CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Using BNP to diagnose, manage, and treat heart failure

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ABSTRACT

A rapid assay for B-type natriuretic peptide (BNP) not only can be used to diagnose heart failure, it can help the clinician evaluate effectiveness of therapy, determine when discharge from the hospital is appropriate, and estimate prognosis. A synthetic formulation of BNP (nesiritide) is used to treat decompensated heart failure, resulting in improved hemodynamics and symptoms.

IN RECENT YEARS, we have gained two important new tools to diagnose and treat heart failure, both based on B-type natriuretic peptide (BNP), a protein produced by the ventricles of the heart:

- An assay for BNP can be used to diagnose heart failure, and can also be used to assess the effectiveness of therapy.
- An intravenous formulation of BNP (nesiritide) can be used to treat decompensated heart failure, improving abnormal hemodynamics and symptoms of heart failure.

THE BNP ASSAY: AN IMPORTANT NEW TEST

The BNP assay has become one of the most important blood tests in cardiology. It helps detect the presence of heart failure, determine its severity, and estimate prognosis.

The author has indicated that he is on the speakers' bureau of Scios, Inc.
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TABLE 1

BNP levels in health and disease

BNP LEVEL (PG/ML)	CLINICAL CONDITION
< 100	Normal
< 500	Goal at hospital discharge
≥ 700	Decompensated congested heart failure
≈ 3,000	During nesiritide infusion

One of four known natriuretic peptides (ANP, BNP, CNP, and DNP), BNP is released from the cardiac ventricles, especially the left ventricle, during pressure or volume overload. It has several physiologic actions:

- It dilates arteries and veins
- It acts as a beneficial neurohormonal modulator by decreasing levels of vasoconstricting and sodium-retaining neurohormones
- Along with atrial natriuretic peptide (ANP), it maintains homeostasis by promoting diuresis and natriuresis.

The BNP assay (Biosite, Inc, San Diego, Calif) is a point-of-care test that is rapid, inexpensive, and simple to perform. It requires a device about the size of the base of a telephone that costs about $4,500. Each test uses a $25 cartridge, requires a simple blood draw, and takes about 15 minutes to complete.

BNP as a diagnostic tool

BNP is secreted in increasing amounts as we age, with women secreting more than men. Normal levels are less than 100 pg/mL. The test has a negative predictive value of at least 96%, so heart failure can confidently be ruled out for patients in the normal range (TABLE 1).

The BNP assay is one of the most important blood tests in cardiology

In a recent survey,[1] emergency room doctors admitted to being unsure of the diagnosis of heart failure in 40% of encounters. The BNP assay can be especially useful in such a situation, where it can help physicians better distinguish dyspnea due to heart failure from dyspnea due to other causes.

To evaluate the assay's utility, Dao and colleagues[2] performed BNP assays on 250 patients who came to an emergency room for shortness of breath. Cardiologists reviewed each case afterwards to determine appropriate diagnosis and management. All involved physicians were blinded to the BNP assay results. Emergency room physicians made an incorrect diagnosis (using the cardiologists' diagnosis as standard) in 12% of the patients: half were diagnosed with heart failure but did not have it, and heart failure was missed in the others. Of the 30 incorrect diagnoses, 29 would likely have been correct had BNP measurements been available.

In a similar study in 1,586 patients,[3] Maisel et al reported similar findings.

Although the cutoff of the normal range for BNP is 100 pg/mL, many people who present to the emergency room with dyspnea due to heart failure will have BNP levels in the range of 1,000 pg/mL.

The sicker the patient, the higher the BNP levels

BNP to guide treatment decisions

Not only can BNP be used to diagnose heart failure, it can be used in a variety of ways, from the emergency room to the hospital bed to the clinic, to assess and manage therapy.

In the emergency room. At The Cleveland Clinic, cardiologists and emergency room physicians use BNP levels to streamline decision-making. If patients have BNP levels between 100 and 500 pg/mL, we treat them in the emergency department and observe them in the clinical decision unit for improvement. Many of these patients can be discharged home.

Patients with levels above 500 pg/mL also are treated in the clinical decision unit. However, many of them require hospital admission for additional therapies.

In the hospital or in the clinic. The sicker the heart failure patient, the higher the BNP levels. Thus, serial BNP assays can be useful in the cardiology clinic or in the hospital to monitor a patient's condition over time and adjust heart failure therapy accordingly. BNP levels can be used to determine the severity of heart failure when symptoms are either vague or excessive.

Just before hospital discharge. The BNP assay may have an important role at hospital discharge to gauge treatment success and help determine prognosis. We aim to halve the BNP level during hospitalization and bring it to at least below 500 pg/mL at discharge. Discharge levels above that indicate that the patient will probably be hospitalized again with decompensated heart failure in the near future. We sometimes keep a patient in the hospital, and forego discharge, on the basis of a BNP test: an extra day of therapy is less expensive than readmission.

Judgment essential: BNP assay less useful in renal failure, other conditions

The BNP assay has a positive predictive value of 90%. This is fairly high, but there are times when an elevated value does not prove useful. Levels must be assessed in the context of the clinical scenario:

- Patients in chronic heart failure have elevated levels but may be stable and not require immediate hospitalization. For instance, a patient waiting for a heart transplant might have a BNP level of 800 pg/mL despite maximal medical treatment.
- Patients in renal failure, on dialysis, or waiting for dialysis may have elevated levels whether or not heart failure is present. As a result, the BNP assay is not useful in renal failure patients.
- Patients with right-sided heart failure (due to pulmonary hypertension, cor pulmonale, or pulmonary emboli) also have elevated levels (usually 300 to 400 pg/mL).
- Infusion of nesiritide (synthetic BNP, see below) causes high levels (≈3,000 pg/mL), making the BNP assay irrelevant during the infusion.

SYNTHETIC BNP (NESIRITIDE): AN 'UP-FRONT' THERAPY FOR DECOMPENSATED HEART FAILURE

Nesiritide (Natrecor), a recombinant form of BNP, is an intravenous agent approved in the fall of 2001 to treat decompensated heart fail-

ure in the emergency room or hospital. It is indistinguishable from the naturally occurring hormone secreted by the cardiac ventricles.

How nesiritide works

Nesiritide's primary physiologic effect is vasodilation, both in the arteries and veins. It works by binding to specialized receptors on the surface of smooth muscle and endothelial cells; when the receptors are activated, the concentration of cyclic GMP increases, resulting in vasodilation.

Nesiritide promotes diuresis, by its hemodynamic effect both in the vasculature and on the kidneys.

Although nesiritide has no inotropic properties, it increases cardiac output via reflex vasodilation. And because it also has no electrophysiologic properties, it will not precipitate ventricular tachycardia or other arrhythmias.

Pharmacokinetics of nesiritide

Nesiritide has a rapid onset of action, with effects apparent within 15 minutes. Because it has a longer half-life (15 to 20 minutes) than other intravenous agents, there is no need to wean the patient from it—one can simply turn off the pump. Effects last from 2 to 4 hours afterwards.

Inactivation occurs in the vasculature, when the drug binds to a clearance receptor or is neutralized by endopeptidase. This is quite different from the inactivation of most other drugs, which require liver metabolism or renal clearance.

Efficacy of nesiritide

In a randomized, double-blind trial in 489 patients with decompensated congestive heart failure,[4] nesiritide lowered the pulmonary capillary wedge pressure more effectively than intravenous nitroglycerin and improved dyspnea faster than standard therapy.

Candidates for treatment

Nesiritide is indicated for patients with:

- Decompensated heart failure
- Fluid overload
- Dyspnea at rest or minimal activities
- Evidence of elevated filling pressures, eg, bulging neck veins.

TABLE 2

Blood pressure monitoring during nesiritide infusion

TIME FROM START	FREQUENCY OF MEASUREMENT
First hour	Every 15 minutes
Second hour	Every half hour
Third and fourth hour	Every hour
Fifth hour on	Every 4 hours

But nesiritide is not for everybody. It should be regarded as "up-front" care for decompensated heart failure, not as a last resort for cachectic, terminally ill patients who are ready for hospice. Contraindications include:

- Low cardiac output state (eg, "overdiuresed," "cold and dry")
- Hypotension (< 90 mm Hg systolic)
- Cardiogenic shock
- Low filling pressures.

In addition, nesiritide is contraindicated in other conditions in which vasodilating agents do not help: aortic stenosis, obstructive cardiomyopathy, restrictive cardiomyopathy, pericardial constriction, and cardiac tamponade. Clinical judgment is important in selecting proper candidates.

Expect patients to diurese vigorously on nesiritide

Administration of nesiritide

Nesiritide is given in a bolus followed by an infusion based on body weight. Most patients do not need to be in the intensive care unit and do not require a pulmonary artery catheter or an arterial line. Telemetry is needed, however, because heart failure patients are prone to develop cardiac arrhythmias.

Additional nursing staff is not necessary, but blood pressure needs to be monitored carefully, especially at first (TABLE 2). One should check fluids and electrolytes to avoid hypokalemia, hyponatremia, or azotemia: expect diuresis to be vigorous.

Nesiritide is not associated with tachyphylaxis and can in theory be given indefinitely. In our first 100 patients who received nesiritide, the drug was needed for an average of about 29 hours, enough to get patients on the road to recovery.

We typically measure BNP levels prior to hospital discharge to assess progress. It should not be assayed while a patient is receiving nesiritide because results will be high and will not reflect heart failure status.

Adjusting other medications

Baseline heart failure therapy must be augmented. An angiotensin-converting enzyme (ACE) inhibitor should be started, or if the patient is already on one, it should be increased to target levels. If at maximum dose already, one should add something else, such as a nitrate, hydralazine, or spironolactone.

Diuretics must be used with care with BNP infusion. We give diuretics normally for the first 2 days, then cut back on day 3 to avoid prerenal azotemia.

Beta-blocker therapy should be left unchanged. Beta-blockers should only be started when a person is euvolemic. They should be neither started nor discontinued when a patient has fluid overload and is decompensated.

Nesiritide is expensive, but worth it

Nesiritide is more expensive than standard agents, costing about $375 per day, but the additional cost is small compared to the savings of avoiding an extended hospital stay and time spent in the intensive care unit.

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