (17)</td>
</tr>
<tr>
<td>Trauma</td>
<td>20/81 (25)</td>
</tr>
<tr>
<td>ARDS</td>
<td>14/81 (17)</td>
</tr>
<tr>
<td>Septic shock/severe sepsis</td>
<td>34/81 (42)</td>
</tr>
<tr>
<td>Cardiovascular collapse</td>
<td>5/81 (6)</td>
</tr>
<tr>
<td>Other illness</td>
<td>8/81 (10)</td>
</tr>
</tbody>
</table>

mands of the body surface area or a subject’s weight, particularly at the extremes of weight. Quite the opposite, fixed weight ratio and body surface area norms revealed systematic errors or wide scatter. Subject age has not been demonstrated to be a factor in BV analysis using the methodology in this study. 8,9,28,30

BV results were then categorized and presented as percent
deviation from the individual’s ideal BV (Table 1). Based on
reference ranges, hypovolemia was defined as less than 0%,
euvolemia was defined as 0% to +16%, and hypervolemia was
defined as greater than +16% deviation from ideal BV. A BNP
of greater than 500 pg/mL was selected as the threshold value
indicative of hypervolemia for statistical analysis, given the
reported strong correlation of BNP concentrations at this level
with myocardial stretch and heart failure in the peer-reviewed
literature. 24 RVEDVI value of 140 mL/m2 or less was selected
as the threshold value indicative of euvolemia, in the frame-
work of evidence-based data, which demonstrates no clinical
benefit of further fluid resuscitation beyond this value. 51

Excel 2010 Microsoft (Redmond, WA) was used for
statistical analysis. Data analysis using the Fisher’s exact test
and univariate linear regression analysis was performed to in-
vestigate the relationship of BNP concentrations and RVEDVI
with hypovolemia, hypervolemia, and euvolemia as determined
by BV analysis. Statistical significance was defined as p ≤ 0.05.

RESULTS

Eighty-one subjects were included in this study. Of the
subjects, 33 were female and 48 subjects were male. Forty-two
percent of the subjects had septic shock/severe sepsis. The
mortality rate of this cohort was 17%. Subject demographics
are presented in Table 2. Intravascular BV results, BNP, and
RVEDVI measurements are summarized in Table 3.

Of the 81 subjects, 16 were hypovolemic, 32 were
euvolemic, and 34 were hypervolemic based on BV analysis.
Among the 39 subjects with a BNP level greater than 500 pg/mL,
6 were hypovolemic, 18 were euvoemlic, and 15 were hypervolemic

on sex, height, baseline weight, and deviation from optimum
longevity-related weight as determined by the Metropolitan
Life Tables and as previously validated by BV studies. 6,8,9,30

This mathematical model is more accurate than using either
the body surface area or a subject’s weight, particularly at the
extremes of weight. Quite the opposite, fixed weight ratio and
body surface area norms revealed systematic errors or wide
scatter. Subject age has not been demonstrated to be a factor in
BV analysis using the methodology in this study. 8,9,28,30

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TABLE 3. Stratification of Subjects by BV Status, BNP Concentration, and RVEDVI

<table>
<thead>
<tr>
<th>Volume Status</th>
<th>BNP ≤ 500 pg/mL</th>
<th>BNP &gt; 500 pg/mL</th>
<th>RVEDVI ≤ 140 mL/m²</th>
<th>RVEDVI &gt; 140 mL/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>16</td>
<td>10</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Euvolemic</td>
<td>32</td>
<td>14</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Hypervolemic</td>
<td>33</td>
<td>18</td>
<td>15</td>
<td>27</td>
</tr>
</tbody>
</table>

(Table 3). There was no statistically significant difference in hypervolemic subjects between those with BNP of greater than 500 pg/mL and in those with BNP of 500 pg/mL or less ($p = 0.82$). Similarly, no statistically significant difference was observed between subjects with BNP levels of 500 pg/mL or less and greater than 500 pg/mL in the euvoletic and hypovolemic cohorts ($p = 0.26$ and $p = 0.41$, respectively).

Of the 81 subjects in this study, 19 had an RVEDVI greater than 140 mL/m². Of these 19 subjects, 5 were hypovolemic, 8 were euvolemic, and 6 were hypervolemic (Table 3). No statistically significant relationships were found among hypovolemic, euvolemic, and hypervolemic subjects and RVEDVI of 140 mL/m² or less or greater than 140 mL/m² ($p = 0.51$, $p = 0.79$, and $p = 0.43$, respectively).

A strong correlation was not demonstrated between BNP and BV, with a coefficient of determination of 0.085 ($p = 0.45$) (Fig. 1). Similarly, no linear relationship was found between RVEDVI and BV ($R = 0.290$, $p < 0.009$) (Fig. 2).

DISCUSSION

In this study, BNP and RVEDVI measurements did not correlate with BV status as determined by the BVA-100 Analyzer in critically ill surgical patients in whom PAC insertion was used to guide treatment. These results suggest that BNP and RVEDVI, in common use clinically, are not precise indices of intravascular volume status although these parameters may reflect cardiac preload. The importance of this study is that clinicians must be cognizant of the limitations of currently available modalities that are being used in clinical decision making to optimize volume loading.

A number of investigators have demonstrated that BNP has diagnostic value in subjects with acute heart failure. In patients with dyspnea, for example, a serum BNP concentration greater than 100 pg/mL has been shown to be the strongest independent predictor of heart failure as the underlying etiology. Furthermore, heart failure is very unlikely in patients with BNP levels less than 100 pg/mL and highly likely with levels greater than 500 pg/mL (90% positive predictive value).32

This corpus of knowledge, regarding the relationship between BNP and heart failure, led a number of investigators to plausibly evaluate whether BNP can be used as a surrogate marker of ventricular function. Despite the fact that ventricular stretch is a major stimulus of BNP release, a close correlation between BNP and filling pressures (PAOP and left ventricular end-diastolic pressures) has not been demonstrated in the published literature.22 A confounding feature is that there are a number of known cardiac and noncardiac causes of BNP elevations.18,23 Previous studies have also reported that BNP does not correlate well with BV, which may be a result of lag time between BV changes and BNP production by cardiac myocytes.33,34 Similar confounders may have contributed to the lack of correlation found between BNP concentrations and BV values in this study. It would have been interesting to further stratify subjects according to the presence or absence of congestive heart failure, to determine if there was a relationship between BNP and BV values in this cohort of subjects, but the sample size in the current study was too small to permit meaningful derivation of conclusions.

RVEDVI is a volumetric, as opposed to a pressure, measurement that is an accurate indicator of the preload supplied to the right ventricle. As borne out in the scientific literature, this cardiac parameter more closely correlates with CI than the traditionally used parameter of the PAOP, in patients with sepsis, ARDS, traumatic injuries, and in those receiving mechanical ventilation.25 Although the ability to measure RVEDVI was available since 1989, the advent of continuous monitoring of this parameter has resulted in a resurgence of interest in evaluating the merits of this hemodynamic variable.35 It is of significance that in the past, the correlation between RVEDVI and CI was attributed in part to mathematical coupling. However, Nelson et al.36 compared RVEDVI and CI prospectively using two independent methodologies and demonstrated that mathematical coupling did not account for the correlation between RVEDVI and CI.

In our study, RVEDVI measurements poorly correlated with BV values. The reason for the lack of association between
RVEDVI and BV is unclear, but similar to BNP, there are a number of cardiac and noncardiac factors, such as pulmonary hypertension, respiratory failure, pulmonary embolism, and ARDS, which can influence this measurement.37 Similar to the consideration for subgroup analysis in the evaluation of the relationship between BNP and BV, the sample size in the current study did not allow for meaningful analysis of the effect of ARDS on RVEDVI. Nonetheless, taken collectively, these data strongly suggest that BNP and RVEDVI should not be used to guide fluid management in this group of surgical ICU patients, consistent with the findings of other investigators.12–15

There are several limitations of this study. First, our study population is not homogeneous, which may have affected our results. In the ICU setting, it is a challenge to control for all patient variables and for all confounders that can affect BNP concentrations, RVEDVI, and BV measurements. Second, our study only compared static variables. We did not examine dynamic, temporal changes in BNP and RVEDVI because BV fluctuated over time. Prevailing literature shows that BNP and RVEDVI may be useful measures of volume responsiveness, and measurement of temporal changes in BNP and RVEDVI conceivably could have shown better correlation with changes in BV values over time. Finally, we did not assess outcomes, but in the larger prospective randomized trial, we did show differences in outcome, where patients who randomized to the BV arm were treated based not on BNP values but on BV values.1 Since the majority of our patients had severe sepsis/septic shock (42%), traumatic injuries (25%), and ARDS (17%), BNP may not be a useful guide for fluid management in this cohort of ICU patients, in contrast to cardiac patients.33,34

In summary, the impact of BNP and RVEDVI measurements on augmenting the clinical determination of circulating BV seems limited at best, when applied to critically ill surgical subjects. No relationship was observed between these two parameters and intravascular volume status in our study. Investigators have yet to identify a rapid, accurate, simple, and generalizable method for estimating intravascular volume status using surrogate markers, to ultimately direct fluid management in the ICU setting, and the evaluation of BV measurements in this regard warrants further study.

AUTHORSHIP

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DISCLOSURE
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