Blood volume and brain natriuretic peptide in congestive heart failure: A pilot study

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Background   Brain natriuretic peptide (BNP) levels rise in response to stretch of ventricular myocytes or increases in wall tension, as in congestive heart failure (CHF). Brain natriuretic peptide can be released in bursts, but nonetheless, BNP levels may lag behind clinical changes. We postulated that concomitant measurement of blood volume (BV), BNP, and hemodynamics during treatment of CHF may elucidate interrelationships among changes in these parameters.

Methods   We studied 10 male patients, aged 60 ± 8 years, who were admitted for pulmonary catheter–guided treatment of CHF. Hemodynamics, venous BNP, and blood and plasma volumes were measured at baseline before treatment and again on the following morning after 12 to 24 hours of acute treatment for CHF.

Results   At baseline, all 10 patients exhibited marked expansion of BV at $29\% \pm 19\%$. At baseline, increased systolic pulmonary artery pressure correlated with BV ($r = 0.615$) and diastolic pulmonary artery pressure (PAD) with BV ($r = 0.609$). After treatment, there was an inverse correlation between change (decline) in expanded BV and change (improvement) in mixed venous oxygenation ($r = -0.775$) and a positive correlation with central venous pressure (CVP) ($r = 0.710$). Poor correlation was found between BNP and any hemodynamic parameter. Little correlation was found between absolute BNP and BV before or after treatment ($r = -0.127$ and -0.126, respectively).

Conclusion   In this pilot study, changes in BV with treatment correlate better with hemodynamics than do changes in BNP, likely reflecting the lag in BNP response to treatment and its tendency to reflect long-term rather than instantaneous volume status. These preliminary data suggest that BV may be a more accurate guide in optimizing CHF treatment than BNP. (Am Heart J 2005;150:984.e1-984.e6.)

Brain natriuretic peptide (BNP) is a peptide produced predominantly by the cardiac ventricles and in lesser quantities by the atria. Brain natriuretic peptide levels rise in response to stretch of ventricular myocytes or increases in wall tension as occurs in congestive heart failure (CHF). Release of BNP is beneficial as it causes vasodilation, diuresis, and natriuresis, thereby counterbalancing the effects of sympathetic activation that occurs in heart failure.

Brain natriuretic peptide can be synthesized and released in bursts; therefore, the level can theoretically change rapidly as hemodynamic status changes.[1] However, it has been observed that, in fact, sometimes BNP levels lag behind the clinical picture, as, for example, in the setting of a patient who has undergone pacing mode change or electrical cardioversion for atrial fibrillation, suggesting that chamber dilatation does not immediately correct.[2] We postulated that concomitant measurement of blood volume (BV) with BNP samplings and hemodynamics during treatment of CHF might elucidate the interrelationships between cardiac pressures, BNP, and BV in this pilot study.

Methods

Patient selection

There were 10 consecutive patients enrolled in the study who were admitted to the Heart Failure Intensive Care Unit. Exclusions were lack of consent; allergy to iodine or albumin; pregnancy or lactation; religious constraints; or nuclear technician inavailability. The study group consisted of 10 men with a mean age of 60 ± 8 years. All clinically exhibited decompensated heart failure. The cause of the underlying heart disease was ischemic cardiomyopathy in 5 and dilated cardiomyopathy in 5. The mean ejection fraction was $19\% \pm 10\%$. All study patients gave consent in accordance with the Institutional Review Board at Cleveland Clinic.

Hemodynamics

Pulmonary artery catheters were inserted in each patient upon admission to the intensive care unit. Baseline

Table I. Medication regimens

Patient	Diuretic	Dobut	Nitro	BB	ACE/ARB	Hyd/Iso	Dig	Nes
1	+			+	+	+	+	+
2	+	+	+		+			
3	+		+	+	+	+	+	
4	+		+	+		+		
5	+			+	+			
6	+		+		+		+	
7	+		+					
8	+	+	+			+		
9	+	+			+	+	+	
10	+		+	+	+	+		

Table II. Pearson correlations between BV, BNP, pulmonary artery pressure, central venous pressure, MVO_2, and CI before and after treatment

	Before Treatment		After Treatment		Change	
	BV	BNP	BV	BNP	BV	BNP
BV		−0.127		−0.126		−0.067
PAS	0.615	0.185	0.093	−0.023	0.173	0.031
PAD	0.609	0.154	−0.244	0.256	0.430	−0.045
PAM	0.589	0.177	−0.016	0.040	0.320	−0.035
CVP	0.827	0.206	0.292	0.211	0.710	−0.158
MVO_2	−0.908	0.005	0.134	0.050	−0.775	0.060
CI	−0.812	0.340	0.272	0.498	−0.533	−0.078

The BNP value after treatment for the patient who received nesiritide was not included in these correlations (which affects both the posttreatment and the change correlations). BV, Blood volume; PAS, pulmonary artery systolic pressure; PAD, pulmonary artery diastolic pressure; MVO_2, mixed venous oxygenation; CI, cardiac index; PAM, pulmonary artery mean pressure; CVP, central venous pressure.

hemodynamics, including central venous pressure, right atrial, right ventricular, and pulmonary arterial pressures as well as cardiac output by Fick technique, were measured at baseline before treatment and then every 4 hours routinely. If doses of any parenteral infusions were changed during treatment, hemodynamics would be repeated in 2 hours. Because of difficulty in obtaining serial pulmonary capillary occlusion (wedge) pressures due to catheter migration, pulmonary artery diastolic pressures were used as a surrogate for pulmonary capillary occlusive pressures. Of those patients who did have initial concomitant pulmonary artery occlusive and pulmonary artery diastolic pressures, however, there was close relationship of these values within 3 mm Hg.

Timing of BV and BNP samplings

Venous samplings of BNP were drawn from each patient at the initiation of each BV study. Blood and plasma volume, red cell mass, and hematocrit were measured at the same time. All patients were on low-sodium (2 g/d) diets. There were two sampling times of BNP and BV: upon admission to the ICU (baseline) and the following morning at 8:00 AM, occurring 12 to 24 hours into the ongoing treatment period.

Medications

Each patient's treatment regimen for CHF was individualized per the discretion of their treating physicians. All patients

received parenteral diuretics. Three received dobutamine and 7 received sodium nitroprusside. Of note, one patient received nesiritide. Table I depicts their regimens.

Blood volume measurement

Blood volume was determined after intravenous administration of I^{131}-labeled albumin.[3-5] A baseline sample of 5 mL of venous blood was obtained as a control for background radiation; then, 10 to 25 μCi of I^{131}-labeled albumin was injected in a peripheral vein from a specialized prefilled flow chamber designed to ensure >99.8% delivery of the radioisotope dose (Volumex, Daxor Corporation, NY). Duplicate matching standards were supplied with the Volumex kit. Five milliliters of venous blood was drawn from an indwelling catheter placed in a forearm vein of the contralateral arm at 12, 18, 24, 30, and 36 minutes after isotope injection. Spun hematocrit was determined in duplicate from each sample and plasma radioactivity of each sample was assayed in duplicate in a semiautomated counter (BVA-100 Blood Volume Analyzer, Daxor Corporation). Plasma volume was determined as the zero-time volume of distribution of the radiolabeled albumin obtained by semi-logarithmic extrapolation of values measured from the 5 samples.[3] Blood volume and red blood cell volume were derived from the plasma volume measurement and the measured hematocrit corrected for trapped plasma and mean body hematocrit and then compared with
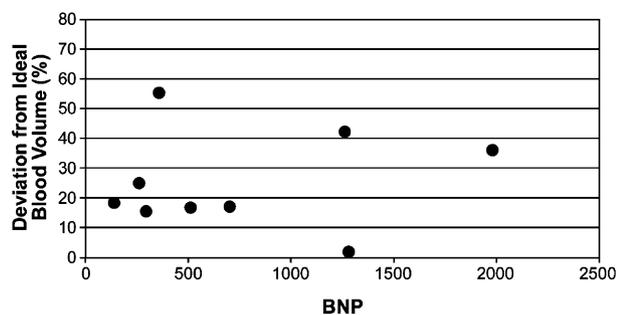
Figure 1
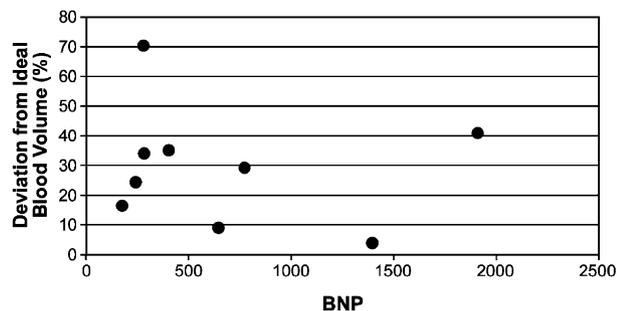
Deviation from ideal BV before treatment versus BNP before treatment.
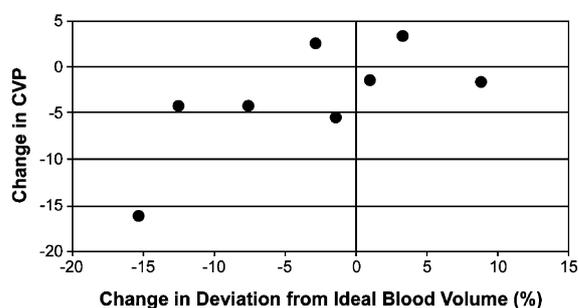
Figure 3
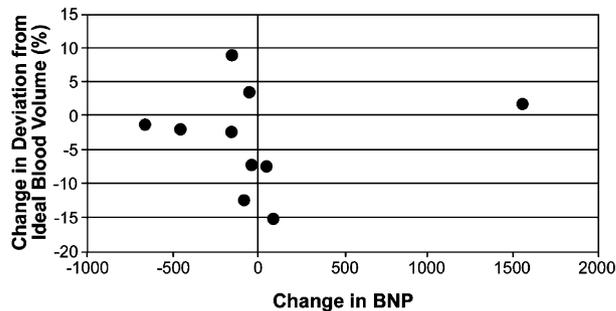
Change in deviation from ideal BV versus change in BNP.

Figure 2

Deviation from ideal BV after treatment versus BNP after treatment.

Figure 4

Change in central venous pressure versus change in deviation from ideal BV.

normal values for age, sex, height, and weight based on the ideal weight system.[4,6,7] This system eliminates errors associated with fixed blood volume/body weight ratios. The coefficient of variance for this analytic technique was <3.5%.[4,8] Normovolemia was defined as a BV measurement within ±8% of the predicted normal value.

BNP measurements

A short 18- or 20-gauge intravenous cannula connected to a 3-way stopcock was used to obtain plasma venous BNP. A total of 2 mL blood was drawn each time. The plasma BNP sample was placed in an EDTA tube and assayed at Cleveland Clinic Foundation by a Biosite analyzer. This technique has 10% variability. Normal BNP levels are <10 pg/mL.

Analysis

Blood volume and BNP were graphically depicted assessing for correlations with each other as well as with individual hemodynamic parameters before and during treatment. Although the sample size was small, no parameters were found to have significantly nonnormal distributions. The BNP and mixed venous oxygen saturation (MVO_2) posttreatment data for one patient were removed as an outlier. The patient had

been treated with nesiritide, which directly raised the BNP, and the MVO_2 value (98%) was clearly an outlier. Pearson coefficients of correlation were determined, but P values were not computed in this pilot study because of sample size.

Results

Table II depicts Pearson correlations comparing percent deviation from ideal BV and BNP with pulmonary artery systolic (PAS), diastolic (PAD), and mean (PAM) pressure, central venous pressure (CVP), MVO_2, and cardiac index (CI), stratified as before treatment, after treatment, and change. Findings in the data (Table II) include the following:
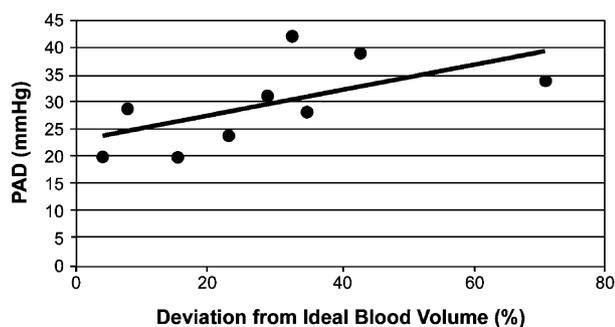
Blood volume and BNP

There is no correlation between BNP and BV before treatment ($r = -0.127$) (Figure 1). After therapy, BNP and BV are similarly uncorrelated ($r = -0.126$) (Figure 2). Figure 3 graphs the change in BV as a result of

Figure 5
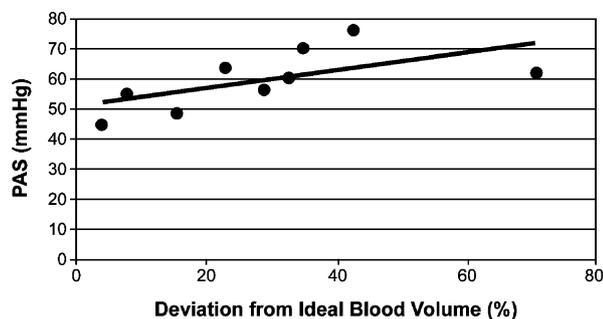
Pulmonary artery systolic pressure before treatment versus deviation from ideal BV before treatment.
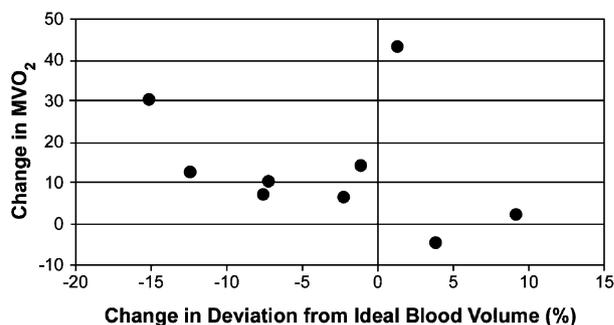
Figure 6

Pulmonary artery diastolic pressure before treatment versus deviation from ideal BV before treatment.

Figure 7

Change in MV_{O_2} versus change in deviation from ideal BV.

Figure 8

Change in CI versus change in deviation from ideal BV.

treatment against the change in BNP as a result of treatment. There is little correlation between changes in BV and changes in BNP ($r = -0.067$).
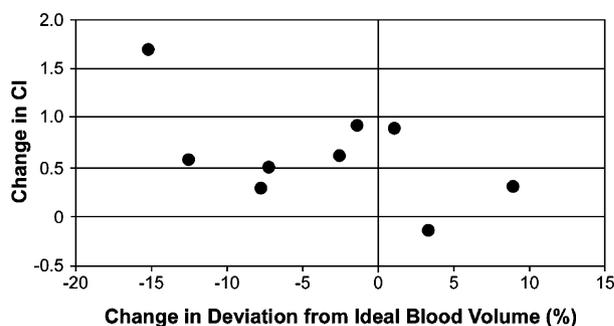
Hemodynamic variables versus BV and BNP

Baseline CVP correlated with BV ($r = 0.827$) as compared with BNP ($r = 0.206$). There was little correlation of CVP with either BNP or BV after treatment. A positive correlation was seen between change in BV and change in CVP ($r = 0.710$) (Figure 4). Before treatment, an increased PAS correlated with an increased BV ($r = 0.615$) (Figure 5). Before treatment, there was a correlation between increased BV and increased PAD at $r = 0.609$ (Figure 6). Baseline MV_{O_2} exhibited a marked inverse correlation with BV ($r = -0.908$) (Figure 7). Baseline CI correlated inversely with BV ($r = -0.812$) as compared with BNP ($r = 0.340$). Change in CI (improvement) tended to correlate with

a change (decrease) in BV ($r = -0.533$) with treatment (Figure 8).

Discussion

Brain natriuretic peptide is produced by myocytes and other cells in the body. Brain natriuretic peptide is produced by atria but predominantly by the ventricles in disease states. Stretch of the left ventricle or increase in wall tension/stress stimulates BNP release. Although blood and plasma volume may be important determinants of BNP levels via wall stress, other factors, including left ventricular size and radius, may be greater determinants of wall stress than pressure. Hence, left ventricular geometry may be as or more important than BV in affecting BNP levels.

Brain natriuretic peptide levels rise with advancing CHF and correlate with New York Heart Association functional class and with pulmonary capillary wedge pressures.[9,10] Tsutamoto et al[11] evaluated the prognostic role of BNP in 85 patients with chronic heart failure.

High levels of BNP were a significant predictor of mortality ($P < .0001$).[11] They found that BNP level provides valuable prognostic information independent of hemodynamic parameters such as pulmonary capillary wedge pressure.

It has been suggested that the turnover of BNP messenger RNA is high and that BNP is produced in bursts.[1] In the clinical setting, after a patient is cardioverted from an atrial arrhythmia, there is a lag in the decrease of BNP. In the setting of pacemakers, when the mode is changed from atrial to ventricular pacing, unsynchronized atrial contractions and rise in atrial pressure are followed by a lag in BNP rise. Therefore, it appears that BNP concentrations reflect long-term volume status rather than instantaneous volume.

Diuretics and dialysis can cause a decrease in BNP levels. Nishikimi et al[12] observed that BNP levels decline after hemodialysis and correlate directly with the degree of fluid retention. Tsutamoto et al[13] elevated the effects of spironolactone on BNP and found that the diuretic caused decreased BNP levels as well as a decrease in left ventricular volume and mass. These studies imply a relationship between BV and BNP.

Given that there appears to be a lag in BNP levels with regard to intravascular volume, our study aimed to assess the interrelationship of actual direct blood and plasma volume measurements with BNP and hemodynamics. The classic assumption in CHF is that plasma volume is expanded, can be monitored by assessing degree of edema, and treated with diuretics. Actual plasma volume in CHF can be much more complex. Feigenbaum et al[14] measured plasma volume in clinically stable patients with CHF. Relative plasma volume was 34.1 ± 12.9 in patients with CHF versus 44.5 ± 9.0 mL/kg in controls ($P \leq .05$), indicating significantly lower intravascular volumes in patients with CHF, possibly due to diuresis and/or deconditioning. In contrast, James et al[15] measured plasma volume in patients with end-stage CHF requiring left ventricular assist devices. In this setting, plasma volume was increased at $123\% \pm 20\%$ of normal. Patients with CHF can therefore have many different volume situations—they may be hypovolemic or they may have true erythrocyte volume depletion, pseudoanemia due to hemodilution, or multiple other scenarios. Accordingly, optimal knowledge of blood and red blood cell volume is important in guiding optimal therapy for CHF.

Androne et al[16] recently reported on BV in patients with CHF. In their series, they found that hypervolemia often fails to be detected in nonedematous patients by clinical examination. In following these patients over time, they also found that increased BV was associated with an increased risk of death or need for urgent transplantation.

Our data revealed a marked expansion of BV both before and after (in the first 12-24 hours) treatment of CHF is initiated. None of the patients were hypovolemic. Of note, these BV data represented only early phase changes, as the patients were sampled at baseline before treatment and again 12 to 24 hours later. This short sampling interval was chosen based on earlier data that this is the interval in which greatest changes in BNP levels occur to try to capture BNP changes with treatment.[17,18] A third sampling of all parameters would have been ideal at the completion of anticongestive therapy immediately before pulmonary artery catheter discontinuation.

Overall, changes in BV correlated better with changes in CI, MVO_2, CVP, and pulmonary artery pressure than did BNP. There was a marked correlation between change (diminution) in expanded BV and improvement in MVO_2. However, knowledge of the CI, MVO_2, and CVP did not provide quantification of the actual BV. Several patients actually exhibited a rise in CVP with initiation of treatment. This may reflect early shifts of volume from interstitial to intravascular compartments as diuresis begins. It has been previously noted that changes in volume occur during intensification of medical treatment or during transition from the edematous to compensated state.[19]

Our data did not reveal a clear relationship between BV and BNP at baseline or after medical treatment of CHF. The BV reflects the peripheral circulation, where BNP is not secreted in great quantities. O'Neill et al[17] have previously shown the lack of strong relationship between BNP and hemodynamic variables in advanced heart failure. Additional explanations for the failure of BNP to correlate well with BV or hemodynamics likely include the high variability of the BNP assay, as well as the complex determinants of BNP levels. The ADEPT study found that diastolic indices of myocardial relaxation, compliance, and filling pressures, as well as diastolic stage, right and left ventricular systolic function, mitral regurgitation degree, age, and creatinine clearance, all affect BNP.[20]

The future role of BV assessment in heart failure merits further study. These pilot data suggest that BV may more accurately depict the hemodynamic status of patients than BNP levels. A potential role of BV measurement might ultimately be in adding fluid status information to the clinical examination in patients with heart failure not ill enough to require PA catheterization, as well as possibly in guiding anticongestive therapy. Blood volume equipment would need to be readily accessible and able to be used by physicians and house staff to allow for timely data acquisition.

This pilot study is limited by a small sample number, but even at current size, yields revealing trends in terms of BV. It is possible that the negative findings with regard to BNP could be attributed to β error. Hopefully, this pilot study will lead to larger scale investigations. Secondly, it would have been desirable

to obtain serial pulmonary capillary occlusion pressure measurements as well. Catheter migration over time precluded this, but multiple other hemodynamic parameters reflecting fluid status were obtained. Lastly, it would be ideal to obtain a third set of data at completion of treatment for CHF to document BV and BNP in the optimized state.

Conclusion

In this series of patients with advanced CHF requiring PA catheter–guided management, expansion of BV was present in all patients. In general, changes in BV with treatment correlated better with actual hemodynamics than did BNP, which likely reflects the lag in BNP response and its tendency to depict long-term rather than instantaneous volume status. These preliminary data suggest that perhaps BV rather than BNP may be a more accurate a guide in the treatment of CHF, even in the absence of invasive monitoring. Larger and longer duration studies are merited to define the most accurate markers of volume status in CHF.

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