Published in final edited form as:

Anesth Analg. 2010 November ; 111(5): 1086–1087. doi:10.1213/ANE.0b013e3181f4db4c.

Do We Really Need Another Biomarker to Diagnose Myocardial Infarction After Coronary Artery Bypass Graft Surgery?

Jeffrey J. Rade, MD and Charles W. Hogue Jr., MD

Johns Hopkins Medical Institutions, The Johns Hopkins Hospital, Baltimore, Maryland

It is estimated that approximately 1.25 million people will suffer a new or recurrent myocardial infarction (MI) in the United States this year.¹ Myocardial necrosis begins within minutes of coronary artery occlusion and progresses rapidly. As a result, prompt diagnosis of MI is essential to facilitate myocardial reperfusion within the 4-to 6-hour window for maximal myocardial salvage.² Unfortunately, as many as 25% of MIs go unrecognized because of the lack of classic symptoms, and 10%–20% of acutely occluded arteries do not produce diagnostic ST segment elevation on the surface electrocardiogram (ECG).^{3,4} Because of this clinical uncertainty, the diagnosis of MI is often made or excluded on the basis of elevated cardiac biomarkers.

Cardiac-specific troponin I (cTnI) and troponin T have become the “gold standards” for the diagnosis of MI because of their high sensitivities and specificities in comparison with other biomarkers for myocardial injury such as creatinine kinase-MB (CK-MB) isoenzyme and myoglobin.⁵ The current cutoff for the diagnosis of MI is set as the 99th percentile of that observed in a healthy population.⁶ Although this low cutoff increases the sensitivity of the troponin assays for the detection of MI, it necessarily reduces their specificity, because small troponin elevations are frequently observed in cardiac conditions not primarily associated with ischemia, such as myocarditis, valvular heart disease, and heart failure. Small troponin elevations are also observed in several noncardiac conditions, including sepsis, cerebrovascular accident, burns, and renal failure.⁵ Diagnosing an MI requires interpreting elevations in cardiac biomarkers within the specific clinical context.

Postoperative cardiac complications are an important source of mortality associated with coronary artery bypass graft (CABG) surgery.⁷ Clinicians need to immediately diagnose a postoperative MI to attenuate myocardial injury and improve outcome. Unfortunately, many of the typical signs and symptoms of MI are obscured in patients after CABG. Diagnosis is further complicated by the fact that serum biomarkers, especially troponins, are routinely elevated in the postoperative period, even in patients destined for an otherwise uneventful recovery.⁸ Elevations in postoperative troponin levels are considered primary evidence of postoperative MI due to graft failure or native coronary artery occlusion. However, postoperative troponin levels are also elevated by preoperative myocardial injury, myocardial ischemia during aortic cross-clamping, or incomplete myocardial revascularization. The challenge in accurately identifying postoperative MI is highlighted in a prospective study by

Address correspondence to Charles W. Hogue, Jr., MD, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Medical Institutions, The Johns Hopkins Hospital, Baltimore, MD 21287. chogue@anesthesia-analgesia.org.

Alter et al., who followed 1000 patients after CABG surgery and performed coronary angiography on all patients with elevated CK-MB isoenzyme (>35 U/L measured 6 hours after surgery), ischemic ST segment changes on ECG, or both.⁹ Of the 40 patients with suspected MI, only 13 (33%) had occlusion of a graft or native vessel. The other 27 patients had no evidence for coronary perfusion insufficiency.

In this issue of *Anesthesia & Analgesia*, Muehlschlegel et al. compare the performance of heart-type fatty acid-binding protein (hFABP) to traditional cardiac biomarkers in predicting adverse outcome after CABG surgery.¹⁰ hFABP is a small (15 kDa) fatty acid transporter protein located in abundance in the cytosol of tissues with active fatty acid metabolism, such as the heart and kidney.¹¹ The kinetics of hFABP tissue release resemble those of myoglobin with appearance in the blood within 1 to 3 hours after the onset of myocardial ischemia followed by rapid clearance in those with normal kidney function.¹² Even though hFABP is present in skeletal muscle, kidney, and brain, its relatively high concentration in the heart permits the diagnosis of MI with approximately the same specificity as CK-MB.¹¹

The study cohort included 1298 patients undergoing primary CABG with cardiopulmonary bypass (CPB) who were enrolled in a parent study evaluating the use of genetic markers to predict outcome after CABG surgery. In a prior analysis of the same study population, Muehlschlegel et al. found that an elevated cTnI on postoperative day 1, but not an elevated CK-MB or perioperative ECG changes, predicted adverse clinical outcome with a 1.4-fold ($P < 0.01$) increased risk of death at 5 years.¹³ The present study compared the ability of hFABP with that of cTnI, CK-MB, and myoglobin in predicting 5-year mortality, length of hospital stay, and ventricular dysfunction (defined as clinical use of ≥ 2 inotropes or need for mechanical ventricular support postoperatively). The authors found that median hFABP levels in the study cohort were highest at the end of CPB in contrast to median levels of other markers that peaked on postoperative day 1. Most strikingly, in the 10% of subjects with hFABP values on postoperative day 2 that exceeded values measured at the end of CPB, the risk of death at 5 years was 11-fold ($P < 0.0001$) higher than for subjects whose hFABP levels declined after surgery. By multivariate modeling, levels of hFABP measured on postoperative day 1 were independent predictors of not only 5-year mortality ($P < 0.0001$) but also of hospital length of stay ($P = 0.0004$) and postoperative ventricular dysfunction ($P < 0.0001$). By comparative analysis, hFABP was superior to cTnI and other biomarkers when added to multivariate models predicting 5-year mortality and hospital length of stay.

By virtue of its early peak and rapid decay, hFABP may be superior to cTnI and other cardiac biomarkers in aiding the identification of patients at risk for adverse outcome after CABG surgery. But how does the measurement of cardiac biomarkers after CABG surgery alter the management of patients? For most patients, even those with elevated levels, it can be argued that the measurement of cardiac biomarkers is probably of little benefit, because postoperative cardiac patients are already receiving appropriate maximal therapy for secondary prevention of cardiac events. The notable exception is in patients with suspected postoperative MI due to acute occlusion of a graft or native vessel, for whom timely secondary percutaneous or surgical revascularization could substantially improve outcome. Given the clinical uncertainty in diagnosing this condition after CABG surgery, a cardiac

biomarker that rapidly and reliably indicates significant coronary ischemia could have substantial utility. The rapid time course of hFABP suggests that it may be uniquely capable of rapidly identifying postoperative patients with acute occlusion of a graft or native vessel. The final verdict awaits future angiography studies that directly correlate abnormal postoperative increases in hFABP levels with loss of graft and coronary artery patency.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Executive summary: heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010; 121:948–54. [PubMed: 20177011]
2. Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? *JAMA*. 2005; 293:979–86. [PubMed: 15728169]
3. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. *N Engl J Med*. 1984; 311:1144–7. [PubMed: 6482932]
4. Krishnaswamy A, Lincoff AM, Menon V. Magnitude and consequences of missing the acute infarct-related circumflex artery. *Am Heart J*. 2009; 158:706–12. [PubMed: 19853686]
5. Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. *J Am Coll Cardiol*. 2006; 48:1–11. [PubMed: 16814641]
6. Apple FS, Wu AH, Mair J, Ravkilde J, Panteghini M, Tate J, Pagani F, Christenson RH, Mockel M, Danne O, Jaffe AS. Future biomarkers for detection of ischemia and risk stratification in acute coronary syndrome. *Clin Chem*. 2005; 51:810–24. [PubMed: 15774573]
7. Hogue CW Jr, Sundt T III, Barzilai B, Schecthman KB, Davila-Roman VG. Cardiac and neurologic complications identify risks for mortality for both men and women undergoing coronary artery bypass graft surgery. *Anesthesiology*. 2001; 95:1074–8. [PubMed: 11684973]
8. Stearns JD, Davila-Roman VG, Barzilai B, Thompson RE, Grogan KL, Thomas B, Hogue CW Jr. Prognostic value of troponin I levels for predicting adverse cardiovascular outcomes in postmenopausal women undergoing cardiac surgery. *Anesth Analg*. 2009; 108:719–26. [PubMed: 19224775]
9. Alter P, Vogt S, Herzum M, Iqbal M, Rupp H, Maisch B, Moosdorf R. Indications for angiography subsequent to coronary artery bypass grafting. *Am Heart J*. 2005; 149:1082–90. [PubMed: 15976792]
10. Muehlschlegel JD, Perry TE, Liu KY, Fox AA, Collard CD, Shernan SK, Body SC. Heart-type fatty acid binding protein is an independent predictor of death and ventricular dysfunction after coronary artery bypass graft surgery. *Anesth Analg*. 2010; 111:1101–9. [PubMed: 20457766]
11. Pelsers MM, Hermens WT, Glatz JF. Fatty acid-binding proteins as plasma markers of tissue injury. *Clin Chim Acta*. 2005; 352:15–35. [PubMed: 15653098]
12. Glatz JF, van der Vusse GJ, Simoons-Sel ML, Kragten JA, Dieijen-Visser MP, Hermens WT. Fatty acid-binding protein and the early detection of acute myocardial infarction. *Clin Chim Acta*. 1998; 272:87–92. [PubMed: 9581860]
13. Muehlschlegel JD, Perry TE, Liu KY, Nascimben L, Fox AA, Collard CD, Avery EG, Aranki SF, D'Ambra MN, Shernan SK, Body SC. Troponin is superior to electrocardiogram and creatinine kinase MB for predicting clinically significant myocardial injury after coronary artery bypass grafting. *Eur Heart J*. 2009; 30:1574–83. [PubMed: 19406870]