Costanzo et al. (1) point out the advantages of greater safety and shorter admissions with their treatment. Perhaps a resurrection of the use of Southey tubes would be even less costly and at least as safe, and would be affordable in third-world countries. It is gratifying to learn of this advance made possible by physiologic reasoning, instead of ever-more complicated and expensive technology.

A final comment: there appears to be a tautology in the title of the investigators' study (1). Doesn't “decompensated” mean the same as heart failure? Why not just “diuretic-resistant heart failure”?

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REFERENCE


REPLY

We thank Dr. Guntheroth for his clinical observation and for raising consideration of the relation between central venous pressure and glomerular filtration rate based on our study (1). The inverse relation between right atrial pressure and glomerular filtration rate has been exquisitely documented, with animal studies demonstrating decreasing glomerular filtration rates with increased right atrial pressure (2–4). Similarly, glomerular filtration rates increase when normal human subjects are subjected to decreased central venous pressure by lower body negative pressure (5). Reduction of central venous filling pressures with Southey tubes, rotating tourniquets, or medicinal leeches could improve glomerular filtration rates. The mechanism of diuresis following Southey tube placement may be more insidious, however, as it is possible that the discomfort of the procedure stimulates catecholamine release, which, in turn, improves cardiac function and renal blood flow.

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Amino-Terminal Pro-Brain Natriuretic Peptide to Diagnose Congestive Heart Failure in Patients With Impaired Kidney Function

We were interested in the data of Anwaruddin et al. (1) demonstrating that in a group of patients presenting with dyspnea, of whom approximately one-third had chronic kidney disease (CKD), there was a strong relationship between amino-terminal pro-brain natriuretic peptide (NT-proBNP) and glomerular filtration rate (GFR) (r = –0.55), which remained independently highly significant in their multiple regression analysis. Despite this, Anwaruddin et al. (1) conclude that the diagnostic performance of NT-proBNP for congestive heart failure (CHF) is unaffected by the concomitant presence of kidney disease.

We have presented comparative data on the effect of BNP and NT-proBNP in a cohort of patients with CKD with a range of GFR between 5 and 60 ml/min/1.73 m² but not yet treated with dialysis, the majority of whom did not have CHF, thereby providing an opportunity to focus on the effect of diminishing GFR. The relationship between GFR and NT-proBNP was similar to that described by Anwaruddin et al. (r = –0.53), whereas that for BNP was less strong (r = –0.36). Anwaruddin and colleagues also report a weaker relationship between GFR and BNP (r = –0.18), although their BNP data were limited to those patients known to have CHF. Using a multiple regression approach we quantified the relationship between GFR and natriuretic peptide concentrations: for each 10 ml/min/1.73 m² decline in GFR, a 21% increase in BNP could be anticipated, compared to a 38% increase in NT-proBNP. We concluded that the effect of declining GFR on natriuretic peptide concentration was greater for NT-proBNP than for BNP. This is explicable from an understanding of the basic biology of these co-secreted peptides, with BNP having several known pre-renal clearance mechanisms in addition to renal elimination, whereas NT-proBNP is believed to be cleared by glomerular filtration alone.

How could 2 such similar datasets arrive at opposite conclusions? Anwaruddin et al. used NT-proBNP in a “rule-in” mode for heart failure, whereas in many studies and practical health service applications, lower thresholds have been proposed to enable use of the test in rule-out mode—a negative test result suggesting further investigation for heart failure (e.g., echocardiography) is probably unwarranted (3). The diagnostic thresholds they have selected (>450 pg/ml at <50 years and >900 pg/ml at >50 years) are therefore higher than the manufacturer’s usual decision thresholds. Despite this, however, 32% of patients with CKD (GFR <60 ml/min/1.73 m²) and no CHF had NT-proBNP concentrations in excess of these thresholds. An upward revision of the cut-point for CKD patients to 1200 pg/ml slightly reduced this nonspecificity such that 28% of CKD patients with NT-proBNP concentrations >1,200 pg/ml did not have CHF: however, this would generally not be considered acceptable performance for a diagnostic test used...
in clinical decision making. We would expect poor performance if NT-proBNP were to be used for rule-out decisions in patients with reduced GFR.

It is unfortunate that the investigators (1) did not undertake BNP testing in their entire cohort so that true comparative diagnostic performance could be evaluated. On the basis of their data, we would disagree with their conclusion that NT-proBNP is useful for diagnosing CHF across a wide range of renal functions.

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Please note: Professor Christopher P. Price is a former employee of Bayer Diagnostics Plc. The research cited in this letter was partly funded by Bayer Diagnostics Plc.

REFERENCES


REPLY

Lamb and colleagues attempt to compare the results of our study to their previously published (1) data, derived from a small cohort of nondyspneic subjects (the vast majority of whom did not have heart failure [HF]). These comparisons are uninformative, and the more appropriate approach would be to examine our data in the context of the currently available data examining the utility of B-type natriuretic peptide (BNP) in the breathless patient (with and without HF) (2).

In our study, the area under the receiver operating characteristic curve (AUC) for amino-terminal pro-B-type natriuretic peptide (NT-proBNP) for diagnosis of acute HF in those with moderate or worse chronic kidney disease (CKD) was 0.88, comparable to the data from such patients in the Breathing Not Properly Multinational Study renal analysis (AUC between 0.81 and 0.86) (2). It is of great interest to us that specificity for BNP in those with CKD was not reported (2); however, with such similar AUC, there is little chance that the specificity of BNP in those with CKD is any different than demonstrated for NT-proBNP in our study. We point out that the specificity of NT-proBNP >1200 pg/ml for acute HF in patients with CKD was 72%, comparing favorably to the overall specificity of 76% reported among all subjects in the Breathing Not Properly Multinational Study of BNP (3). As well, NT-proBNP <300 pg/ml had 100% negative predictive value in patients with CKD in our study, and concentrations of NT-proBNP were also strongly prognostic in those with CKD.

Thus, although correlations between renal function and BNP or NT-proBNP may differ, at optimal cut-points it would be rather hard to argue that a clinically meaningful difference between BNP and NT-proBNP exists in those with CKD, and the assertion by Lamb and colleagues that NT-proBNP has “unacceptable performance” in the patient with CKD is not accurate.

Lamb and colleagues quite incorrectly suggest that we asserted NT-proBNP testing to be “unaffected” by renal function. We emphasized the effects of renal function on NT-proBNP, but concluded “even in the presence of impaired renal function, NT-proBNP measurement is a valuable tool for the diagnostic and prognostic evaluation of dyspneic patients,” a conclusion supported by our data.

 Whereas observational studies demonstrate that CKD leads to elevations in both BNP and NT-proBNP (with modest differences with respect to the magnitude of elevation of each), it is dangerous to necessarily ascribe such phenomena entirely to differential dependence on renal clearance. Indeed, early mechanistic studies of renal function and natriuretic peptides suggest the kidneys clear both markers equally (and at only 20%) (4).

The interaction between natriuretic peptides and CKD is a complex one; we concede the potential for difficulties in interpretation of NT-proBNP concentrations in those with impaired kidney function, but we strenuously emphasize that this is a circumstance that also hinders use of BNP (5). In summary, the available data do not support a clinically meaningful difference between NT-proBNP and BNP in those with CKD, and the data contradict the tacit suggestion by Lamb and colleagues that BNP is superior to NT-proBNP in those with impaired renal function.

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