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Diastolic Function

A Barometer for Cardiovascular Risk?

PERIOPERATIVE cardiovascular risk assessment has undergone significant advances, including development and validation of multivariable risk indices for prediction of major cardiac complications,[1–3] advances in detecting ischemic heart disease, and noninvasive detection of symptomatic reductions in left ventricular (LV) ejection fraction.[4] However, we have recently recognized that current preoperative assessments may fail to fully appreciate a patient's vulnerability after a major noncardiac surgery, because early and late cardiac events can occur in the absence of coronary artery disease or heart failure symptoms.[5–7] In this issue of ANESTHESIOLOGY, Flu *et al.*[8] extend these findings, identifying the effect that subclinical LV systolic and diastolic dysfunction (DD) has on postoperative outcomes in patients undergoing open vascular or endovascular surgery. Because the current American College of Cardiology/American Heart Association perioperative guidelines fall short in discussing the clinical implications of DD, a closer look at this disorder is warranted.

Diastolic dysfunction and diastolic heart failure are not synonymous. The former refers to a preclinical state involving abnormalities in cardiac filling, which result from a combination of slowed LV relaxation and increased stiffness, usually associated with hypertension, diabetes, or ischemia. In contrast, diastolic heart failure, also called heart failure with normal ejection fraction, is the presence of signs and symptoms of heart failure with a normal ejection fraction (>50%), in the absence of significant valvular and pericardial disease, usually with echocardiographic or angiographic evidence of DD.[9] Diastolic heart failure is a true heart failure syndrome, producing nearly identical signs and symptoms, as well as alterations in neurohormonal activation and impairments in exercise tolerance and exercise cardiac output, similar to those with heart failure associated with reduced ejection fraction.[10,11]

Diastolic dysfunction is also a real disorder that merits clinical recognition, prevention, and treatment. Asymptomatic DD is common in the general population, even in patients without heart failure,[12] it increases with age and is particularly prevalent among older women with systemic hypertension and ventricular hypertrophy. The presence of DD alone predicts worse outcome, with a worsening prognosis as the degree of DD increases.[12] Furthermore, up to 50% of all heart failure patients have a normal ejection fraction (≥0.50) in the absence of major valve disease.[13,14] Compared with classic systolic heart failure, DD is increasing in incidence and prevalence,[13,15,16] triggers at least as many hospitalizations and healthcare expenditures as possible,[17] causes equivalent exercise intolerance,[18] and has a nearly similar death rate,[14] particularly among older patients who are hospitalized.

Work to date has suggested that diastolic function may be an additional barometer of cardiovascular risk not only in patients with established symptomatic heart disease[19–23] but also in patients undergoing major cardiothoracic and vascular surgery. In patient's undergoing coronary artery bypass graft surgery, Doppler-derived markers of DD were found to be more accurate in predicting cardiac events and mortality than traditional risk scores, including preoperative LV ejection fraction.[24,25] Preoperative DD, defined by the transmitral peak early filling velocity-to-late diastolic filling velocity (E/A) ratio or transmitral peak early filling velocity-to-early diastolic annular velocity (E/e′) ratio, before cardiac surgery has also been shown to be associated with the need for early inotropic support and increased intensive care unit length of stay.[26,27] Similarly, reductions in transmitral flow propagation velocity predicts postoperative heart failure and prolonged hospital stay after major vascular surgery.[28]

In their eloquent study reported in this journal, Flu *et al.*[8] included an important and a timely information to the prognostic value of preclinical LV dysfunction in patients undergoing vascular surgery. They examined the independent contribution of (1) asymptomatic isolated DD as defined by conventional Doppler parameters,[29] or (2) asymptomatic systolic dysfunction (defined by LV ejection fraction less than 50% with or without accompanying DD) for predicting 30-day cardiovascular events and longer term mortality in 1,005 consecutive patients, undergoing open vascular or

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endovascular surgery. All patients were followed up for a mean of 26 months. Interestingly, of the patients with overall LV dysfunction (n = 506/1005), 80% (n = 405) were without heart failure symptoms. The majority of these patients (n = 205) had isolated DD that corresponds to the widespread occurrence of preclinical diastolic function abnormalities noted in the general population.[12] Although preclinical systolic dysfunction portended a greater in-hospital risk for cardiovascular events than isolated DD (odds ratio 2.3, 95% confidence interval 1.4–3.6), the risk associated with DD was not trivial—the probability of cardiac events was nearly twice that of the patient with normal LV function (odds ratio 1.8, 95% confidence interval 1.1–2.9). Furthermore, patients with preoperative DD had three times the risk of cardiac death than those found not to have LV dysfunction (hazard ratio 3.0, 95% confidence interval 1.5–6.0), and those with asymptomatic systolic dysfunction had nearly five times the risk of death when compared with patients with normal LV function. In summary, the authors found that asymptomatic LV dysfunction, whether due primarily to diastolic or to systolic dysfunction, independently predicted unfavorable outcomes in their patients who underwent *open* vascular procedures.

These important results regarding the predictive value of DD are not surprising. Normal diastolic function enables the left ventricle to quickly adapt to the varying loading conditions typical of the perioperative state. Furthermore, one of the earliest manifestations of ischemia is abnormal diastolic function.[30] This is because diastolic function depends not only on passive properties but is also an active, adenosine triphosphate-requiring process, thus providing a quick and reliable "barometer" of myocardial health.

This study also has some limitations. First, there was no differentiation between the stages of DD. Does early diastolic impairment (E/A $<$ 0.8) portend the same risk as more advanced stages (E/A $>$ 2)? Certainly, the restrictive filling pattern of the LV has been shown to independently predict mortality after a myocardial infarction,[31] in patients with hypertrophic cardiomyopathy,[32] and in patients with severely reduced LV ejection fraction.[33] Second, because conventional diastolic parameters are highly influenced by changes in volume status, blood pressure, and heart rate, and the Doppler examinations were performed in the immediate preoperative period, following overnight fasting and presumably bowel preparation, there may have been an underestimation of the prevalence of advanced DD with seemingly even higher perioperative risk. The authors recognize this limitation and suggest that load-independent measures, such as early diastolic flow propagation velocity, or mitral annular velocity,[29] in conjunction with the E/A ratio could better characterize DD.

So what are the clinical implications of this study? With the changing demographics of our patients, we will need more robust biomarkers and noninvasive imaging techniques to aid in identification of patients who are at higher risk than suspected on clinical grounds alone. This study indicates that detection of preclinical LV dysfunction will improve risk estimates and should enable intensified management of perioperative therapy aimed toward mitigating cardiovascular events. These strategies might include optimization of preoperative cardiac medications, enhanced monitoring, specialized fluid management strategies, or more intensive postoperative surveillance, although the relative merit of these interventions is currently unknown. In a prior publication from this same data set, Flu *et al.*[34] showed that patients are often not managed preoperatively with standard medications. Nonetheless, in ambulatory, nonperioperative patients with overt, symptomatic diastolic heart failure, clinical trials of angiotensin-converting enzyme inhibitors (Perindopril for Elderly People with Chronic Heart Failure), angiotensin receptor antagonism (I-PRESERVE), digoxin, and β-adrenergic antagonism (SENIORS) with Nebivolol (Menarini Ricerche S.p.A., Bologna, Italy) have not convincingly demonstrated reductions in morbidity and mortality.[35] Accordingly, current American College of Cardiology/American Heart Association management guidelines have assigned all therapies aside from the treatment of hypertension to a "C" level of evidence.[36] Given the paucity of data, management of these patients with overt DD in the perioperative period is presently based on individualized, empiric principles, such as careful fluid management and control of hypertension and tachycardia.

Importantly, the data from Flu *et al.*[8] indicate that identification of subclinical LV dysfunction by the resting Doppler echocardiogram could be used to frame specific therapeutic patient care decisions, for example, open *versus* minimally invasive surgical approach. In this study, adverse outcomes among the patients receiving endovascular repair (n = 356) were only associated with those patients with preoperative symptomatic LV dysfunction; odds ratio for 30-day cardiovascular events was 1.8 (95% confidence interval 1.1–2.9), and the odds ratio for long-term cardiovascular mortality was 10.3 (95% confidence interval 5.4–19.3).

Thus, the study by Flu *et al.*[8] has made an important contribution to the literature on the perioperative cardiovascular risks associated with asymptomatic LV dysfunction. Taken together with the prior studies of Hammill *et al.*[5] and Hernandez *et al.*,[6] it is our opinion that there has evolved strong enough support for the following modification of the 2009 American College of Cardiology/American Heart Association Preoperative Cardiac Risk Assessment Guidelines: Resting echocardiography for assessment of LV systolic and diastolic function in asymptomatic patients undergoing high-risk noncardiac surgery is recommended.

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