community organizations, and both professional and public education, the results have been, in general, disappointing.[8-12] Several studies have identified prehospital delays ranging from 150 to 420 minutes.[8-] Four studies (in Sweden, Switzerland, Australia, and Chicago) demonstrated mixed results, with little change in the use of emergency medical services (EMS) and relatively small changes in the time to treatment among patients with confirmed MI, despite an intensive community campaign.[8,11-13] A recent trial conducted in 20 US cities in 10 states showed an increase in the use of EMS but little change in prehospital delay.[7] The authors concluded that new strategies are needed to bring rapid and effective care to patients in the community who have acute MI.

A third issue relates to the entity of "clinically unrecognized MI," in which patients who have survived an MI escape detection until an electrocardiogram is performed subsequently, during a screening examination or for another clinical purpose. Past studies have suggested that 25% to 40% of MIs are clinically unrecognized.[14-18] It is somewhat disconcerting to note that in a recent study using the Cardiovascular Health Study database of individuals 65 and older, the majority of whom were free of cardiovascular disease at study entry, a previous MI was clinically unrecognized in 22.3% of patients.[15] Independent predictors of "silent" MI were an absence of both prior angina and prior congestive heart failure. Moreover, the subsequent survival of patients with and without clinically recognized MI was similar. The clinical implications are profound. There is a great deal we do not understand about symptoms and the pathophysiology of MI. Cost-effective screening mechanisms need to be identified, and the most effective method of risk stratification of such patients needs to be verified.

In "The Winter's Tale", William Shakespeare stated: "I have tremor cordis on me: my heart dances." What we have to realize is that the dancing heart beats to many different rhythms, and furthering our understanding of the symptomatology of the infarcting heart has enormous implications for management. There is much we still have to learn. ■

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Congestive Heart Failure

BNP as Treatment Marker

Reviewed by Gregg C. Fonarow, MD
UCLA Division of Cardiology, Los Angeles, CA
[*Rev Cardiovasc Med.* 2001;2(3):174–176]

For patients with heart failure, agents that confer survival benefits, such as angiotensin-converting enzyme (ACE) inhibitors, ß-adrenergic blockers, and aldosterone antagonists, target neurohormonal activation. In clinical trials, the dosing method for these therapies has been to titrate up to a target dose, unless it

was not tolerated. The relative benefits of prescribing diuretics at the lowest possible dose to relieve overt congestion or at higher doses to normalize ventricular filling pressures is still debated. Significant questions remain as to which medication dosages provide the greatest benefit and by what parameters heart failure therapy should be guided. Plasma neurohormonal levels are elevated in patients with heart failure and are independent markers of prognosis. Since neurohormonal levels are predictive and are impacted by the medical treatments for heart failure, medication dosing for patients with heart failure that is guided by neurohormonal levels has the potential to result in superior clinical outcomes, compared with conventional clinical guidance.

Atrial natriuretic peptide and brain natriuretic peptide (BNP) are cardiac hormones that are synthesized, stored, and released from atrial and ventricular tissue in response to increased pressure. This endogenous cardiac hormonal system appears to have a compensatory function in heart failure.[1] The hormones bind to specific receptors located on endothelial cells and vascular smooth-muscle cells, activating guanylate cyclase; this results in increased glomerular filtration, enhanced renal sodium excretion, peripheral vasodilation, and attenuation of the activation of the sympathetic and renin-angiotensin systems. Serum concentrations of BNP and aminoterminal (N)-BNP are related to left-ventricular filling pressures and wall stress. For patients with symptomatic heart failure, the degree of increase in these hormone concentrations correlates with the severity of the heart failure.[2] BNP concentrations fall after patients receive treatment with loop diuretics and ACE inhibitors, reflecting a reduction in left-ventricular filling pressure. Previous reports have shown that it may be possible to titrate heart failure medications to reduce BNP levels toward the normal range.[3] BNP levels thus represent an attractive target by which to guide heart failure therapy.

Treatment of Heart Failure Guided by Plasma Aminoterminal Brain Natriuretic Peptide (N-BNP) Concentrations

Troughton RW, Frampton CM, Yandle TG, et al.
Lancet. 2000;355:1126-1130.

Troughton and colleagues further investigated whether BNP levels could serve as targets for titration of heart failure therapy. In this study, 69 patients with symptomatic heart failure from systolic dysfunction were randomized to heart failure treatment guided by concentrations of N-BNP or by a total clinical score based on scores assigned to 10 signs or symptoms of heart failure (Framingham criteria). In patients in whom the treatment targets were not reached, medical therapy was intensified by following a stepwise protocol.

N-BNP guidance led to use of higher doses of ACE inhibitors and diuretics and greater utilization of spironolactone than did clinical guidance. During a mean follow-up of 9.5 months, total cardiovascular events (death, hospital admission, or heart failure decompensation) were fewer in the N-BNP–guided group than in the clinically guided group (19 vs 54, $P = .02$). At 6 months, a first cardiovascular event had occurred in 27% of patients in the BNP group and in 53% of the clinical group ($P = .034$). Changes in left-ventricular function, quality of life, renal function, and adverse events were similar in both groups studied.

This study represents a major advance in development of biologic markers to guide the treatment of patients with heart failure. Increased wall stress in heart failure triggers alteration of gene expression and apoptosis, increases intracellular calcium, promotes left-ventricular dilation, and stimulates cardiac sympathetic activity. As N-BNP is a marker of transmural pressure and wall stress, there is strong rationale for titrating therapy to normalize levels (Figure). Restoration of N-BNP concentrations to normal may be beneficial in itself by decreasing the stimuli for cardiac-hormone receptor down-regulation and coupling and by helping to restore the responsiveness to volume changes. Monitoring of N-BNP levels may allow the clinician a method to assess intracardiac filling pressures, without invasive catheterization. The ongoing Evaluation Study of Congestive Heart Failure and Pulmonary Catheterization Effectiveness (ESCAPE) trial, which will measure N-BNP levels and compare heart failure therapy guided by pulmonary artery catheterization or by clinical parameters alone, will provide additional insight. Although further confirmation is required, this study by Troughton and associates lays the groundwork for developing a routine strategy to tailor the medical management of heart failure to normalization of neurohumoral levels. ■

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