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EXTENDING THE UTILITY OF NATRIURETIC PEPTIDE TESTING: CURRENT CONCEPTS AND FUTURE REALITIES

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REVIEW

ABSTRACT. USE OF NATRIURETIC PEPTIDE TESTING as a cornerstone in the diagnosis of heart failure is now widespread. Important recent advances in the understanding of natriuretic peptide testing have led to the recognition that these valuable assays for B-type natriuretic peptide (BNP) or its amino-terminal fragment (NT-proBNP) may have applications well outside the realm of heart failure. However, in order to refine these applications, a thorough understanding of the finer physiologic and pathophysiologic mechanisms affecting BNP and NT-proBNP is necessary. Such an understanding will not only enable clinicians to interpret BNP or NT-proBNP levels more properly when evaluating patients with heart failure, but also will lead to a more confident use of these markers in different clinical applications, such as evaluation of other disease states, reviewed within. This paper will review the influence of the common patient-specifiic physiologic and pathophysiologic factors known to affect BNP and NT-proBNP other than heart failure, and will discuss opportunities for future, more novel applications for natriuretic peptide testing.

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1. INTRODUCTION

Measurement of natriuretic peptide (NP) levels is now becoming routine in clinical practice as a tool for the diagnosis of heart failure (HF) in dyspneic patients, however recent advances in the understanding of the optimal application of testing for natriuretic peptides have led to the recognition of a broad range of potential future applications. In order to understand future applications, it is necessary to review some important basic points about natriuretic peptides in health and disease.

2. NP BIOCHEMISTRY AND PATHOPHYSIOLOGY: A BRIEF REVIEW

There are two related BNP-type markers, derived from a common intracellular 108-amino acid precursor peptide. This 108 amino acid precursor, $proBNP_{108}$, is synthesized mainly in the atrial and ventricular cardiomyocytes in response to myocyte stretch, but several other non-cardiac sites, including the central nervous system, adrenal glands and kidneys, have been recognized as sites of active synthesis and release [1-3]; the relative percentage of circulating BNP is thought to be largely from the myocyte, however, fibroblasts in the perimyocardial regions are also thought to contribute to the process of BNP release [4,5]. At the time of its release from the cardiomyocyte, $proBNP_{108}$ is cleaved by the enzyme furin to release two portions in equimolar amounts: the biologically inert amino-terminal portion, NT-proBNP, and the carboxy-terminal portion, BNP, which represents the bioactive portion of the molecule, with a characteristic 17-amino acid ring formed by disulfide-linked cysteines, essential for biological activity [6,7]. BNP has multiple effects, including induction of natriuresis, diuresis, and vasodilation. BNP also has effects on cardiomyocyte growth/hypertrophy, and may improve myocardial relaxation. Given its biologic activity, BNP is quickly cleared by several mechanisms, which include endocytosis by natriuretic peptide receptors, neutral endopeptidase degradation in the circulation and probably passive renal excretion. It has a half-life of about 20 minutes [3,7].

NT-proBNP is believed to have no neurohormonal effects. Unlike active BNP, NT-proBNP is thought to be cleared passively, with approximately 20% of NT-proBNP clearance achieved via renal excretion, with the rest removed through other systems such as the reticulo-endothelial system [3,7]; given the more passive clearance of NT-proBNP, its half life is thought to be around 60 to 120 minutes. FIG. 1 provides a simplified overview of the mechanisms that intervene in the release and clearance of BNP and NT-proBNP.

3. NP TESTING: CURRENT APPLICATIONS

At present, the use of BNP and NT-proBNP is largely restricted to the diagnosis and triage of patients with dyspnea considered to be due to heart failure. This application is based on the recognition of the value of these tests for such uses [8-10]. However, the original optimistic embracement of testing for natriuretic peptides by clinicians was soon followed by the recognition that although large-scale studies of natriuretic peptide testing were supportive of the use of these tests, fine details regarding the 'in's and out's' of natriuretic peptide testing were not evident. The situation is even more complex, as the future focus of natriuretic peptide testing will shift to office-based use; in such an environment, a more refined understanding of the factors that influence BNP and NT-proBNP is even more necessary, as the degree of release of these markers is typically an order of magnitude lower than in the acute setting, and factors that may not be as important in the acute setting have a much greater significance in the office.

Thus, while in the clinical trial setting one may paint with 'broad strokes' with interpretation of testing for natriuretic peptides, correct interpretation of individual natriuretic peptide concentrations in 'real world' patients should be done with 'finer strokes', as natriuretic peptides may be influenced by a number of patient-specific physiologic factors, including age, gender, the presence of obesity, renal dysfunction and co-morbid structural heart disease. This review will consider these issues, and identify opportunities for future

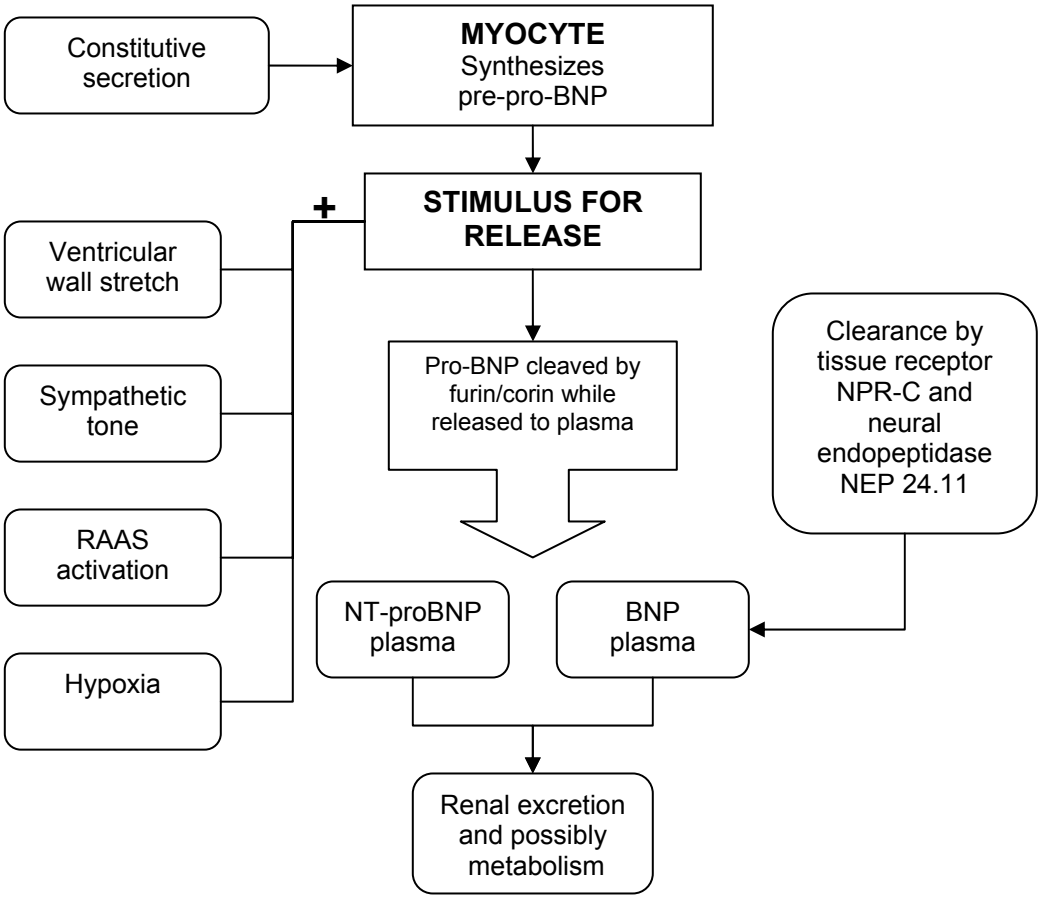

FIGURE 1. BNP AND NT-PROBNP RELEASE AND CLEARANCE.

applications of natriuretic peptide testing in areas other than acute dyspnea evaluation.

4. AGE AND GENDER MODIFY NP LEVELS

In a landmark investigation, Wang et al. [11] used a healthy reference sample of subjects with normal left ventricular systolic function who were free of hypertension, valvular disease, diabetes, atrial fibrillation, obesity, coronary heart disease, heart failure or renal failure, and measured plasma BNP levels to assess the impact of age, sex, and other physiologic characteristics on natriuretic peptide levels. They found that the strongest predictors of higher natriuretic peptide levels were older age and female gender. Other multivariable predictors included lower diastolic blood pressure (higher pulse pressure), lower body-mass index, and higher left atrial size.

The importance of age on natriuretic peptide values was further demonstrated in an even more elderly cohort (with a mean age of 83 years). In this study, it was shown that even among elderly inpatients without cardiovascular diseases and with normal renal function, BNP levels were often significantly elevated, confirming that age (with associated 'normative aging processes' such as hypertension and sub-clinical cardiac diastolic abnormalities) was an independent factor affecting BNP concentrations [12].

The obvious ramifications of a better understanding of such an influence of age and gender on the concentrations of BNP or NT-proBNP in the general population is to further 'hone' the accuracy

TABLE 1. OPTIMAL BNP AND NT-PROBNP CUT POINTS FOR DIAGNOSIS OF CHF IN DIFFERENT CLINICAL SETTINGS.

Setting	BNP (pg/mL)	NT-proBNP (pg/mL)
Acute CHF	100 [8]	450 (< 50 years old); 900 (50–75 years old); 1800 (> 75 years old) [9,10]
Renal failure	200 [30]	1200 (GFR < 60 mL/min) [31]
Outpatient evaluation	Unknown (possibly 30–40)	125 (< 75 years old); 450 (> 75 years old); manufacturer recommended

of testing for these peptides in dyspneic patients presenting to the emergency department, as well as for screening of 'apparently well' patients for identification of sub-clinical cardiovascular abnormalities. Preliminary data suggest potential opportunities for such an approach in 'apparently well' patients: in a recent study from the Mayo Clinic, receiver operating characteristic analysis for the ability of BNP to detect an ejection fraction ≤40% was performed in each age/gender stratum in the entire cohort (N = 2,042) and confirmed that discriminatory values for BNP for detection of reduced ejection fraction were higher in women and older persons [13].

For the symptomatic patient in the primary care setting, current recommended guidelines suggest the use of natriuretic peptide testing as a step prior to referral for echocardiographic or specialist evaluation [14]. At present, the recommended cut-points for out-patient evaluation are

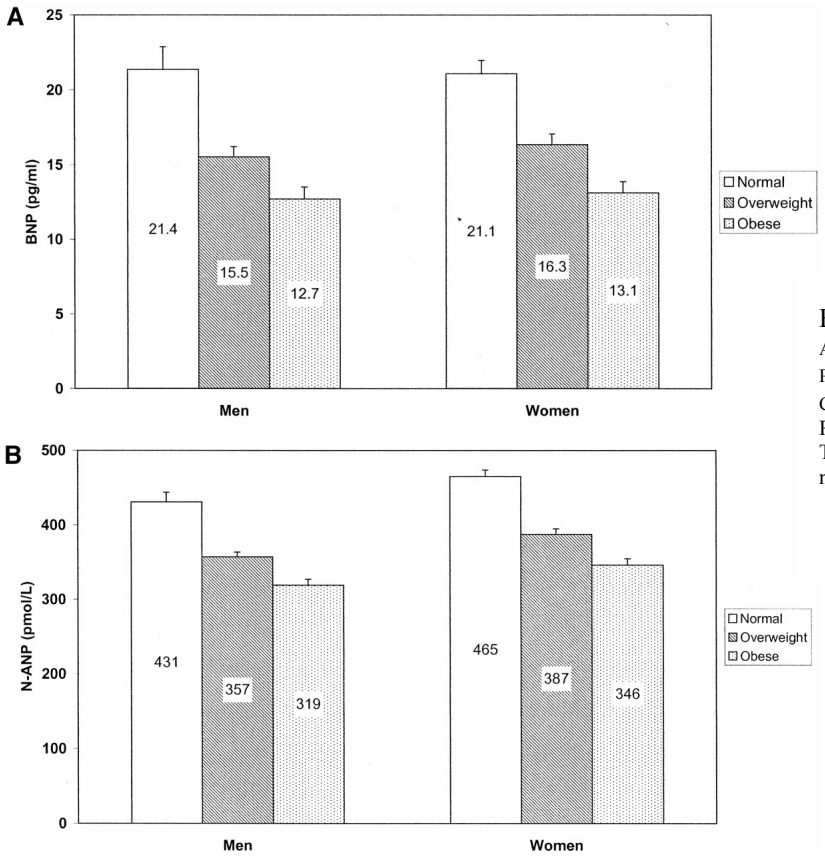

FIGURE 2. MULTIVARIABLE-ADJUSTED ANALYSES SHOW A PROGRESSIVE DECREASE IN PLASMA BNP LEVELS WITH INCREASING BMI CATEGORY FOR THIS FRAMINGHAM COHORT. Reproduced with permission from ref. [20]: Wang TJ, et al. [2004] Impact of obesity on plasma natriuretic peptide levels. Circulation 109: 594-600.

TABLE 2. SUMMARY OF BNP AND NT-PROBNP PLASMA LEVEL MODIFIERS.

	BNP	NT-proBNP	Comments on mechanism or utility
Age	↑	↑	Strong correlation with CHF persists in age/gender-stratified analyses.
Female gender	↑	↑	
Obesity	↓↓	↓	BNP more affected given higher levels of clearance receptors in fatty tissue.
Renal failure	↑↑	↑↑↑	NT-proBNP shows slightly stronger correlation to GFR.
Aortic valve disease	↑	↑	Possible utility for identifying replacement candidates and postoperative follow-up.
Mitral valve disease	↑	↑	Same as above, levels may be good estimates of hemodynamics. May predict AF onset
AF	↑	↑	Suspected direct release by fibrillating myocytes.
VT	↑	↑	Likely association with abnormal wall stress, amiodarone decreases BNP levels.
Myocardial ischemia	↑	↑	Probably from impaired wall relaxation and contractility and myocardial hypoxia.
Pregnancy	↑	↑	Minor physiologic elevation. Pronounced increase seen in preeclampsia and CMP.
Neonatal state	↑	↑	Physiologic increase from early volume shifts.
Diabetes mellitus	↑	↑	Nephropathy causes downregulation of renal tubule receptors
PE, PPH, COPD with cor pulmonale	↑	↑	Released due to RV straining and closely related to degree of ventricular dysfunction.
Critical illness	↑	↑	Increase in hemodynamic counterregulatory mechanisms. Useful to guide management and as predictors of mortality.
Intracranial hemorrhage and embolic stroke	↑	↑	Salt wasting syndrome. Also, injured brain causes ventricular release of NPs for hemodynamic homeostasis.

well-established for NT-proBNP (TABLE 1). The optimal out-patient cut-points remain uncertain for BNP, most likely well below the recommended cut-point of 100 pg/mL, which is best reserved for acutely dyspneic patients in the emergency department setting. Irrespectively, when applied in a logical fashion, use of natriuretic peptide screening in the form of NT-proBNP was recently found to be cost-effective in a community-based screening approach for LV dysfunction, especially in high-risk subjects [15].

5. THE INFLUENCE OF OBESITY IN NP TESTING

Given that obesity is a pathologic condition that puts individuals at risk for comorbidities that increase the risk for heart disease such as hypertension and diabetes, as well as the fact that obesity itself may be associated with symptoms or signs that mimic heart disease (dyspnea, edema), a biomarker to identify sub-clinical abnormalities in obese patients would be welcome. The cardiovascular system in obese individuals is probably affected by a component of renal sodium and water retention as well as increased activation of the renin-angiotensin system [16]. Also, it is well established that human adipose tissue contains very high levels of natriuretic peptides clearance receptor messenger RNA, possibly determining decreased biological activity and/or increased clearance of natriuretic peptide in adipose tissue [17,18]. These mechanisms could very well account for the so-called "natriuretic peptide handicap" [19] believed to be present in obese individuals independent of hypertension affecting their regulation of sodium homeostasis and neuro-

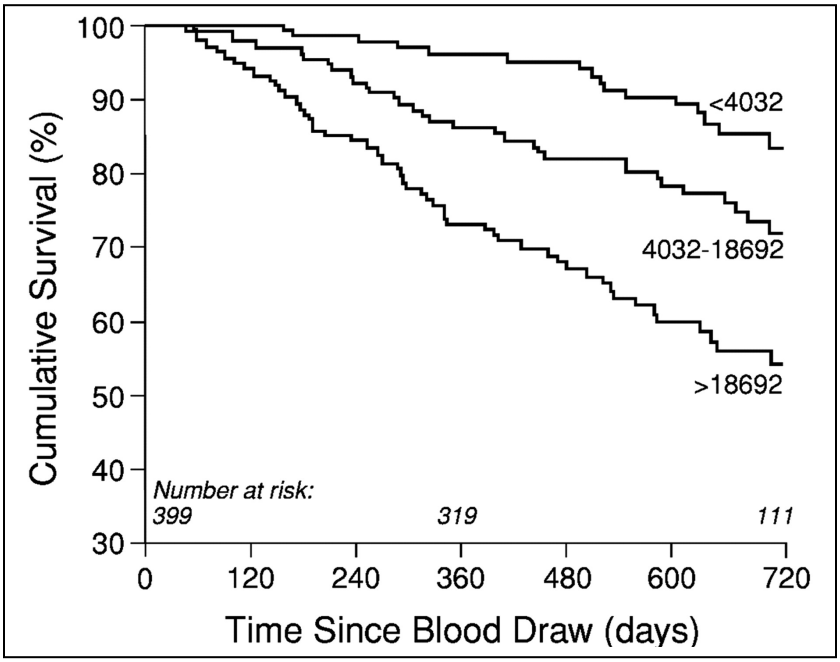

FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES BY BASELINE NT-PROBNP TERTILES IN 399 ESRD PATIENTS. Elevated NT-proBNP potently predicted death in this population. Reproduced with permission from ref. [29]: Apple FS, et al. [2004] Multi-biomarker risk stratification of *N*-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactive protein, and cardiac troponin T and I in end-stage renal disease for all-cause death. Clin Chem 50: 2279-2285.

hormonal feedback. Thus, there are reasons to suggest that natriuretic peptide testing might not be as useful in subjects with higher body-mass index.

A study measuring plasma natriuretic peptides on more than 3000 individuals in the Framingham Heart Study was designed to evaluate the impact of obesity on natriuretic peptide levels independently from that of hypertension, diabetes, and other characteristics. Mean plasma BNP levels in lean (< 25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2) men and women were significantly lower in parallel with body-mass index (FIG. 2) [20]. It is therefore tempting to speculate whether this finding could possibly explain the heightened susceptibility to hypertension and hypertension-related disorders obese patients, but this remains unresolved.

To evaluate the how natriuretic peptide levels behave in obese individuals with heart failure physiology, a recent study examined NT-proBNP and BNP levels in 204 subjects presenting with acute HF [21]. The authors found the levels decreased with increasing BMI across clinical strata of normal (< 25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2) patients. In this study NT-proBNP and BNP exhibited generally similar overall sensitivity for the diagnosis of HF, however NT-proBNP assays fell below the diagnostic cutoff for HF less often than BNP in overweight and obese individuals, possibly because clearance receptors are not involved in the elimination of the *N*-terminal fragment from the circulation — in other words the lower levels of natriuretic peptides in patients with high body-mass may reflect reduced release (NT-proBNP and BNP) as well as enhanced clearance (BNP).

Whether the 'obesity handicap' for BNP and NT-proBNP testing would interfere with the ability of these markers to prognosticate risk in patients with HF remains to be seen, however preliminary results suggest that at least for NT-proBNP, its powerful prognostic value as a marker is preserved

in patients with acute HF (Januzzi JL, personal communication).

6. NP TESTING IN KIDNEY DISEASE

Of the many variables involved in the synthesis, release and clearing of natriuretic peptides, renal function remains one of the most invoked, but perhaps least understood. Since both BNP and NT-proBNP depend on renal clearance for their removal from the circulation, it is not at all surprising that at a glomerular filtration rate (GFR) threshold of 60 mL/min/1.73 m^2, multiple studies have confirmed increased baseline plasma levels of natriuretic peptides [22,23], however, at this point in GFR is also the threshold where survival curves worsen for those with HF [24]. There also seems to be a very strong co-linearity between renal function and the risk for the development of structural heart disease [25], with more prevalent risk factors in parallel with renal disease, such as hypertension or diabetes mellitus.

At present, it is understood that both BNP and NT-proBNP have a dependence on renal function for their clearance. NT-proBNP can be detected in urine [26], clearly demonstrating the role of the kidneys in clearing the marker. It is also known that both are cleared by pathways other than renal mechanisms.

An important consideration is whether one marker is more affected by renal failure purely on the basis of clearance; in univariable correlations, compared to BNP, NT-proBNP has typically been found to have a stronger correlation with GFR. Whether this is due to exaggerated effects of reduced clearance on NT-proBNP, or enhanced sensitivity for the detection of cardiac abnormalities in patients with impaired renal function is a hotly debated subject.

It is not surprising, really, that markers of volume overload may be elevated in patients with severe renal failure, as such patients typically are fluid overloaded. A frequent question that thus arises is whether natriuretic peptides might be useful to gauge adequacy of dialysis. The answer is not entirely clear: studies have shown ANP and BNP to be significantly decreased after hemodialysis (on average, ANP by 36% and BNP by 16%); while NT-proANP and NT-proBNP values tend to increase (NT-proANP by 14.4% and NT-proBNP by 9.5%) [22]. Thus, whether these markers may be used to guide renal replacement therapy remains unknown and not well-explored.

From a clinical utility perspective, both BNP and NT-proBNP may have utility in the evaluation of patients with chronic kidney disease. Studies specifically designed to evaluate patients with CRF who were not undergoing dialysis have found that plasma BNP and NT-proBNP levels are reliable in identifying LV overload, LVH and underlying ischemic heart disease [25,27,28].

In patients with renal failure requiring hemodialysis, natriuretic peptides are often grossly elevated, however they still seem to be useful in gauging the risk of future cardiovascular events. Indeed, studies have shown that BNP concentrations are higher in ESRD patients who died from cardiovascular events than in those who survived longer than 15 months [22,25], and a 2004 investigation that evaluated multiple biomarkers to predict adverse outcomes in 399 ESRD patients, found that while NT-proBNP was frequently elevated, it was, in fact, a strong predictor of survival (FIG. 3), providing confidence for use in risk stratification for ESRD patients [29].

Irrespective of the putative relationships between renal function and natriuretic peptides, what matters most is clinical utility for the most commonly used indication for BNP and NT-proBNP, namely evaluation of the dyspneic patient with suspected HF. Among dyspneic patients, the Breathing Not Properly Multinational Study was pivotal in establishing the correlations between GFR and BNP in those with and without HF, establishing CKD does appear to influence the optimum cut-points for BNP in the diagnosis of acute HF in dyspneic subjects. The investigators argued that as CKD stage advances, a higher cut-point of BNP is needed [30], in the range of 200 pg/mL. Similar findings were recently reported for the use of NT-proBNP in dyspneic subjects [31]. In this analysis, univariable correlations between GFR

and NT-proBNP were higher than those reported for BNP, but at optimal NT-proBNP cut-points, there were no differences between the results of NT-proBNP testing and those reported for BNP in patients with renal failure. As well, NT-proBNP remained highly prognostic for death in patients with renal failure, arguing that elevations of NT-proBNP in patients with chronic kidney disease represent more 'signal' rather than 'noise'.

7. CARDIOVASCULAR MODIFIERS OF NP CONCENTRATIONS AND POTENTIAL APPLICATIONS

7.1. VALVULAR HEART DISEASE

Given that the stimulus for the release of natriuretic peptides is mainly atrial and ventricular wall stress, it is expected BNP and NT-proBNP levels will be altered in patients with valvular heart diseases, however the optimal utility of these markers for evaluating patients with valvular heart disease remains unclear.

Among the cardiac valve lesions where natriuretic peptide testing might be of greatest use is in the evaluation of patients with significant aortic valve disease. It is well documented that BNP and NT-proBNP are elevated in patients with valvular aortic stenosis (AS), with correlation to severity as NYHA stage [32] and a more recent trial showed a consistent relation of NT-proBNP to severity of aortic stenosis and insufficiency, suggesting NT-proBNP should be considered for the monitoring of disease during pre-operative follow-up [33]. For those patients managed surgically, it is established that NT-proBNP levels decline after successful aortic valve replacement [34], and testing for NT-proBNP provides prognostic information for symptom-free survival and post-operative outcome in these patients as well [35]. Thus, it is believed that BNP and NT-proBNP testing may have utility for identifying those patients with aortic valve disease who are in need of consideration for valve replacement, as well as those at higher risk for adverse outcomes after aortic valve replacement.

In the case of mitral valve disease, studies have shown that in patients with mitral regurgitation, NT-proBNP levels correlate positively with disease severity, and track closely with risk for adverse outcomes [36,37]. This is an important observation, as the timing of mitral valve repair or replacement for those with regurgitation is often determined by the onset of ventricular decompensation, symptom onset, or both, a circumstance where prognosis is worse.

With respect to mitral stenosis, both BNP and NT-proBNP may correlate with stenosis severity [38], and may have utility for estimating changes in hemodynamic parameters after percutaneous transvenous mitral commissurotomy. Furthermore, natriuretic peptides may reflect pulmonary artery hypertension in patients with mitral stenosis, and may be predictive of onset of atrial fibrillation in these patients [39].

7.2. ARRHYTHMIAS

Atrial fibrillation is not an uncommon finding in patients with HF, however accurately studying the effect of AF by itself on BNP or NT-proBNP levels is difficult as there are many confounders, including the hypothesis that AF by itself can cause cardiomyocytes to release BNP or NT-proBNP into the circulation, independent of hemodynamic triggers [40]. Among patients with dyspnea, permanent/paroxysmal AF was associated with significantly higher BNP levels [41]. Lending further support to this observation is the recognition that BNP levels have been reported to fall following cardioversion of AF. In a recent study, BNP levels dropped (260 ± 255 vs. 190 ± 212 pg/mL, $P < 0.05$) 40 min after cardioversion, decreasing in 33 of 41 subjects who achieved sinus rhythm, contrasting with a lack of change in subjects in whom cardioversion was not successful. It would seem the rapid fall in BNP after cardioversion reflects prompt hemodynamic improvement associated with rhythm change [42]. Importantly, it is now recognized that levels of natriuretic peptides may be useful to differentiate those subjects more likely to have durable results from cardioversion than those at high risk for the recurrence of atrial arrhythmia, even in the absence

of structural heart disease [43].

As ventricular arrhythmias are a common modality of death in patients with HF, a biomarker predictive of such risk would be welcome. As natriuretic peptides represent a strong prognostic factor in patients with treated HF, arrhythmia is a prominent cause of death in patients with high levels of BNP or NT-proBNP. However, surprisingly, there are few data available regarding the utility of BNP or NT-proBNP for predicting ventricular arrhythmias. In a study that looked at 52 patients with ventricular premature contractions (VPC) but no manifestations of heart failure and no digoxin or beta-blocker therapy showed that this association could be a response to abnormal wall stress [44]. Interestingly, amiodarone appears to have a decreasing effect on plasma BNP level in patients with heart failure and ventricular tachyarrhythmia [45].

7.3. ISCHEMIC HEART DISEASE

NP LEVELS IN RISK STRATIFICATION OF PATIENTS WITH ACUTE ISCHEMIA. A potential application of natriuretic peptide testing for patients other than acute HF is the evaluation of patients with acute coronary ischemia. It is well established that BNP and NT-proBNP concentrations may be affected during ischemic events, and this relationship has powerful prognostic ramifications.

One of the postulated mechanisms for release of BNP or NT-proBNP during ischemia seems to be related to a transient change in ventricular systolic and diastolic function, as impairment of both myocardial relaxation and contractility occurs even in the absence of infarction [46]. Alternately it also seems that myocardial hypoxia per se can cause increased BNP gene expression and plasma release during ischemic events even without ventricular dysfunction [47]. Irrespective of the mechanism, experimental studies involving measurement of either BNP or NT-proBNP before and after exercise-induced ischemia have demonstrated measurable differences in those patients with ischemia detected on nuclear perfusion imaging, compared to those without ischemia [48,49].

Among patients with acute coronary syndromes (ACS), both BNP and NT-proBNP have powerful prognostic value. One of the earliest studies to demonstrate this value was a large, contemporary cohort of patients with ACS, consisting of 204 patients with ST-elevation myocardial infarction (MI), 220 with non-ST segment elevation MI and 185 with unstable angina. Results showed that in patients with no evidence of clinical heart failure, NT-proBNP remained a significant predictor of mortality after adjustment for age and ejection fraction providing additional prognostic information beyond conventional risk markers [50]. Similar findings were reported demonstrating the value of BNP in patients with varying types of ACS [51]. In the case of patients with non-ST segment elevation MI, NT-proBNP has been identified as a valuable marker of increased risk for early cardiovascular events [52] superior to other markers of risk in this setting, including measures of renal function, and even troponin testing [53] for predicting death.

Of note, recent evidence has surfaced that suggests the time interval from onset of symptoms to first blood collection is an important determinant for NT-proBNP values on admission in patients with an ACS; this should be kept in mind when testing patients with suspected ACS: typically, highest highest values are observed 24-36 h after onset of symptoms [54]. In light of this finding, it is not surprising that recent data suggest that serial measurements of NT-proBNP or BNP [55] may be more useful for identifying those ACS patients at highest risk than a single isolated measurement at presentation. It is suggested that if measuring natriuretic peptides for optimal risk stratification of patients with ACS, that at least 2 measurements (at presentation and at >24 hours) be obtained.

NP LEVELS IN RISK STRATIFICATION OF PATIENTS WITH CHRONIC STABLE ANGINA. A recent study demonstrated that NT-proBNP testing strongly predicted mortality in a population of patients with chronic stable angina, even when controlling for all factors known to influence NT-proBNP concentrations, such as age, LV function,

and renal function [56]. Whether a therapeutic imperative exists for such patients remains yet unclear.

8. NATRIURETIC PEPTIDE TESTING FOR MONITORING NON-CARDIAC DISEASE STATES

8.1. PREGNANCY

Studies evaluating natriuretic peptides levels in pregnancy have been mostly designed with the objective of identifying BNP or NT-proBNP as early markers of pregnancy induced hypertension, preeclampsia, or peri-partum cardiomyopathy, circumstances all associated with increased myocardial stretch. Although natriuretic peptide levels might be expected to be altered during pregnancy because the increased cardiac output and expanded plasma volume seen in normal pregnancy [57], in most cases, an elevated natriuretic peptide concentration in a gravid patient is more often associated with cardiovascular abnormalities or complications of the pregnancy. Indeed, in normal pregnancies, median BNP values are typically only 20 pg/mL, and stable throughout gestation. In severe preeclampsia BNP levels are elevated, probably reflecting ventricular stress and/or subclinical cardiac dysfunction associated with preeclampsia [58]. Another recent study that looked at 46 hospitalized black African women with heart failure due to peripartum cardiomyopathy suggested that low values of NT-proBNP were indicative of complete remission [59]. Thus, the potential for applying testing for natriuretic peptides in pregnant women to identify risk for severe complications from their pregnancy and to track their clinical course appears significant.

Notably, it has been shown that neonates frequently demonstrate dramatically elevated natriuretic peptide concentrations, perhaps reflecting volume overload related to the early shifts in circulation observed in the first days of life. Importantly, the concentrations of natriuretic peptide observed in normal neonates may frequently be in the range typically associated with acute, severe HF, but rapidly fall to normal levels after a few weeks of life [60]. Following this fall, natriuretic peptide testing in infants may be useful for the detection of congential heart disease [61].

8.2. DIABETES MELLITUS AND HYPERGLYCEMIA

As it is a condition associated with heightened likelihood for symptomatic heart disease, natriuretic peptides might have value for the earlier detection of structural cardiac abnormalities in patients with diabetes mellitus. Indeed, data suggest that higher values of BNP and NT-proBNP might be observed in patients with diabetes mellitus, compared to non-diabetic patients.

The mechanism of higher natriuretic peptide concentrations in diabetic patients may be related to both cardiovascular and extra-cardiovascular effects of diabetes. Although there is conflicting evidence, it is thought that diabetic nephropathy (through down-regulation of the A-type guanylate cyclase-coupled receptor on the renal tubules), may explain the increased plasma levels of both BNP and ANP in diabetic patients. Importantly, despite the potential risk of confounding of NP measurement by the diabetic milieu, it is reassuring to note that DM per se will not interfere with testing for BNP or NT-proBNP: in a physiologic study designed to examine if acute hyperglycemia confound testing of NP levels, 8 subjects were clamped at normoglycemia by intravenous infusion of insulin. The authors found that plasma ANP concentrations increased with dextrose infusion, and were higher with dextrose than saline infusions. In contrast plasma concentrations of BNP were not significantly altered by infusion of either dextrose or saline [62].

The recognition of the relationship between BNP or NT-proBNP and heart disease in patients with DM is growing stronger. Initial studies investigating plasma levels of BNP in diabetic patients showed that microalbuminuria was associated with significantly higher NP levels than in diabetic patients with normoalbuminuria [63]. There have been more recent clinical studies of diabetic patients that have sought to evaluate NT-proBNP as a screening tool for LVD and vascular complications in type 2 diabetes. One study looking

at asymptomatic LVD in patients with type 2 diabetes found higher adjusted NT-proBNP values in DM2 than control subjects with important prognostic ramifications [64]. In another study, only diabetics with vascular complications had significantly increased plasma NT-proBNP levels [65].

While NT-proBNP and BNP may be elevated in a prognostically meaningful fashion in diabetic patients without clinically overt heart disease, this does not mean that these markers lose utility for evaluating the diabetic patient with suspected acute HF, as demonstrated a recent study [66].

8.3. PULMONARY DISEASE

The right ventricle (RV) contains BNP and NT-proBNP, and as such, disease states resulting in strain of this cardiac chamber may result in elevations in natriuretic peptide concentrations.

Several disease states marked by RV strain have been associated with prognostically meaningful elevation in NT-proBNP levels, including thromboembolic disease, primary pulmonary hypertension, as well as chronic obstructive pulmonary disease with cor pulmonale.

PULMONARY EMBOLISM. In the setting of acute pulmonary embolism, natriuretic peptide levels were higher in patients with RV dysfunction [67]; since RV dysfunction is associated with worsened prognosis in pulmonary embolism, it is not surprising that BNP and NT-proBNP concentrations are predictive of morbidity and mortality in this setting [68,69].

In a recent landmark study, an NT-proBNP concentration >1000 pg/mL was associated with a higher likelihood for RV dysfunction on echocardiogram and as such was associated with a 12-fold elevation in complication risk compared with patients with low NT-proBNP ($P = 0.002$) [69]. These and other data illustrate potential utility of NT-proBNP testing for evaluation, triage, and possibly management of such patients.

For chronic thromboembolic pulmonary hypertension, plasma BNP levels have been evaluated as markers of efficacy for 34 patients who underwent pulmonary endarterectomy. Plasma BNP levels were strongly associated with the severity of pulmonary hypertension and levels in those with successful surgery were seen to decrease markedly post-procedure [70].

PRIMARY PULMONARY HYPERTENSION. It is well established that BNP and NT-proBNP levels increase in proportion to the degree of right ventricular dysfunction in primary pulmonary hypertension (PPH) [71]. The first study to evaluate the prognostic significance of plasma BNP in patients with PPH found that survival was strikingly worse for patients with a markedly elevated BNP, suggesting that baseline and follow up increases in plasma BNP were strong, independent predictors of increased mortality rates in such patients [72]. Given that plasma BNP levels are closely related to the functional impairment of ventricular function in PPH, parallel to the extent of pulmonary hemodynamic changes and right heart failure, its been proposed that serial measurements of plasma BNP or NT-proBNP measurements could be useful to guide therapy (such as the use of pulmonary vasodilators) [73].

Another interesting conclusion of NP testing in PPH is that since upregulation of the natriuretic peptide pathway has been shown to reduce cardiac hypertrophy and pulmonary arterial hypertension, there could be therapeutic potential using infusions of recombinant BNP for control of pulmonary arterial hypertension and management of RV dysfunction in PPH patients [74].

SCREENING OF PATIENTS WITH OBSTRUCTIVE AIRWAY DISEASE FOR "MASKED HEART FAILURE". Clinically, a common challenge is to correctly identify the cause of dyspnea in a patient with dyspnea who has prior obstructive airways disease, such as asthma or chronic obstructive pulmonary disease (COPD) as well as HF. Since wheezing is a common finding in both obstructive airways disease and HF, it is not surprising to learn that heart failure patients with lung disease may frequently have both presence and severity of their HF under-appreciated [75].

Lending support to this concept was the recognition of the value of NT-proBNP testing for

recognizing heart failure in 1186 primary care patients with stable chronic obstructive pulmonary disease (COPD). The authors of this study found that the addition of measurement of NT-proBNP to a standard clinical model had the largest added diagnostic value of all variables measured, with a significant increase in diagnostic discrimination, followed by other more commonly used tests such as electrocardiography, C reactive protein and chest radiography which had limited added value [76]. With better treatment of co-morbid HF (which may trigger obstructive airway exacerbations), as well as the mortality benefits already established for treatment of HF with drugs such as beta blockers or angiotensin converting enzyme inhibitors, the identification and treatment of such "masked" heart failure would not only be expected to improve symptoms and reduce hospital use, but possibly lower risk for death in patients with concomitant pulmonary and heart insufficiency.

8.4. CRITICAL ILLNESS

Given the relationship between BNP concentrations and filling pressures in patients with HF [77], there was interest in the potential applicability of testing for natriuretic peptides as a non-invasive measure of filling pressures in diagnoses other than HF, such as shock in the intensive care unit, where knowledge of cardiac filling pressures and hemodynamics may be incrementally useful to guide fluid resuscitation.

Several studies have now demonstrated that both BNP and NT-proBNP are elevated in patients with critical illness, and very frequently such elevations are independent of cardiac filling pressures [78,79]. Notably, while elevated BNP or NT-proBNP concentrations in critically ill ICU patients may lack good positive predictive value for identifying acute HF, lower concentrations of both markers can demonstrate a powerful negative predictive value (95%) for excluding cardiogenic shock, suggesting that in the presence of a low BNP or NT-proBNP concentrations, a clinician may be able to continue management with fluid resuscitation or vasopressors as needed in situations where PA catheter placement is not an option [78,79].

One interesting observation from studies of natriuretic peptide testing in critically ill patients is that both BNP and NT-proBNP represent strong predictors of ICU mortality, superior to the ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II SCORES in this regard. This enhanced ability to risk-stratify patients with critical illness may be leveraged for differential management of the patient: recent data suggest that the successful use of activated protein C for treatment of gram-negative sepsis was more likely to be seen in patients with elevated NT-proBNP concentrations [80].

In retrospect, since NPs are cardiac hormones with natriuretic, vasorelaxant, and aldosterone-inhibiting properties for many self-regulating hemodynamic mechanisms, it is not that surprising that elevation of these markers may be present in critically ill patients in the absence of heart failure. Furthermore, in analogy to troponin release in critical illness [81], it is not surprising to see prognostically meaningful relationships between natriuretic peptides and critical illness.

8.5. NEUROLOGIC CONDITIONS

Subarachnoid hemorrhage (SAH) often presents with a salt wasting syndrome, and one hypothesis on the mechanism of this disease is that the natriuretic response by the kidney is due to an increased activity of the dopaminergic and sympathetic nervous systems. However another possibility involves a mechanism of release of natriuretic factors including ANP, BNP and CNP as counter-regulatory hormones released by the ventricles but triggered by the injured brain, for the purpose of homeostatic natriuresis and vasodilation with increased intracranial pressure [82].

A prospective trial examined the temporal relationship between serum BNP elevation, hyponatremia, and the onset of delayed ischemic neurological deficits to determine whether serum BNP levels correlated with the 2-week outcome after SAH. Authors found that a more than threefold increase in admission serum BNP levels

were associated with the onset of hyponatremia, and they significantly increased in the first 24 hours after onset of delayed ischemic neurological deficits, BNP level also predicted the 2-week Glasgow Coma Scale score [83]. Another study looking at BNP levels in SAH due to ruptured aneurysms, found that the concentration of BNP in ruptured anterior communicating artery aneurysms was more pronounced when compared with other sites of aneurysms, suggesting that the hyper-secretion of BNP maybe caused by direct mechanical damage at the anterior hypothalamus by these aneurysms [84].

The release of BNP and NT-proBNP among patients with severe neurologic illness may be related not only to cerebral abnormalities, but also to the well-described syndrome of marked reversible cardiac abnormalities related to cerebral injury, such as reversible cardiomyopathies [85].

As in SAH, levels of ANP and BNP have been found to be elevated in patients with stroke up to 6 days after the event [86], the neurohumoral activation seen in these patients is possibly reflecting a counterbalancing vasodilatory response to cerebral ischemia, but there is still controversy on whether it could be simply be a systemic hemodynamic mechanism related to direct myocardial stress from acute blood pressure elevation and other cardiac abnormalities that are known to follow ischemic stroke [87]. In any case, epidemiologically NT-proBNP has been shown to significantly predict mortality after stroke and remains a strong independent predictor even after adjustment for age, diabetes, coronary artery disease, and medications [88].

9. CONCLUSION

A summary of the most commonly seen clinical modifiers of natriuretic peptide levels is provided (TABLE 2).

Testing for BNP and NT-proBNP is here to stay. At present, the most common indication for these tests is for the evaluation of the acutely dyspneic patient with possible or proven HF; however, it is easy to appreciate the broad range of potential future clinical applications of natriuretic peptide testing. With the results of future studies now coming, in regards to the application of these important tests in areas such as out-patient evaluation and management of patients with a broad variety of cardiovascular and non-cardiovascular illnesses, more widespread use of natriuretic peptide testing is sure to follow.

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