What's New in Cardiac Testing?

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Susan's concern

Susan, 55, comes to you concerned about her risk of a cardiovascular event. Her father died of a sudden heart attack at 60. She travels a lot in her work, and she does not have an active lifestyle. She has no history of hypertension or diabetes, and she is a non-smoker. She is not taking hormone replacement therapy, nor any other medications. Blood work includes:

- Total cholesterol: 5.3 mmol/L
- High-density lipoprotein (HDL): 0.9 mmol/L
- High sensitivity C-reactive protein (CRP): 3.5

What is her estimated 10-year risk of coronary artery disease using the Framingham Data and the (CRP) measurement?

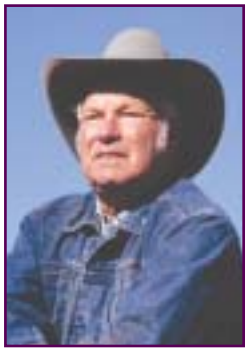
What are the treatment goals for this patient?

With a new estimated risk, are the treatment goals any different?

For a followup on Susan, go to page 62.

Although there have been impressive gains in improving morbidity and mortality once a cardiovascular event has occurred, we are still lagging in primary prevention of acute coronary syndromes. Cardiac risk factors fail to predict the development of coronary artery disease (CAD) in many cases (25% to 50%).[1] For example, more than one-third of the patients presenting with myocardial infarction (MI) have total cholesterol levels in the normal range.[2]

Harold's case



Harold, 72, presents with increasing shortness of breath over the last 2 days. His history is significant for multiple admissions for chronic obstructive pulmonary disease (COPD) exacerbations, necessitating intravenous steroids, antibiotics, and salbumatol (as needed). He also had a coronary bypass surgery 8 years ago, and has a known systolic dysfunction, with the most recent echocardiogram showing an ejection fraction of 40%. His exam shows:

- Tachypneia: heart rate 102 beats/minute
- Blood pressure: 154/80 mmHg
- Oxygen saturation: 88% on room air
- B-type natriuretic peptide (BNP): 678 pg/mL

His jugular venous pressure is 4 cm above sternal angle, diffuse crackles at lower bases, with mild wheezes throughout the lung fields. You cannot hear any extra heart sounds. Electrocardiogram (ECG) shows left-bundle branch block which was present before; chest X-ray is consistent with hyperinflated lungs, cardiomegaly, some hilar predominance, and evidence of congestive heart failure (CHF). Cardiac enzymes are negative 8 hours apart, and his creatinine is within normal range.

What is the cause of his dyspnea?

How helpful are clinical signs and symptoms in diagnosing CHF?

What is BNP?

How can one use BNP in the assessment of acute dyspnea on presentation?

What's the appropriate therapy for this patient?

For a followup on Harold, go to page 62.

A followup on Susan

Using the Framingham Data*, Susan has a 15% chance of a cardiac event within the next 10 years; this puts her at moderate risk for an event. Current therapy would dictate that she be placed on acetylsalicylic acid and a statin, with a goal of low-density lipoprotein (LDL) cholesterol < 4, and a total cholesterol (TC):HDL ratio < 5. When one also considers the additional prognostic information of hs-CRP of 3.5, her 10-year risk is now roughly 30%, placing her in the "very high" risk group. Her treatment goals are more aggressive with LDL < 2.5 and TC:HDL ratio < 4.

This case illustrates how the additional value of CRP moved this patient from moderate risk to very high risk, a phenomenon that should surely affect target blood pressure and lipid control, as well as aggressive behavioural modification.

*Grundy SM, Pasternak R, Greenland P, et al: Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations. Circulation 1999; 100(8):1481-92.

What happend to Harold?

Harold's presentation can be consistent with CHF, COPD exacerbation, or both. The clinical symptoms and signs, including ECG and chest X-ray, do not sway us one way or the other. Harold definitely has the substrate for CHF with cardiomegaly, and previous bypass surgery. However, he also has documented COPD, and his presentation could be consistent with an exacerbation.

The only factor that could account for high BNP on presentation would be his baseline left ventricular dysfunction; however, a value of 678 pg/mL is high enough to suggest diagnosis of CHF, irrespective of other factors during this admission.

While hyperlipidemia, hypertension, and diabetes, as well as the behavioural risk factors of smoking and diet, remain major critical modifiable risk factors for vascular disease, our understanding of cardiovascular risk has evolved to include thrombotic markers, such as lipoprotein(a), D-dimer, and homocysteine; inflammatory markers, such as C-reactive protein (CRP), fibrinogen, and interleukin-6; and genetic markers.

The buzz words for atherosclerosis risk factor identification are "inflammatory markers". Most of these markers are currently still research tools, and do not fulfill the criteria for achieving clinical utility. Such criteria include consistency of prospective data, strength and magnitude of association, a standardized measure with low variability, high reproducibility, biologic plausibility, and low cost. CRP is a marker that meets such criteria, and has the analyte and assay characteristics most conducive to use in practice.

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What about CRP?

Although CRP is a non-specific marker of systemic inflammation, it activates the endothelium, and accumulates in the plaque, suggesting an important role in inflammation. CRP has been shown in several prospective, nested case-control studies to be associated with an increased risk of MI,[3,4,5] stroke,[6] sudden death from cardiac causes,[7] and peripheral arterial disease.[8] The high-sensitivity CRP (hs-CRP) has shown the strongest independent predictor of cardiovascular events. From the above trials, there is a dose-response relationship between the level of hs-CRP and risk of incident CAD. Through stratification or multivariable statistical adjustment, hs-CRP retains an independent association with incident coronary events after adjustment for age, total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking, body mass index, diabetes, history of hypertension, exercise level, and family history of CAD.[9] When combined with the triglycerides and HDL ratio, hs-CRP were significantly better at predicting risk than lipids alone.[10]

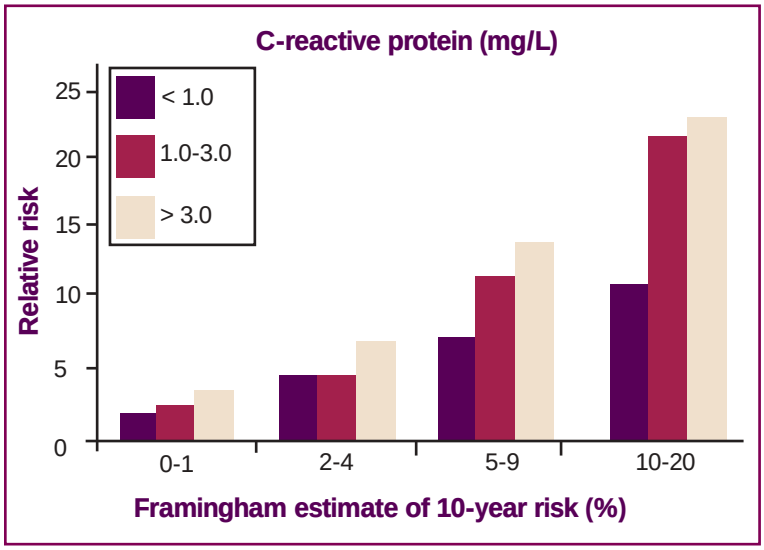

Figure 1. CRP adds prognostic information at all levels of the Framingham risk score, most notably in those with intermediate risk (> 10%).

According to the American Heart Association (AHA) guidelines,[11] measurement of hs-CRP has a class IIa recommendation for use in a clinical setting for the purpose of an independent marker of risk in those judged at intermediate risk by global risk assessment (10% to 20% risk for congestive heart disease for 10 years). It is noteworthy that this is not a class I recommendation, as CRP-lowering therapy has had equivocal results on risk and remains to be studied.

Perhaps the most important limitation is inflammatory states which tend to raise the CRP above 10 mg/L (Table 1). Therefore, it is prudent to consider the patient and not just the CRP for risk stratification.

An hs-CRP above the level of 3.0 mg/L elevates the risk of patients with intermediate risk factors (Figure 1).[12] This magnitude in the elevation of risk is not seen in patients whose 10-year risk of CAD is below 10%.

The AHA consensus statement classified hs-CRP measurements to identify differential risk assignment. It is recommended to repeat the hs-CRP measurements after three weeks if the value is above 10 mg/L.

In conclusion, hs-CRP will certainly be included in our future guidelines of risk

Table 1
Causes of increased and decreased hs-CRP

Increased levels of hs-CRP	Decreased levels of hs-CRP
• Cigarette smoking • Elevated BP • Elevated BMI • Diabetes/metabolic syndrome • Low HDL/high LDL • HRT use • Chronic inflammatory states (infections, connective tissue disorders)	• Moderate alcohol consumption • Increased activity • Weight loss • Medications -Statins -Fibrates -Niacin

hs-CRP: High-sensitivity C-reactive protein
BMI: Body mass index
LDL: Low-density lipoprotein
BP: Blood pressure
HDL: High-density lipoprotein
HRT: Hormone replacement therapy

Table 2
Factors accounting for high BNP levels in patients with dyspnea

- Age > 75
- Renal failure
- Creatinine clearance < 60 mL/min/1.73m^2
- Acute coronary syndrome
- Lung disease with right-sided failure
- Acute pulmonary embolism
- Sepsis
- Baseline left ventricular dysfunction

BNP: B-type natriuretic peptide

stratifications. There are still many unanswered questions, such as the role of CRP in low-risk patients, their role during an acute coronary syndrome, as well as their nature as a marker versus a mediator of atherosclerosis.

The acutely ill patient with dyspnea in the setting of the emergency department (ED) is a diagnostic challenge. A wrong diagnosis could lead to incorrect treatment, and could significantly jeopardize the patient. Unfortunately, it is not always possible to distinguish between congestive heart failure (CHF) and noncardiac causes of dyspnea. A helpful history is often not obtainable in the acutely ill patient, and dyspnea can be nonspecific. Physical signs, such as elevated jugular venous pressure, a third heart sound, pulmonary crackles, and edema are often absent in patients with CHF, and their sensitivity and specificity range from 20% to 99%.[13] Routine laboratory tests, electrocardiograms, and X-rays are also not accurate enough to always make the appropriate diagnosis.

What about the B-type natriuretic peptide (BNP)?

Initially isolated from the brain, BNP is secreted primarily from ventricular myocardium in response to abnormal intraluminal pressure and stretching of the myocardial wall due to heart failure. This fact suggests that BNP may be a "distress hormone", being released in ventricular overload syndromes.[14] BNP is stable in whole blood, and a portable 15-minute assay with an analytical range of 5 pg/mL to 5,000 pg/mL, and a coefficient variation of approximately 15%.[15] Roughly 10 years ago, Davis et al. noticed that admission plasma BNP concentrations more accurately reflected the final diagnosis of CHF than ejection fraction levels.[16] Within the last decade, this finding has been confirmed not only in systolic dysfunction, but also in a subset of patients with dias-

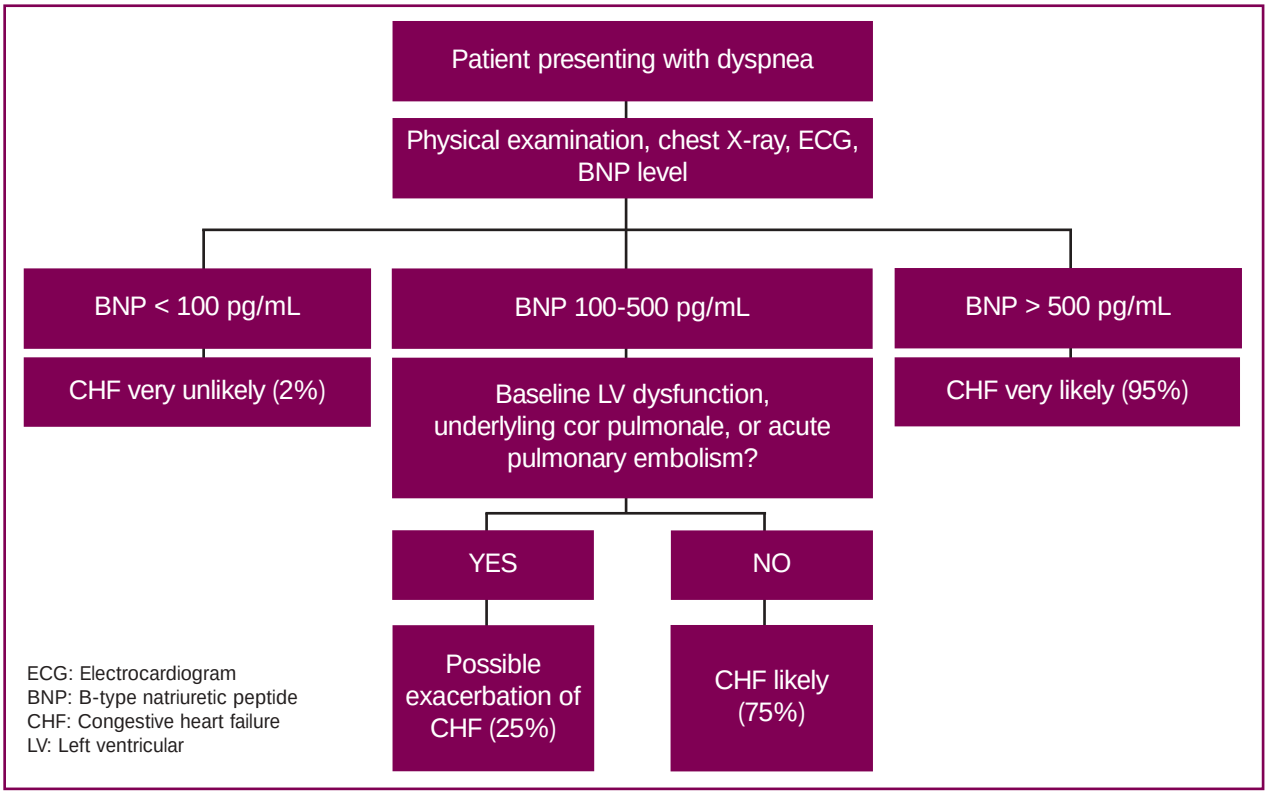

Figure 2. Approach to patients with dyspnea using BNP.

tolic dysfunction with concomitant pulmonary disease.[17]

In a landmark prospective study of 1,586 patients who came to the ED with acute dyspnea, BNP levels by themselves were more accurate than any historical or physical findings or laboratory values in identifying CHF as the cause of dyspnea.[18] The diagnostic accuracy of BNP at a cutoff of 100 pg/mL was 83%. Measurements of BNP added significant independent predictive power to other clinical variables in models predicting which patients had CHF. Patients with a diagnosis of acute CHF had a mean BNP of 675±450 pg/mL, whereas those without CHF had BNP of 110±225 pg/mL.

Clinical judgment needs to be used in older patients, patients with pulmonary disease, and those with baseline left ventricular dysfunction. However, if all the features mentioned in Table 2 can be ruled out, it is highly likely that BNP levels between 100 pg/mL and 500 pg/mL represent CHF. There is currently

ongoing research for the use of BNP in monitoring patients for CHF, and as a prognosticator of death and hospitalizations in patients with CHF, right ventricular infarctions, acute MI, and pulmonary embolus.

In an attempt to put the entire picture together, Figure 2 illustrates an algorithm adopted by the San Diego Veteran's Affairs Healthcare System. After a baseline assessment and consideration of underlying right ventricular dysfunction, one can interpret BNP levels. Essentially, any measurement above 500 clenches the diagnosis of CHF, irrespective of other pathology.

The general practitioner's role at this time is to keep abreast with the new developments in biochemical markers. These markers will likely be making their way into our hospitals within the next two years. CRP is an example of a marker that all primary care physicians could use for outpatients, but CRP use at this time is still premature until further guidance and availability. BNP is an example of a very useful marker that could be readily used in the ED and could be a very helpful diagnostic tool in CHF. It is still not readily available, but should make its mark in the very near future. CME

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References
1. Magnus P, Beaglehole R: The real contribution of the major risk factors to the coronary epidemic: Time to end the "only 50%" myth. Arch Intern Med 2001; 161(22):2657-60.
2. Castelli WP: Lipids, risk factors and ischaemic heart disease. Atherosclerosis 1996; 124(Suppl):S1-9.
3. Ridker PM, Cushman M, Stampfer MJ, et al: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336(14):973-9. [Erratum, N Engl J Med 1997;337:356.]
4. Tracy RP, Lemaitre RN, Psaty BM, et al: Relationship of C-reactive protein to risk of cardiovascular disease in the elderly: Results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol 1997; 17(6):1121-7.
5. Koenig W, Sund M, Froelich M, et al: C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: Results from the MONICA Augsburg Cohort Study, 1984 to 1992. Circulation 1999; 99(2):237-42.
6. Rost NS, Wolf PA, Kase CS, et al: Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: The Framingham Study. Stroke 2001; 32(11):2575-9.
7. Albert CM, Ma J, Rifai N, et al: Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. Circulation 2002; 105(13):2595-9.
8. Ridker PM, Stampfer MJ, Rifai N: Novel risk factors for systemic atherosclerosis: A comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001; 285(19):2481-5.
9. Ridker PM: High sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103(13):1813-8.
10. Ridker PM, Hennekens CH, Buring JE, et al: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342(12):836-43.
11. Pearson TA et al, Markers of inflammation and cardiovascular disease. AHA/CDC Scientific Statement. Circulation 2003; 107(15):499-511.
12. Ridker PM, Rifai N, Rose L, et al: Comparison of C-reactive protein and low-density lipoprotein Cholesterol Levels in the prediction of first Cardiovascular Events. N Engl J Med 2002; 347(20):1557-65.
13. McCullough PA, Philbin EF, Spertus JA, et al: Opportunities for improvement in the diagnosis and treatment of heart failure. Clin Cardio 2003;26(5):231-7.
14. Luchner A, Stevens TL, Borgeson DD, et al: Differential atrial and ventricular expression of myocardial BNP during evolution of heart failure. Am J Physiol 1998; 274(5 Pt 2):H1684-9.
15. Triage BNP TEST (package insert). San Diego, CA: Biosite Incorporated; 2002.
16. Davis M, Espiner E, Richards G, et al: Plasma brain natriuretic peptide in assessment of acute dyspnea. Lancet 1994; 343(8895):440-4.
17. Krishnaswamy P, Lubien E, Clopton P, et al: Utility of B-natriuretic peptide (BNP) in elucidating left ventricular dysfunction (systolic and diastolic) in patients with and without symptoms of congestive heart failure at a veteran's hospital. Am J Med 2001; 111(4):274-9.
18. Maisel AS, Krishnaswamy P, Nowak RM, et al: Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347(3):161-7.