CARDIOVASCULAR participation in the regulation of salt and water balance occurs through at least two different physiologically reciprocal mechanisms, one to retain and one to lose salt and water. The first includes cardiac participation in well-described complex neural-vascular feedback loops involved in the regulation of renin-angiotensin secretion and sympathetic nervous system activity, recognized as critical components in the clinical pathophysiology of heart failure (3). The second mechanism, cardiac synthesis of vasoactive natriuretic peptides, has now captured the interest and imagination of clinical researchers. In the family of natriuretic peptides, the B-type natriuretic peptide (BNP) system offers relative stability and ease of assay and recently has become a favorite target for clinical investigators. Cardiac myocytes synthesize the 108 amino-acid parent peptide, proBNP, “on demand” with minimal, if any, intracellular storage. The proBNP is cleaved to produce two stable molecules, the physiologically active 32 amino-acid peptide BNP and inactive N-terminal pro-B-type natriuretic peptide (NT-proBNP). B-type natriuretic peptide is cleared from the circulation with a half-life of approximately 18 min, primarily by endothelial natriuretic peptide A-receptors; membrane-bound endopeptidase also plays a role in clearance (4–6). The NT-proBNP fragment is cleared primarily by the kidney. Its half-life in humans is not known, but in sheep, the half-life of NT-proBNP is substantially longer than that of BNP (6).

Because of differences in their metabolic fate, BNP and NT-proBNP levels are not necessarily clinically interchangeable. Widely available commercial assays have facilitated clinical studies of both the active moiety, BNP, and the inactive fragment, NT-proBNP. To date, clinical studies have clearly documented the utility of BNP levels in facilitating the diagnostic evaluation of patients complaining of acute dyspnea (7,8). Additional data also suggest that increased levels of BNP have prognostic importance in the setting of acute ischemic events (9–11). These studies have looked at two fundamentally different problems. The first involves the response of BNP to abnormal ventricular loading and acute diagnosis; the second involves the elevation of BNP associated with myocardial ischemia and long-term prognostic assessment.

In this issue of the Journal, Lindahl et al. (12) present a substantial addition to the existing data on the prognostic importance of NT-proBNP levels during and after non–ST-segment elevation acute coronary syndromes. They report observations in 1,352 of the 3,489 patients enrolled in the Fragmin and fast Revascularization during InStability in Coronary artery disease (FRISC-II) trial, a randomized trial of early invasive versus noninvasive management and three months subsequent treatment with dalteparin versus placebo. They measured NT-proBNP levels at randomization, which was a median of 38 h after onset of the most recent symptoms, then at 48 h, 6 weeks, 3 months, and 6 months after randomization. Initially, NT-proBNP levels were markedly elevated. A rapid early decline was followed by a prolonged slow decrease during the ensuing six months. At each time point, the subjects with elevated NT-proBNP levels had a greater risk of subsequent death, but “the absolute levels of NT-proBNP associated with a certain specificity are vastly different in stable and unstable phases.” For example, “an NT-proBNP level >264 ng/l at six months had the same specificity for subsequent death as a level above 722 ng/l at randomization.” In their discussion, the authors hypothesize that the acute phase NT-proBNP elevations reflected myocardial damage, perhaps associated with microembolization. In contrast, persistent elevation of NT-proBNP levels at three to six months after the acute event was associated with chronically impaired left ventricular function.

These data have important implications for both clinicians and investigators. We clinicians have another carefully performed clinical trial confirming the prognostic importance of elevated levels of BNP in the setting of acute coronary syndromes. Given the potential benefits of intervention for high-risk patients set against the risk and expense that accrue to low-risk individuals, honing our ability to discriminate these subsets of patients is increasingly important to cost-effective and evidence-based management. The well-documented observation that the absolute NT-proBNP level associated with a given risk falls with time (or, conversely, that the risk associated with a given BNP level rises with time) once again highlights the critical importance of interpreting laboratory data in clinical context. From a practical viewpoint, patients with persistently elevated NT-proBNP levels at three months after acute
coronary syndrome should undergo careful re-evaluation for interventions to reduce long-term risk. Unfortunately, the FRISC-II study data do not include information on the impact of angiotensin-converting enzyme inhibitors and beta-blockers on NT-proBNP in these subjects.

For investigators, these data raise a number of questions. As the authors point out, the substantial elevations of BNP levels associated with acute coronary syndromes cannot be explained by the mechanical stimulus of reduced global left ventricular function. The acute coronary syndrome must include a stimulus for de novo synthesis of the natriuretic peptides. Lindahl et al. (12) speculate that interleukin-6 may play a role in this process, but they offer no direct evidence to support this assertion. In fact, the signal transduction involved in regulating the physiologic and pathophysiologic production of the natriuretic peptides at the molecular level remains something of a mystery. Goetz (4) has recently reviewed BNP expression in ischemic heart disease. The available data suggest that multiple processes impact BNP levels, including both chronic hemodynamic loading and acute ischemia. (Fig. 1) These insights may help to explain a number of previously puzzling findings, including substantial rises in BNP levels after cardiac surgery.

Unraveling the physiology of the natriuretic peptides remains a challenge.

Certainly, we have more data and more tools than Harvey, and we live in a more complex world. However, it is unlikely that any of us are inherently brighter or more astute thinkers than he, or more articulate than his fellow Elizabethan Englishman, William Shakespeare. Looking at these data reinforce the importance of context, as Hamlet so succinctly told Rosencrantz and Guildenstern, “for there is nothing either good or bad but thinking makes it so” (The Tragedy of Hamlet, Prince of Denmark, Act II, Scene 2).

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