Highly Sensitive Troponin and other Cardiac Biomarkers

Use of Highly Sensitive Troponin and other Cardiac Biomarkers in Suspected Myocardial Infarction/Acute Coronary Syndromes and Heart Failure

by

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Diagnosing a classically presenting myocardial infarction(MI) or acute coronary syndrome(ACS) is relatively straightforward, but a dilemma for emergency department physicians and cardiologists has been how to avoid sending home an atypical MI/ACS. Patients may present with fatigue, shortness of breath, atypical chest pain or abdominal pain, and EKGs may be non-diagnostic in a non-ST segment elevation MI(NSTEMI), making a correct diagnosis difficult. In 2000 a study from ten U.S. emergency departments, and in 2006 one from all the hospitals in Ontario, Canada both reported exactly the same finding; that the missed MI rate in emergency departments averaged 2.1%.[1,2] According to the CDC there are an estimated 805,000 MIs per year in the U.S.[3] A 2.1% miss rate would mean almost 17,000 people in the U.S. who seek care in emergency departments would be mistakenly sent home with a missed MI, which is both an issue of patient morbidity, and a significant malpractice issue. In this article we will look at ways to decrease that MI miss rate, using highly sensitive troponins(also known as high sensitivity troponins), and rapid MI/ACS rule out protocols/algorithms. In addition, a more rapid MI/ACS rule in or out decreases length of stay, frees up beds, is better for patients, and can lead to cost savings.[4] We will also discuss troponin as a prognostic tool, new cardiac markers that may have some utility, and look at B-type natriuretic peptide (BNP); what can it tell you, and how accurate it is.

Troponin

In the past, cardiac markers such as LDH(lactate dehydrogenase), CKMB(creatine kinase-MB), and myoglobin were used to try to determine whether a chest pain patient had an MI/ACS.[5]

Those markers are no longer in use, either due to the length of time it took for the marker to rise, not being sensitive enough to pick up mild disease, or they lacked specificity for cardiac disease, with many false positives requiring more testing and admissions.[6] CKMB may still be in use in some centers, due to physicians still ordering it, but the American College of Cardiology guidelines recommend that it no longer be used.[7] The currently recommended cardiac marker is troponin, and more recently, highly sensitive troponins. Consensus guidelines from both the European Society of Cardiology and the American College of Cardiology state that cardiac troponin is the only biomarker recommended for the diagnosis of an acute MI, due to its superior sensitivity and accuracy.[8,9] Highly sensitive troponins also may be mildly elevated in myocardial ischemia without infarction, allowing identification of those patients.

Troponins are released after myocardial injury, no matter what the etiology. Higher troponin levels generally correlate with more cardiac myocyte injury. The reason troponin rises quickly after a cardiac injury is that 5–8% is free in the cardiac myocyte cytoplasm, which is called the early releasable troponin pool. Bound troponin releases more gradually over several days.[10] Troponin levels typically start to rise within two to three hours after the onset of chest pain, and typically peak 12 and 48 hours later. The troponin level will begin to fall over the next four to ten days to a normal level. This typical rise and fall of troponin can potentially distinguish a MI/ACS from other causes of elevated troponin.[11]

Troponins are found in skeletal and cardiac muscle cells, but not in smooth muscle cells. There are three subtypes: troponin I, troponin T, and troponin C. Skeletal and cardiac subunits of troponin C are identical, and the two types cannot be differentiated by standard laboratory testing, making troponin C measurement unhelpful in diagnosing MI/ACS. The skeletal and cardiac subunits for both troponin I and troponin T are different, and current serum immunoassays can measure solely the cardiac component.[12] Troponin T in muscle cells binds with calcium, freeing myosin binding sites on actin filaments which allow myosin and actin fibers to contract.[13,14] Troponin T binds to the myosin blocker tropomyosin, which opens up myosin binding sites on actin fibers. Troponin I inhibits the interaction of myosin with actin in conjunction with tropomyosin helping end muscle contraction.[14] Troponin I assays are available from a number of manufacturers and have different reference ranges. The troponin T test is sold only by one manufacturer in the U.S. Highly sensitive troponin testing has been used in Europe since 2010 and was introduced in the U.S. in 2017.[10]

Normal values for a high sensitivity troponin test are defined as anything below the 99th percentile of values found when testing at least 300 normal individuals. An abnormal troponin level is defined as a value above the 99th percentile.[15,16] As testing has improved, highly sensitive tests are able to detect troponin at concentrations that are lower than 50% of the level of the 99th percentile.[16] The term high sensitivity with respect to troponin refers to analytical sensitivity, not to clinical sensitivity. In the past troponin tests were less analytically sensitive, and almost any detectable troponin level was abnormal, while today highly sensitive troponin

assays can measure detectable troponin levels in many people without cardiac disease.[16] When a test is more clinically sensitive, it typically means that the test is less specific, with more false positives, and this is true of highly sensitive troponins.[12]

Another issue in setting normal and elevated troponin levels is that the troponin 99th percentile level in females is lower than in males, and it is recommended that different norms be used depending on gender. Typical normal levels of troponin T are ≤ 15ng/L in men, and ≤ 10ng/L in women.[17] If a blended male and female 99th percentile level is used to define a normal test, MI/ACS may be underdiagnosed in women, because some elevated troponin levels for them will then be considered normal. A blended male-female normal range may possibly also over diagnose MI/ACS in some men.[18] It should be noted that not all authorities agree that using separate values for men and women is the correct option.[19]

Non-ACS Causes of Troponin Elevation[20,21]

Myocardial ischemia or infarction are the most clinically relevant etiologies for a rise in serum troponin levels, but there are many other conditions that can also lead to an elevation in the serum troponin level, as listed below. Given the wide variety of causes of an elevated troponin level, clinicians should always consider the clinical situation before reflexively diagnosing MI or ACS in a patient.

Causes of Elevated Troponin

- Aortic valvular disease, aortic dissection
- Cardiac contusion, ablation, pacing, implantable cardioverter-defibrillator firings, cardioversion, endomyocardial biopsy, cardiac surgery
- Chemotherapeutic agents such as adriamycin, 5-fluorouracil, Herceptin
- Congestive heart failure
- Critically ill patients
- Drug overdose
- Dysrhythmias
- Strenuous exercise
- Heterophile antibodies
- Hypothyroidism
- Infiltrative diseases such as amyloidosis, hemochromatosis, sarcoidosis, and scleroderma
- Extensive skin burns
- Markedly elevated alkaline phosphatase levels
- Myocarditis, pericarditis, endocarditis
- Pulmonary embolism
- Renal Failure
- Sepsis
- Snake venom
- Stroke, subarachnoid hemorrhage
- Takotsubo cardiomyopathy, hypertrophic obstructive cardiomyopathy
- Transplant vasculopathy

Renal Failure

Troponin tends to rise in renal failure and presents a diagnostic challenge in the chest pain patient. Troponin elevations in renal failure patients may reflect subclinical myocardial injury, an inflammatory response to chronic renal failure, or a chronically volume overloaded state.[22] One study of 171 patients with renal insufficiency found almost all patients had at least one highly sensitive cardiac troponin T(hs-cTnT) measurement elevated above the 99th percentile. On average, hs−cTnT increased by 16% per year in renal failure patients. Lower baseline glomerular filtration rates resulted in higher hs−cTnT levels.[23] Some authors have suggested using adjusted troponin levels in renal failure patients might help accuracy.[24] A metanalysis of 13 studies using troponin to diagnose MI in renal failure patients found that the pooled sensitivity for hs-cTnT was only 94%, and the specificity was 56%. Serial troponin sampling seemed to improve diagnostic accuracy.[25] For unknown reasons, troponin I levels are less commonly elevated in renal failure compared to troponin T,[26,27,28] and troponin I may be a more sensitive cardiac marker for MI/ACS in this group of patients.[28]

Considering the issues of using troponin measurements in renal failure patients, the best strategy appears to be understanding that this group may have both a higher incidence of heart disease and also more false positive troponin results than people with normal renal function. Clinical presentation, combined with serial EKGs, observing for changing troponin levels over time, and use of additional diagnostic cardiac testing, may be required to confirm or rule out an MI/ACS diagnosis in a renal failure patient.

Rapid Rule out MI/ACS Algorithms

Chest pain is one of the most common chief complaints seen in the Emergency Department(ED). Visits for acute chest pain and possible acute coronary syndromes(ACS) amount for an estimated 6 million patient-visits per year. The estimated total cost to the U.S. economy for these events is as high as $10-$12 billion.[29] Rapid rule out MI/ACS algorithms decrease emergency department length of stay, which opens beds up for new patients, and by discharging patients who might have been admitted in the past reduces hospital admissions, which can lead to significant cost savings. A European study of a 1-hour MI/ACS rule out protocol compared to longer ones found that the1-hour protocol would reduce bed space hours by an average of 2.1 hours per patient resulting in a savings of approximately 50,000 days of emergency department bed space per year in the United Kingdom.[30]

Missed MI is the number one diagnosis in terms of dollars paid out in malpractice litigation, and the third most common claim in malpractice against emergency physicians.[31] The search for algorithms that allow more rapid diagnosis of patients who present to the ED with chest pain has to overcome the difficulty of determining which patients have an atypical MI/ACS presentation,

limitations of laboratory testing, and the lack of 100% sensitivity of EKGs for MI/ACS. As emergent cardiac catherization decisions in MI/ACS are made on the basis of either elevated ST segments on EKG consistent with an MI(STEMI), or a clinical condition such as cardiogenic shock in a non-ST segment elevation MI(NSTEMI), rapid rule out algorithms/protocols do not change that aspect of care and are used mainly to decide who can be safely discharged from the emergency department. Some of these algorithms in the past also added cardiac stress testing, echo stress testing, nuclear stress testing or CT coronary angiograms prior to discharge to further narrow down who had an ACS. Although there is some variance depending on the study, most rapid protocols using highly sensitive troponins have demonstrated negative predictive values(NPV) of MI/ACS of between 99 to 100%, which represents a major reduction in in the missed MI rate.[10]

European Society of Cardiology Algorithm[8]

The European Society of Cardiology(ESC), in its 2020 guidelines, recommends a hs-troponin drawn on arrival and 1 or 2 hours later, known as either a 0/1 or 0/2-hour algorithm, the choice of which is dependent on institutional comfort. They also have 0-hour and 0/3-hour pathways as offshoots of the basic algorithm. There are seven different troponin I assays, but only one troponin T assay used in Europe. Each test has different normal and elevated values, as well as different measures of what is considered an abnormal delta(Δ) or change between the first and second blood tests that would be considered positive for MI/ACS. In the ESC algorithm, these are the cutoff values they used for highly sensitive troponin T for the 0/1 and 0/2-hour algorithms:

	Very low	Low	No Δ(delta)	High	Δ positive
hs-cTnT in ng/L 0 h/1-h algorithm	<5	<12	<3	≥52	≥5
hs-cTnT in ng/L 0 h/2-h algorithm	<5	<14	<4	≥52	≥10

Low Risk

In a low-risk patient, if the EKG is stable, troponin is negative and remains unchanged on repeat testing, and the chest pain started three or more hours prior to arrival, then the patient may go home if clinically indicated. The ESC algorithm makes a further recommendation that if the arrival troponin is very low in a low-risk patient, and the EKG and other clinical factors are favorable, the patient may then be considered for discharge. If a low-risk patient arrives at the ED not having had three hours of prior chest pain, a 3-hour algorithm is recommended. Options

for the low-risk patient include sending them home for outpatient follow-up, or if felt to be necessary, doing additional cardiac stress testing or imaging prior to discharge depending on the clinical scenario.

According to their data review, low-risk patients have less than a 0.3% of having a missed MI, and less than a 0.5 % chance of having a 30-day major adverse cardiovascular event(MACE).

Intermediate Risk

For patients who have intermediate risk such as continuing pain, other clinical concerns or risk factors, non-diagnostic troponin testing, or do not clearly fit into a rule-in or rule out algorithm, a 3-hour algorithm is recommended along with echocardiography to try to identify other diagnoses that can cause chest pain before a discharge or admit decision is made. As late increases in cardiac troponin have been described in a small group of patients, continued serial cardiac troponin testing should be performed if clinical suspicion remains high, or if the patient develops recurrent chest pain. Stress cardiac imaging for the intermediate risk patient before discharge if hospitalized, or shortly after discharge if sent home may pick up additional positive ACS cases.

Intermediate risk patients put into the 0/3-hour algorithm plus echocardiography have about a 10% chance of having an MI, and a 15-20% chance of a 30-day MACE.

High Risk

Any patient not needing an acute cardiac catheterization lab intervention, who has an elevated troponin, NSTEMI(non-ST segment elevation myocardial infarction) EKG changes, a significant change in troponin values over time, or clinical factors that increase cardiac risk, is admitted to the hospital under this algorithm for further observation and diagnostic testing.

In the high-risk group in the ESC protocol, about 2/3s were found to have an MI.

Other Algorithm Studies

There are multiple studies that have tested a 0/1-hour MI/ACS rule out algorithm or compared a 0/1-hour to a 0/3-hour one or even longer protocols.[32,33,34,35,36] All these algorithms use both the absolute highly sensitive troponin value, as well as the delta, or change in value from the first to second blood draw. Repeat EKGs and reassessment of the patient's clinical situation are also important components. Many of the studies found the sensitivity of the 0/1 and 0/3-hour algorithms to rule out MI/ACS in emergency department patients was between 99.6% to 100%. Length of stay was also shown to decrease as the time frame of the algorithm decreased. 30-day survival for the 0/1-hour algorithm was 99.8% in one study,[36] and 99.6% in another that also included new onset MI within 30 days of discharge in that figure.[34]

Even with highly sensitive troponins and strict protocols there will be some missed MIs. However, the miss rate is approximately two in a thousand rather than two in a hundred as in the past, a ten-fold reduction.

Troponin as a Prognostic Tool

Studies have revealed that an elevated troponin T level at baseline on hospital arrival, was an independent predictor of mortality in ACS patients.

In the ARTEMIS study, which attempted to test the hypothesis that cardiac biomarkers might predict future cardiac events in diabetic patients, it was found that high levels of highly sensitive troponin T were an independent strong predictor of cardiac death or hospitalization for heart failure.[37] Data from GUSTO-IIa, a trial of antithrombotic agents in ACS, found that troponin T levels were significantly predictive of 30-day mortality.[38] In acute decompensated heart failure, an elevated troponin T level has been shown to correlate with both increased short and long-term mortality, and to a lesser extent hospital readmission rates.[39] Elevated cardiac troponins in renal failure patients who do not have an MI/ACS appears to have negative prognostic value with respect to 6-month mortality.[22]

Other Cardiac Markers

Myeloperoxidase(MPO) is an enzyme released by activated neutrophils, which has pro-oxidative and proinflammatory properties. It is abundant in ruptured arterial plaque, but neutrophil activation can occur in any infectious, inflammatory, or infiltrative process, so an elevated result may not be specific for cardiac disease.[40] However, elevated levels of MPO are associated with the presence of angiographically proven coronary atherosclerosis, and may identify patients with CAD who might otherwise not be identified.[40,41] High levels of MPO are associated with increased cardiovascular events and mortality.[42] However, an emergency department study did not find MPO useful as an MI/ACS screening tool.[43]

Ischemia modified albumin(IMA) is another acute marker of possible myocardial ischemia that is generated when serum circulating albumin is in contact with ischemic myocardium. Ischemia changes the albumin's configuration making it less able to bind metals like cobalt, which allows for differentiation from normal albumin.[44] IMA also rises in conditions without myocardial ischemia, such as: cerebral infarct, MI, pulmonary infarct, mesenteric infarct, skeletal muscle ischemia, cirrhosis, bacterial infections and certain cancers.[44,45,46] IMA has a high sensitivity for an ACS but low specificity. One study of hs-troponin and IMA found that use of an IMA level right after the onset of chest pain, before troponin has had a chance to rise, may be of help diagnostically. In that study IMA sensitivity for an ACS was 91.3%, specificity was 81.1%, positive predictive value (PPV) was 74.4%, and negative predictive value (NPV) was 93.9%.[47]

However, other authors feel that in the era of highly sensitive troponins, IMA adds little due to its low specificity.[48] In an acute setting, IMA may have some value in a patient where EKG and troponin levels are nondiagnostic, but it currently is not a routine part of MI/ACS rule out algorithms.[49,50].

Heart-type fatty acid-binding protein (H-FABP) is involved in the metabolism of fatty acids in cardiac myocytes, and has been investigated as a marker for the early diagnosis of acute MI/ACS,[51] as it is released early to the bloodstream within two to three hours after an MI.[52] In one study of emergency department patients, an arrival H-FABP level was 40% more sensitive than hs-troponin in ruling out an acute MI in patients with non-ischemic EKGs.[53] However, a metanalysis of studies comparing H-FABP to hs-troponin found H-FABP used alone or with hs-troponin did not improve diagnostic accuracy over use of hs-troponin alone for acute MI. The authors reported that the data did not support the routine use of H-FABP as an early risk stratification strategy for suspected MI.[54] H-FABP has not as of yet been approved for use in the U.S.

High sensitivity C-reactive protein (hsCRP) is a pattern recognition protein produced in the liver.[55] Pattern recognition proteins are capable of recognizing molecules found in pathogens or released by damaged cells.[56] There has been much literature with regard to the relationship between arteriosclerotic disease, inflammation and prognosis. Inflammatory cells are frequently activated in unstable angina and are especially abundant in coronary plaques where they can play a key role in plaque disruption and acute thrombosis.[57] With respect to levels of hsCRP and cardiac risk, <1 mg/L = low risk; 1–3 mg/L = intermediate risk; 3–10 mg/L = high risk. Over 10 mg/L is a nonspecific elevation and may be from an acute infection or inflammatory process.[55] There are a number of other inflammatory and infectious diseases that can also raise hsCRP. In the JUPITER trial of 17,802 subjects, an elevated CRP above 2.0 was associated with increased ischemic events, even in apparently healthy individuals. Rosuvastatin decreased the hsCRP level by 37%, and the incidence of death, stroke, MI, and unstable angina by 44% compared to placebo.[58] hsCRP appears not to be useful in acute care settings as a biomarker for AMI/ACS but is a fairly reliable prognostic and diagnostic tool to guide cardioprotective therapy in patients with hsCRP elevations.[59]

Brain natriuretic peptide (BNP)

In patients presenting with dyspnea, clinical diagnosis of whether that patient has heart failure or not may prove difficult. Clinical findings have variable specificities for heart failure; orthopnea (89%), edema (72%), elevated jugular venous pressure (70%), cardiomegaly (85%), added heart sounds (99%), lung crepitations (81%) and hepatomegaly (97%). However, the sensitivity of these features was low, ranging from 11% for additional heart sounds to 53% for peripheral edema. CXR was moderately specific at 76–83%, but insensitive at 67–68%.[60] In addition,

there is no clinical way to determine if diastolic heart failure(also called heart failure with preserved ejection fraction-HFpEF) is present.[61] Thus, the search for a marker that could be helpful in distinguishing heart failure from other causes of dyspnea led to the use of BNP. In one large study BNP was more accurate in diagnosing heart failure than any physical finding. [62,63]

Brain natriuretic peptide (BNP), originally discovered in brain tissue,[64] is a hormone secreted from cardiac myocytes in response to stretching of its fibers due to volume overload, and plasma levels increase in both systolic(heart failure with reduced ejection fraction-HFrEF), and diastolic heart failure(heart failure with preserved ejection fraction-HFpEF). Small amounts of a precursor protein, pro-BNP, are continuously produced by the heart. Pro-BNP is then split by an enzyme into active hormone BNP and an inactive fragment, amino-terminal pro-BNP(NT-proBNP). Both BNP and NT-proBNP testing are used to measure heart failure but have differing positive and negative cutoff ranges. Levels tend to increase with age, renal disease, and women tend to have higher levels than men. Levels may be lower in obese patients. Pulmonary embolism, pulmonary hypertension, and chronic hypoxia may also raise BNP levels.[61]

A literature review found that studies using recommended cutoff points for BNP in emergency department patients had pooled sensitivities of 86 to 100% and specificities of 31 to 97%. For NT-proBNP, sensitivity and specificity for heart failure was found to be 91% and 67% respectively.[65] A systematic review of the use of BNP and NT-proBNP in the primary care patient setting found the pooled sensitivity of BNP was 82% and the specificity was 64%. For NT-proBNP, the pooled sensitivity was 88% and the pooled specificity was 58%.[66] There was no significant advantage of using one test over the other. The authors of both studies concluded that both BNP and NT-proBNP are useful diagnostic tools to identify patients with heart failure. However, the tests have better utility to rule out heart failure than to diagnose it.[65,67]

Sensitivities of BNP or NT-proBNP vary with the serum level. In one study of acute dyspnea in the emergency department, if the BNP was below 100pg/ml there was an 89% negative predictive value to exclude heart failure. If the level was less than 50pg/ml the negative predictive value was 96%.[68] Typically between 100 and 400 pg/ml is considered a grey area.[65] If the level was > 400pg/ml there is an estimated 63% sensitivity to diagnose heart failure according to one source.[69]

There are also issues with age differences and normal values. In one study NT-proBNP was 100% sensitive in diagnosing ejection fractions below 40% in men 45 to 64 years of age, and women 55 to 74 years old. Sensitivity dropped with age and was 91% in men aged 65-74, 89% in men over 75 years, and only 75% in women over 75 years.[70] In another study of emergency department patients, age differential cutoff points of NT-proBNP were suggested. They found an NT-proBNP at cutpoints of >450 pg/ml for patients <50 years of age and >900 pg/ml for patients ≥50 years of age were highly sensitive and specific for the diagnosis of acute heart failure with sensitivities of 93% and 91% and specificities of 95% and 80% respectively. A NT-proBNP level

of <300 pg/ml in that study had a negative predictive value of 99% for heart failure.[71] Use of age adjusted NT-proBNP values is now the norm in most labs.[72]

Reference values of BNP and NT-proBNP recommended for use in renal failure patients were found to be inconsistent in one literature review, and their use in these patients to diagnose heart failure is problematic.[65] However, low BNP levels in renal insufficiency may help exclude heart failure.[67]

Use of BNP testing may help decrease length of stay and hospital costs by allowing a more rapid diagnosis of the cause of the dyspnea. A Swiss emergency department study of dyspnea patients, comparing BNP testing versus a control group, found the length of stay was 3 days shorter in the BNP group(8 vs 11 days) and the cost of care was $1,854 less in the BNP group than the controls($5,410 vs. $7,264). The BNP test was most helpful when a low value made heart failure unlikely and other potential causes of dyspnea were searched for.[62]

There are many studies in the literature that have found that elevated BNP levels are associated with an increased risk of death or cardiovascular events. One pooled review of five studies showed that each BNP increase of 100 pg/mL resulted in a 35% increase in the risk of death.[73] An emergency department study found that BNP levels drawn at admission were highly predictive of 1-year mortality with median BNP values of 3,277 pg/ml in those that died vs. 299 pg/mL in survivors.[74]

BNP and NT-proBNP are far from perfect tests, but when very high or low, may assist the clinician in ruling in or ruling out heart failure in a patient with dyspnea. However, one must keep in mind there will be a significant number of false positives and negatives. Its use in renal failure is problematic. It can be used for long term follow-up of heart failure patients and has some value as a prognostic tool.

Conclusion

The arrival of highly sensitive troponins has revolutionized cardiac care in emergency departments, allowing 0/3-hour, 0/1-hour, or even 0-hour MI/ACS rule out algorithms to safely decrease the missed MI rate. While troponin levels can be used as a prognostic tool, the greatest benefit of the highly sensitive troponins is to allow more accurate and rapid admit or discharge decisions of chest pain patients seen in the emergency department. Given that emergent cardiac catherization in MI/ACS has been found beneficial only in patients with STEMIs, and in NSTEMI patients in cardiogenic shock, the newer highly sensitive troponins haven't affected the immediate care of MI/ACS patients, other than to identify them more quickly, admit them more expeditiously, and not send them home in error. Unfortunately, the MI/ACS rule-out testing algorithms are not perfect, and while significantly improved at about a 10-fold improvement, a small number of missed MIs will still be sent home. However, if institutionally approved validated algorithms are scrupulously followed, malpractice risk may be mitigated.[75] These rapid algorithms can free up beds, and potentially reduce costs. The wide variety of conditions

that can cause increased troponin levels means that clinicians still need to consider the whole clinical picture, and not just rely on a positive lab test to automatically mean that the etiology is an MI/ACS.

Other cardiac markers such as hsCRP and MPO appear to be useful as prognostic tools for cardiovascular disease. Acute phase MI/ACS markers such as HT-FAPB and IMA do not appear to add much to a hs-troponin only strategy in an AMI/ACS algorithm.

BNP and NT-proBNP tests are most accurate in ruling out heart failure in a patient with dyspnea, due to the relatively high negative predictive value of the tests. If values are very high they have utility in diagnosing heart failure. These tests may be helpful in diagnosing subtle presentations of heart failure, including both heart failure with reduced ejection fraction, and heart failure with preserved ejection fraction, and do have prognostic significance. In the outpatient setting they may be used to follow how heart failure treatment is progressing.

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