Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload

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BACKGROUND: Transfusion-associated circulatory overload (TACO) occurs when the transfusion rate or volume exceeds the capacity of a compromised cardiovascular system. Characteristic symptoms and signs associated with TACO are neither sensitive nor specific. B-natriuretic peptide (BNP) is a 32-amino-acid polypeptide secreted from the cardiac ventricles in response to ventricular volume expansion and pressure overload. This study was performed to explore the usage of BNP in the differential diagnosis of TACO.

STUDY DESIGN AND METHODS: Pre- and posttransfusion BNP levels were determined in 21 patients with suspected TACO and 19 control patients. The BNP was considered significant if the posttransfusion-to-pretransfusion ratio was at least 1.5 and the posttransfusion BNP level was at least 100 pg per mL.

RESULTS: The BNP test has a sensitivity and specificity of 81 and 89 percent, respectively, in diagnosis of TACO. It has a positive predictive value of 89 percent, a negative predictive value of 81 percent, and an accuracy of 87 percent. In logistic regression analysis, BNP was found to have significant predictive power independent of other clinical variables in models predicting which patients had TACO.

CONCLUSIONS: Our study suggests that in patients who present symptoms suggestive of TACO, BNP can be a useful adjunct marker in confirming volume overload as the cause of acute dyspnea and symptoms related to cardiovascular compromise.

Acute respiratory distress during or shortly after transfusion may be due to transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), allergic reactions, or underlying disease. The risk of TACO is generally believed low; however, the incidence can be as high as 1 percent in patients who receive transfusions.[1] The risk factors associated with TACO include an impaired cardiovascular system, renal insufficiency, and anemia with expanded plasma volumes. Elderly people and infants are especially susceptible to TACO.

Because fluid overload increases central venous pressure, resulting in pulmonary edema, TACO can present as dyspnea, tachypnea, tachycardia, acute hypertension, jugular venous distension, S3, and pulmonary rales. In severe cases, cardiomegaly and pulmonary edema can be seen on chest X-ray (CXR). These manifestations and CXR findings, however, are not specific for TACO and some may be observed in TRALI, febrile nonhemolytic transfusion reactions (FNHTRs), and allergic reactions. Most FNHTRs and allergic reactions can be readily differentiated from TACO. It could be difficult in some cases, however, to exclude other reactions and confirm TACO as the underlying cause of transfusion-associated acute respiratory distress. It is essential to exclude TRALI as causes of respi-

ABBREVIATIONS: BNP = B-natriuretic peptide; CHF = congestive heart failure; CXR = chest X-ray; FNHTR(s) = febrile nonhemolytic transfusion reaction(s); TACO = transfusion-associated circulatory overload.

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Received for publication August 6, 2004; revision received November 17, 2004, and accepted December 29, 2004.

doi: 10.1111/j.1537-2995.2005.04326.x

TRANSFUSION 2005;45:1056-1063.

ratory distress and pulmonary edema in the setting of transfusion because of its relatively high mortality.[2,3] Central venous and pulmonary wedge pressures are elevated in patients with TACO but should be normal in TRALI; however, these measurements are invasive and not consistently diagnostic and are not always readily available. Therefore, there is at present no easy-to-perform diagnostic test in the differential diagnosis of acute respiratory distress in the setting of transfusion.

Because TACO causes volume expansion in the cardiovascular system including the ventricular compartment, we sought to determine whether the measurement of the brain-type natriuretic peptide (BNP) could be used as an adjunct test in the differential diagnosis of transfusion-related acute respiratory distress or change of vital signs. BNP is a 32-amino-acid polypeptide secreted from the cardiac ventricles in response to ventricular pressure overload and volume expansion.[4-6] BNP promotes natriuresis and diuresis, acts as a vasodilator, and counteracts the renin-angiotensin aldosterone system.[7,8] Studies have shown that plasma BNP concentrations increase in patients with systolic dysfunction, diastolic dysfunction, and left ventricular hypertension.[9-13] Several large-scale clinical trials have demonstrated the usefulness of BNP as a diagnostic marker of heart failure in patients presenting with acute dyspnea in the emergency department.[14-17] A low BNP concentration (<80 pg/mL) can rapidly rule out decompensated heart failure, whereas high BNP values can confirm a diagnosis of heart failure. Furthermore, plasma BNP concentrations have been shown to yield prognostic information that supplements conventional clinical, biochemical, neurohormonal, invasive, and noninvasive evaluations in patients with chronic heart failure or in patients after an acute myocardial infarction.[18]

In this study, we tested whole-blood BNP levels by a rapid immunoassay in patients who presented with shortness of breath or other symptoms and signs suggestive of TACO during or shortly after receiving transfusion. We sought to determine whether BNP testing could serve as a useful aid in the differential diagnosis of acute respiratory distress or change of vital signs in the setting of transfusion.

MATERIALS AND METHODS

Patient selection

This study was approved by the University of Michigan Institutional Review Board and conducted at the University of Michigan Hospital between September 2003 and June 2004. Forty patients were included in the study. Among these 40 patients, 21 initially presented symptoms and signs of acute respiratory distress and/or acute hypertension and tachycardia associated with transfusions during the study period and were diagnosed with TACO. This number represented an incidence of TACO of 0.025 percent of all blood components transfused and 10 percent of all reported transfusion reactions during the study period. We randomly selected an additional 19 patients who received transfusions during the study period as controls. These 19 cases included 6 patients with FNHTRs, 3 patients with allergic reactions, and 10 patients without reactions (52.6%).

Laboratory evaluation of transfusion reactions

A blood sample collected in tubes containing ethylenediaminetetraacetate (EDTA) was requested when a transfusion reaction was reported to the blood bank (usually within 2 hr after the transfusion was stopped). Clerical checks, visual checks for hemolysis, and direct antiglobulin tests were performed by blood bank technologists as the initial work-up on both posttransfusion and pretransfusion samples. In addition, the patient's ABO type was reconfirmed. The transfusion reaction was then signed out by the blood bank resident and the blood bank attending physician based on these test results and a careful review of the patient's symptoms and signs, CXR findings, and pertinent clinical history (e.g., patient's fluid balance 8 and/or 24 hr before transfusion, microbiologic studies, cardiac status, respiratory status). TACO was diagnosed based on the patient's respiratory symptoms, central venous or pulmonary wedge pressure (when available), arterial oxygen saturation, physical findings such as jugular venous distension and pulmonary rales, and related medical information such as positive fluid balance before transfusion, pulmonary edema or cardiomegaly on CXR, and improvement of dyspnea in response to diuresis. TRALI was excluded in all cases after careful assessment including an extensive review of the patient's clinical history and presentation and laboratory studies based on the consensus definition of TRALI during or within 6 hr of transfusion not temporally related to a competing etiology of acute lung injury.[19] We also compared posttransfusion and pretransfusion white blood cell counts, if available, in every patient who was not neutropenic.[20]

Measurement of BNP

Blood samples collected in tubes containing EDTA for laboratory transfusion reaction investigations were used for quantitative determination of BNP. Whole-blood BNP levels were measured by use of a BNP test (Triage, Biosite Inc., San Diego, CA). The Triage BNP test is a fluorescent immunoassay for whole-blood and plasma BNP level determination. The technologist who performed the BNP testing was blinded to the type of reaction the patient had experienced. The BNP level from a pretransfusion sample from the patient (usually a type-and-screen sample) was determined at the same time. All blood samples were

stored at 4°C once received. In most of the cases, BNP tests were performed immediately after samples were collected. Pretransfusion samples and a few posttransfusion samples were stored up to 72 hours before BNP tests were performed. A BNP ratio from the posttransfusion sample to that from the pretransfusion sample was then calculated.

Statistical analysis

The study was designed as a nested case control study. Baseline characteristics were reported in proportions or mean ± SD values or medians as appropriate. Univariate comparisons were made with Fisher's exact test or a t test for paired data as appropriate. We constructed receiver-operating-characteristic curves to evaluate various cutoff values for BNP. We selected the posttransfusion-to-pretransfusion BNP ratio of 1.5 as the cut point for a positive test on the receiver-operating-characteristic curve that maximized both sensitivity and specificity. In addition, for a BNP level to be determined as positive, the posttransfusion level should be greater than 100 pg per mL.[21] We used computer software (KaleidaGraph, Sydney Software, Fugerson, MO) to draw the box-and-whisker plot. Finally, we used a multiple logistic regression model (SPSS, Version 12.0, SPSS Inc., Chicago, IL) combining clinical findings and BNP values to predict the final diagnosis. All independent variables in a block were entered in a single step as in a "simultaneous" method. The success of this model in predicting the criterion variable was then assessed.

RESULTS

Patient characteristics

The characteristics of the 40 patients are shown in Table 1. Patients were divided into two groups on the basis of diagnosis. Twenty-one of 40 patients were diagnosed as having TACO according to the criteria used under Materials and Methods, whereas the control group was composed of patients without transfusion reactions (n = 10), as well as patients with FNHTR and allergic reactions. Male and female subjects were equally distributed in both groups. Among those patients who were diagnosed with TACO, 33.3 percent had hypertension, 9.5 percent had history of diabetes mellitus, 14.3 percent had coronary artery disease, 33.3 percent had congestive heart failure (CHF), and 33.3 percent had impaired renal function. The percentage of patients with TACO who had CHF or hypertension was not different from the control group. More patients in the control group had diabetes and coronary artery disease (21.1 and 26.3%, respectively), whereas fewer patients in the control group had impaired renal function (21.1% in the control group vs. 33.3% in patients with TACO).

TABLE 1. Patient characteristics*

Demographics	TACO (n = 21)	Control (n = 19)
Age (years)	57 ± 20	63 ± 15
Sex (male/female)	10/11	10/9
Hypertension	7 (33.3)	7 (36.8)
Diabetes mellitus	2 (9.5)	4 (21.1)
Coronary artery disease	3 (14.3)	6 (26.3)
CHF	7 (33.3)	7 (36.8)
Impaired renal function	7 (33.3)	4 (21.1)

* Data are reported as number (%). Hypertension, diabetes mellitus, coronary artery disease, CHF, and impaired renal function are defined based on patients' medical notes.

Stability of BNP during storage and their levels in TACO and controls

The measurable range of the BNP assay was 5.0 to 5000.0 pg per mL. The coefficient of variation for interassay precision is determined to be 9.9, 12.0, and 12.2 percent for BNP levels of 71, 630, and 4100 pg per mL, respectively. The standard deviation is 7.0, 69, and 475.5 pg per mL for the aforementioned three BNP levels, respectively. Because posttransfusion BNP levels were compared to those of pretransfusion samples that could be stored for up to 3 days, the stability of BNP in the EDTA-anticoagulated tube was determined. Whole-blood BNP levels have been shown stable for up to 48 hours at 20°C with or without aprotinin.[22] We found that the whole-blood BNP levels decreased slightly after 72 hours storage at 4°C with a mean recovery of 83.3 ± 7.6 percent.

Figure 1 presents a box plot of both pre- and posttransfusion BNP values for the two groups of patients. Patients with TACO had median pretransfusion BNP levels of 216 pg per mL. The median posttransfusion levels were 389 pg per mL. The mean difference between posttransfusion and pretransfusion BNP level was 486 ($p = 0.003$ by paired t test). Patients in the control group had a median pretransfusion BNP level of 181 pg per mL and a median posttransfusion BNP level of 124 pg per mL, respectively. The mean difference between posttransfusion and pretransfusion BNP levels was 127 ($p = 0.49$ by paired t test). Because significant variation between patients was observed for BNP levels in both groups, the BNP ratio of after transfusion to before transfusion was used to compare between the study group and the control group. The median posttransfusion-to-pretransfusion BNP ratio was 2.1 in patients with TACO and 1.0 in the control group (Fig. 2). The difference between groups was significant for BNP ratio ($p < 0.05$) but not for pretransfusion BNP levels ($p = 0.54$) or posttransfusion BNP levels ($p = 0.23$) by paired t tests. Because the control group is composed of a mixture of patients with no transfusion reactions, FNHTRs, and allergic reactions, we also compared BNP

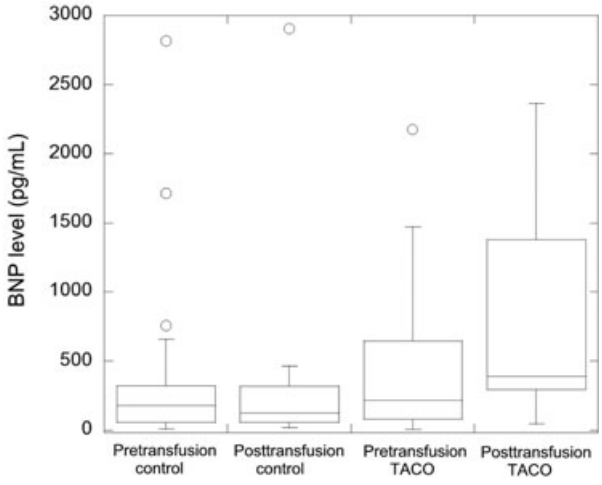


Fig. 1. Box-and-whisker plot of BNP levels in pretransfusion and posttransfusion whole-blood samples in patients with TACO and patients with other transfusion reactions (control). The horizontal line indicates the median; the box limits indicate the first and the third quartile. Open circles indicate outliers. Some of the outliers in TACO and control patients were not shown. Detailed pre- and posttransfusion BNP levels in each individual are displayed in Fig. 3.

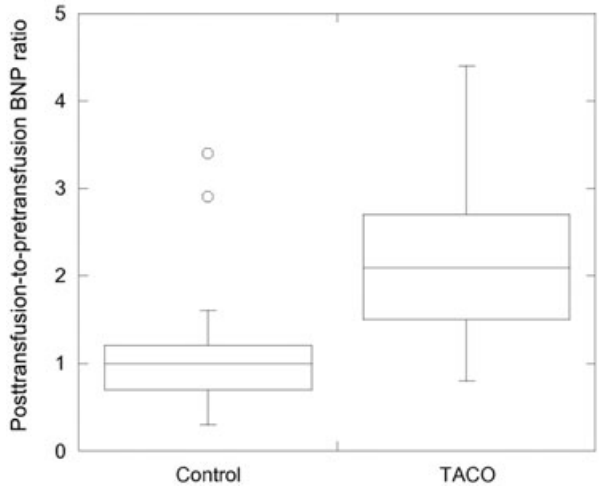


Fig. 2. Box-and-whisker plots of the ratio of the posttransfusion-to-pretransfusion BNP levels for patients with TACO and patients with other transfusion reactions (control). The horizontal line indicates the median; the box limits indicate the first and the third quartile. The lines extending from the top and bottom of each box mark the minimum and maximum values within the data set that fall within an acceptable range. Open circles indicate outliers.

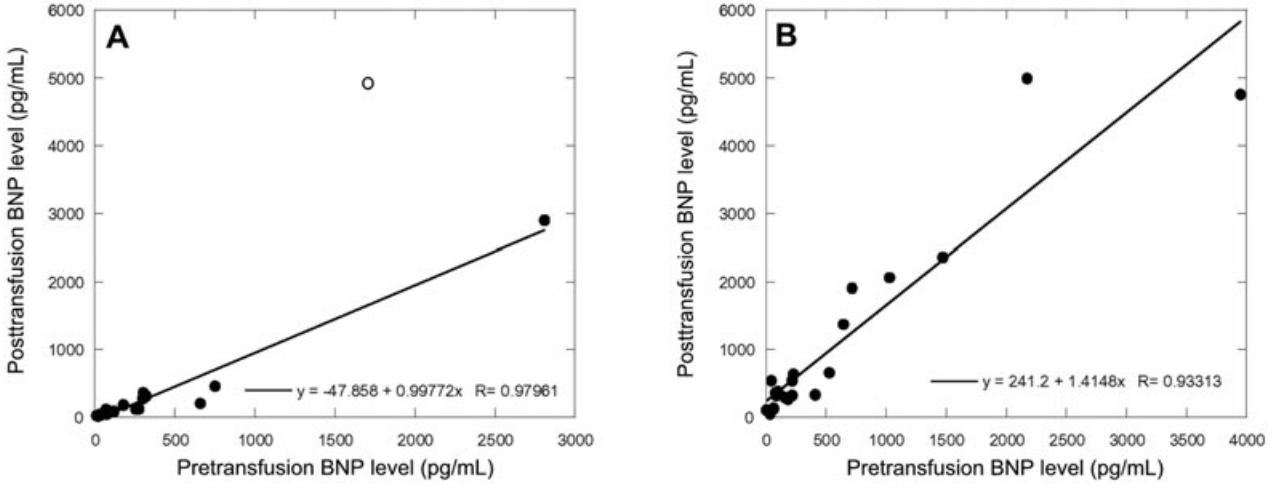


Fig. 3. Posttransfusion BNP levels versus pretransfusion BNP levels in each individual in TACO patients (B) or controls (A). The open circle in A indicates the data point that does not fit with the rest of the data. The relation between post- and pretransfusion BNP levels is displayed in the equation shown within each graph.

levels only in patients who had no transfusion reactions. The pre- and posttransfusion median levels of BNP were 228 and 157 pg per mL, respectively, and the median BNP ratio was 0.9. The mean difference between post- and pretransfusion BNP levels was 46.3 ($p = 0.37$ by paired t test). The p value for the difference of BNP ratio between those 10 patients and patients with TACO was 0.093, whereas the p values between these two groups for the difference of pretransfusion BNP levels and posttransfusion BNP levels were 0.74 and 0.20, respectively.

Figure 3 shows plots of posttransfusion BNP levels against pretransfusion BNP levels in individual patients. Although a linear relationship was observed in both groups, there were distinct differences in kinetics. In patients with TACO (Fig. 3B), the relative increase in BNP after transfusion (1.5×) was much higher then that of controls (0.9×). There was one outlier in the control group that did not fit with all the other data points (indicated by the open circle in Fig. 3A). This patient had a history of CHF and presented with febrile reactions after receiving trans-

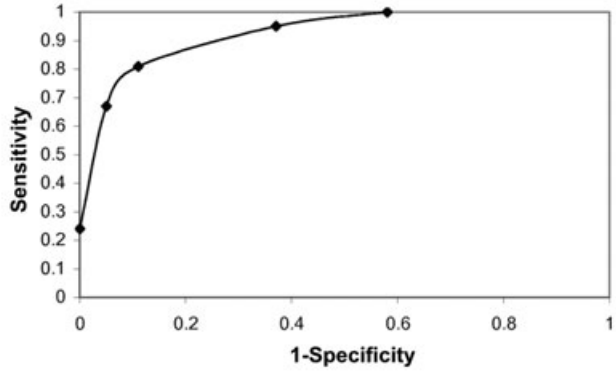
fusions. His pre- and posttransfusion BNP levels were both significantly elevated, but did not have any respiratory symptoms or significant change of blood pressure or posttransfusion tachycardia. It is unclear whether his elevated posttransfusion BNP level was caused by fluid overload or due to deterioration of his heart failure.

Figure 4 shows the receiver-operating-characteristic curve for various cutoff levels of posttransfusion-to-pretransfusion BNP ratios in differentiating TACO from other reactions. The area under the curve was 0.91 ± 0.05. A BNP ratio of 1.5 was selected as the cut point for our study. It had a sensitivity of 81 percent, a specificity of 89 percent, a positive predictive value of 89 percent, a negative predictive value of 81 percent, and an accuracy of 87 percent. Lower values such as a ratio of 0.7 were associated with greater negative predictive values (92%).

Comparison of BNP and clinical risk factors in TACO

Clinical data were reviewed for all patients included in this study (Table 2). Only acute dyspnea, posttransfusion systolic hypertension (increase of systolic blood pressure by greater than 30 mmHg), and elevated BNP levels were different between the TACO patients and the control group. Tachycardia or significant change in heart rate (increase of heart rate greater than 20/min) after transfusion, multiple blood product transfusion, history of CHF, and impaired renal function were not significantly different between the two groups by Fisher's exact test.

Multivariate logistic regression was used to compare the ability of BNP and other clinical factors to predict TACO (Table 3). The independent variables used in the model were patient's age (>65 years), male sex, history of CHF, renal function impairment, transfusion of multiple blood products, acute dyspnea during or shortly after transfusion, systolic hypertension, significant change in heart rate during or shortly after transfusion, and a positive BNP test. Based on the results shown in Figs. 3 and 4, a positive BNP test was defined as a posttransfusion-to-pretransfusion BNP ratio equal to or greater than 1.5 and posttransfusion BNP level of equal to



Posttransfusion-to-pretransfusion BNP ratio	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
0.5	100	42	65	89	70
0.7	100	42	71	92	70
1.0	95	63	73	86	80
1.5	81	89	89	81	87
1.7	67	95	93	72	80
3.0	24	100	100	54	60

Fig. 4. Receiver-operating-characteristic curve for various cutoff levels of BNP in diagnosis of TACO.

TABLE 2. Comparison of clinical features in TACO and control patients by Fisher's exact test*

Clinical features	TACO (n = 21)	Control (n = 19)	P value
Acute dyspnea	13 (61.9)	2† (10.5)	0.0002
Tachycardia after transfusion (change in heart rate ≥20 beats/min)	6 (28.6)	5 (26.3)	1.0
Significant change in systolic blood pressure after transfusion (change in systolic blood pressure ≥30 mmHg)	12 (57.1)	2 (10.5)	0.003
Transfusion of multiple units	16 (76.2)	11 (57.9)	0.31
History of CHF	7 (33.3)	7 (36.8)	1.0
Impaired renal function	7 (33.3)	3 (15.8)	0.28
BNP (posttransfusion-to-pretransfusion ratio, >1.5; posttransfusion BNP level, >100 pg/mL)	18 (85.7)	2 (10.5)	<0.0001

* Data are reported as number (%).
† Including one patient who presented acute dyspnea with an underlying diagnosis of pneumonia.

TABLE 3. Multivariate logistic regression analysis of the ability of BNP and other clinical indicators to identify TACO

Indicator	P value	OR	95% CI
Age > 65 years	0.19	0.17	0.01-2.46
Male sex	0.64	0.59	0.06-5.62
History of CHF	0.92	0.88	0.08-10.19
Impaired renal function	0.55	0.45	0.03-6.03
Acute dyspnea	0.095	14.09	0.64-311.35
Transfusion of multiple units	0.24	0.26	0.03-2.44
Significant change in systolic blood pressure after transfusion (change in systolic blood pressure ≥30 mmHg)	0.049	22.05	1.03-473.36
Tachycardia after transfusion (change in heart rate ≥20 beats/min)	0.48	0.43	0.04-4.47
BNP (posttransfusion-to-pretransfusion ratio, >1.5; posttransfusion BNP level, >100 pg/mL)	0.027	25.63	1.45-452.30

or greater than 100 pg per mL.[21] The presence of TACO was the dependent variable. Only a positive BNP test and systolic hypertension contributed significantly to the identification of TACO. The odds ratio (OR) for BNP was 25.63 ($p = 0.027$).

DISCUSSION

At present, BNP is probably best used as a diagnostic tool in the evaluation of acute dyspnea in the emergency department.[15,16] We have shown in this study the application of BNP as a diagnostic adjunct test in confirming TACO as the cause of acute dyspnea and symptoms related to cardiovascular compromise.

In our study, we determined the pretransfusion, posttransfusion, and post- and pretransfusion BNP levels in patients with a diagnosis of TACO compared to a control group of patients who received transfusions. Among control patients who received transfusions, there was little or no increase in BNP levels after transfusion (BNP ratio, 1.0), suggesting that routine transfusion has minimal effect on whole-blood BNP levels, even in the presence of febrile and allergic reactions, which are frequently encountered in patients receiving transfusions. This was also true in a subanalysis of transfused patients without transfusion reactions (BNP ratio, 0.9), which represented 52.6 percent of all controls. In contrast, the median pre- and posttransfusion BNP levels and BNP ratio were all significantly increased among TACO patients. Our results suggest that BNP may be a useful diagnostic test for differentiating TACO from other transfusion reactions in patients presenting transfusion-associated respiratory distress or change of vital signs. Because of the wide range of baseline BNP levels observed in some patients in both study and control groups, we believe that the post- and pretransfusion BNP ratio more accurately reflects the intravascular response to transfusion, particularly in the presence of confounding clinical conditions (CHF, renal failure) which were present in one-third of all subjects.

Consistent with the other two large studies in which it was concluded that BNP levels by themselves were more accurate than any other clinical factors (historical, physical, or laboratory) in identifying heart failure as the cause of dyspnea,[16,17] our study also suggests that the BNP level and its kinetic changes (posttransfusion-to-pretransfusion ratio) is the single most accurate predictor of the presence or absence of TACO. The diagnostic accuracy of BNP posttransfusion-to-pretransfusion ratio at a cutoff value of 1.5 was 87 percent, with a sensitivity of 81 percent and a specificity of 89 percent. In comparison, although acute dyspnea and systolic hypertension are both closely associated with TACO, the diagnostic accuracy was 75 and 73 percent, respectively. Furthermore, through a multivariate logistic regression analysis, we determined that a BNP ratio of 1.5 (posttransfusion/pretransfusion) was the strongest independent predictor of TACO, with an OR of 25.63.

The majority of patients with TACO can be readily identified based on symptoms of acute dyspnea, decreased arterial oxygen saturation, tachypnea, systolic hypertension, or pulmonary rales in the setting of transfusion. Other transfusion reactions, however, can present overlapping symptoms and signs that can be difficult to differentiate from TACO in some cases. An increase in both respiratory rate and systolic blood pressure, without a rise in temperature, has been shown to be suggestive of TACO in a retrospective review of 151 suspected transfusion reactions.[23] Allergic reactions and nonspecific events unrelated to transfusion, however, may also present with these signs. Although patients with TRALI more likely present hypotension rather than hypertension, hypotension in response to acute volume expansion is also observed in patients with decompensated heart failure. Both patients with TACO and TRALI may show pulmonary edema on CXR, making CXR less useful in the differential diagnosis. Compared with other invasive tests such as measuring of central venous and pulmonary wedge pressure, BNP immunoassay is a rapid, point-of-care test, whose result is readily available in 15 minutes. Therefore, in cases where TACO and other transfusion reactions, especially TRALI, are not easily differentiated, measuring BNP levels can be a useful tool to augment clinical judgment.[24] We did not encounter any cases of TRALI during the study period. Therefore, whether BNP can be used to

differentiate TACO from TRALI needs to be further evaluated.

BNP is one of the three major natriuretic peptides, all sharing a common 17-amino-acid ring structure: atrial (A-type) natriuretic peptide (ANP), BNP, and C-type natriuretic peptide (CNP).[25] The major source of plasma BNP is cardiac ventricles, and its release is directly proportional to ventricular volume expansion and pressure overload.[4,5] BNP is a 32-amino-acid biologically active fragment released from the BNP precursor, proBNP, which is a hormone of 108 amino acids. The remaining part is a 76-amino-acid N-terminal fragment called NT-proBNP.[26] Both BNP and NT-proBNP levels have been shown to accurately reflect heart failure severity.[17] In patients with left ventricular dysfunction, NT-proBNP levels rise 2 to 10 times more than BNP.[27] Measurement of NT-proBNP has recently become available in the clinical laboratory (Roche Diagnostics). It remains undetermined whether NT-proBNP is comparable with or even better than BNP to predict TACO in the setting of transfusion. With a half-life of 22 minutes in blood, BNP can accurately reflect pulmonary capillary wedge pressure changes every 2 hours. The plasma half-life of NT-proBNP, in comparison, is much longer (120 min), suggesting that it can be used to measure hemodynamic changes every 12 hours.[21] Therefore, the BNP level at the time it is drawn may be more reflective of acute volume expansion and ventricular pressure overload at that moment. Unlike BNP, which is mainly cleared by neutroendopeptidase, NT-proBNP is mainly cleared by the kidneys. Its level is therefore significantly influenced by renal function as well as age. Given the differences between these two tests, we believe that the BNP is the test of choice for transfusion reaction evaluation at this time.

In our study, BNP levels varied greatly among patients (5-5000 pg/mL). Pretransfusion BNP levels were consistently higher in patients with history of CHF and/or impaired renal functions. To our surprise, however, we found that neither CHF nor history of impaired renal function is associated with or can predict TACO. This can be partly explained by the relatively small size of patient groups included in the study and also possibly due to biased patient selection since CHF and impaired renal functions are frequent in patients in a tertiary care hospital. Among the symptoms presented with TACO, acute dyspnea and systolic hypertension, but not tachycardia, are clinical indicators of TACO. Although tachycardia is frequently observed in acute volume expansion, it is also associated with FNHTR. In addition, our study shows that it is difficult to use multiunit transfusion as a predictor of TACO, probably due to the reason that most of the individuals in our study are hospitalized patients with complicated medical presentations that require frequent transfusion of multiple blood products.

In conclusion, we have shown that BNP testing is a valuable adjunct in confirming or excluding TACO as the cause of transfusion-associated acute dyspnea or change of vital signs. The diagnosis of TACO in most cases, however, does not require BNP testing. Complicated cases presenting acute pulmonary symptoms in the setting of transfusion are not infrequently seen, especially in patients with compromised cardiopulmonary functions and impaired renal functions. With its high sensitivity and predictive values, the addition of BNP testing in the setting of transfusion-associated acute respiratory distress has been proved useful in helping clinicians to differentiate TACO from TRALI.[24] Low BNP levels can exclude TACO whereas high BNP levels favor TACO. High BNP levels, however, do not exclude the diagnosis of other transfusion reactions such as TRALI or allergic reactions because those conditions can coexist. Finally, the diagnosis of TACO should not be based on the BNP levels alone; instead, this information should be considered in the context of the other clinical information obtained.

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