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YEAR IN CARDIOLOGY SERIES

The Year in Echocardiography

Arthur E. Weyman, MD, FACC
Boston, Massachusetts

During the past year, progress in echocardiographic research has again been incremental with reports describing both expanded and refined applications of tissue Doppler imaging (TDI), myocardial contrast echocardiography (MCE), stress echocardiography, and real-time 3-dimensional (RT3D) imaging. The primary focus this year has been on the use of TDI and speckle tracking (ST) to identify left ventricular (LV) systolic and/or diastolic dyssynchrony (DYS) and determine its prevalence and functional significance in specific patient subgroups (systolic heart failure [SHF], diastolic heart failure [DHF], a narrow QRS [N-QRS] interval, right ventricular [RV] pacing, and myocardial infarction). Additionally, the effects of cardiac resynchronization therapy (CRT) on atrial function, exercise-induced mitral regurgitation (MR), and clinical and echocardiographic parameters of cardiac function in patients with both prolonged (P-QRS) and N-QRS intervals have been explored. In other areas, 2 excellent studies have examined: 1) the potential of contrast echocardiography using targeted microbubbles to detect remote ischemia based on 'ischemic memory'; and 2) the potential clinical toxicity of contrast echocardiography. Several large studies have examined the relationship of a negative stress echocardiogram and cardiovascular events during long-term follow-up, the association between patent foramen ovale (PFO) and stroke in a prospectively followed population, the relationship of aortic atheroma and long-term outcomes in a surgical population, and the significance of wall motion abnormalities in a population without evidence of cardiovascular disease. Studies in valvular heart disease have described the significance of low flow/low gradient severe aortic stenosis in patients with normal ejection fraction (EF), the shape of the proximal flow convergence region by RT3D echocardiography and its impact on the quantitation of MR, and the effects of ischemic MR on post-infarct remodeling. As always, it is impossible to review all of the studies published in the past year, and as a result this review attempts to focus on new observations, areas of particular focus, and confirmation of small group data in larger populations.

From the Massachusetts General Hospital, Cardiac Ultrasound Laboratory, Boston, Massachusetts.
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LV DYS

In patients with DHF. A number of studies have validated the role of (TDI and ST in assessing mechanical systolic DYS in patients with congestive heart failure, prolonged QRS intervals and poor systolic LV function. Less is known about the presence of systolic and diastolic DYS in patients with DHF. Wang et al. (1) compared the prevalence and significance of systolic and diastolic DYS in patients with SHF (n = 60), DHF (n = 60), and control subjects (n = 35). Systolic DYS was based on the maximal time difference between the shortest and longest interval from the onset of the QRS complex to both onset and peak of TDI systolic velocity for the 4 basal LV segments. Diastolic DYS was measured from the QRS to the onset of the early diastolic velocity in the same segments. In the DHF group, there were 20 patients (33%) with systolic DYS (time delay >35 ms). Of these 20 patients, 15 had time delays >60 ms. The QRS duration was significantly longer in these 20 patients than in the remaining 40 (118 ± 25 ms vs. 93 ± 30 ms, $p < 0.05$) with a weak correlation between QRS duration and systolic time delay ($r = 0.33$, $p = 0.04$). Patients with DHF and systolic DYS had significantly lower measures of stroke work, EF, end systolic pressure/end systolic volume, midwall fractional shortening, and Sa velocity than those without DYS. Mean pulmonary capillary wedge pressure (PCWP) was significantly higher, and τ was significantly longer. Thus systolic DYS is not uncommon in patients with DHF and is indicative of a more advanced stage of diastolic dysfunction. *Diastolic DYS* was present in 35 of 60 patients (58%) with DHF. All of the patients with systolic DYS showed evidence of diastolic DYS. In general, hemodynamic and echocardiographic indexes of LV systolic performance were similar between patients with DHF and no DYS and those with isolated diastolic DYS. However, there was a significant correlation between diastolic time delay and both PCWP ($r = 0.76$) and τ ($r = 0.84$). There were also significant correlations between the diastolic time delay and LV mass, as well as Doppler and 2-dimensional measurements of LV diastolic function including deceleration time, Ar-A duration, left atrial (LA) volume, LV mass/end-diastolic volume (EDV) ratio, and E/Ea ratio. Patients with SHF had a prevalence of systolic and diastolic DYS of 40% and 60%, respectively. Overall, diastolic function was also worse in patients with SHF and diastolic

DYS than in those with SHF without diastolic time delay. Short-term treatment of systemic hypertension (3 to 15 days) in patients with DHF produced a significant decrease in the diastolic intraventricular time delay but not the systolic time delay. A significant positive correlation was noted between the decrease in LV end-systolic pressure (ESP) and the shortening in diastolic time delay ($r = 0.71$) (1). In turn, the shortening in diastolic time delay correlated with shortening in τ, and increase in Ea velocity ($r = -0.75$), and decrease in E/Ea ratio ($r = 0.8$). The significant correlation between decrease in LV ESP and the shortening in diastolic time delay suggests that increased afterload may have a detrimental effect of LV relaxation, mediated, in part, through increased diastolic DYS.

In a similar study, Yu et al. (2) studied 373 heart failure patients (281 with SHF and 92 with DHF) and 100 normal subjects using TDI (2). Diastolic and systolic DYS were determined by measuring the standard deviation of time to peak myocardial systolic (Ts-SD) and peak early diastolic (Te-SD) velocity using a 6-basal, 6-midsegmental model. In addition, the maximal difference in time to peak systolic velocity (Ts-diff) and peak early diastolic velocity (Te-diff) between any 2 of the 12 segments was calculated. Both heart failure groups had prolonged Te-SD compared with the control group. Normal synchrony, isolated systolic, isolated diastolic, and combined DYS were observed in 39.1%, 25%, 21.7%, and 14.1% of DHF patients, respectively, similar to findings in the SHF group. Systolic DYS was more common in patients with SHF 55.9% versus 34.8% for DHF. The Ts-diff was 54 ± 23, 93 ± 46, and 108 ± 42 in control subjects, patients with DHF, and SHF, respectively. The correlation between systolic and diastolic DYS and myocardial velocities and corresponding mechanical function was weak. A wide QRS (>120 ms) was rare in DHF (10.9%), suggesting that the DYS was due to myocardial disease rather than electromechanical delay. The study also found systolic dysfunction based on decreased TDI systolic velocities in about one-half of the DHF group confirming some earlier reports. However, this issue remains controversial as another study this year found no difference in systolic function in DHF patients (3) .

Thus, both of these studies show that systolic and diastolic DYS are common in patients with DHF. Beyond that, these 2 studies are difficult to compare due to differences in methods (4 vs. 12 segments) and parameters examined. This is evident in the control groups where the control values (Te-diff = 63 ± 25 ms vs. 10 ± 9 ms, Ts-diff = 54 ± 23 ms vs. 12 ± 10 ms, and Sm 6.5 ± 1.0 cm/s vs. 13 ± 4 cm/s for Yu et al. [2] vs. Wang et al. [1], respectively) were quite different. Although the prevalence of systolic DYS was similar in the studies of Wang et al. (1) and Yu et al. (2) (33% vs. 39%, respectively), diastolic DYS was more common in the report of Wang et al. (1) (58% vs. 36%). In the study of Wang et al. (1), all patients with systolic DYS had diastolic DYS while in the study of Yu et al. (2) approximately one-third of patients with systolic DYS had diastolic DYS. However, the numbers in each case were small. Yu et al. (2) also found, in contrast to the study of Wang et al. (1), that the presence of DYS only weakly (but significantly) related to myocardial systolic function (perhaps due to the relatively low values for Sm in the control group) and that systolic and diastolic DYS was not tightly coupled. The latter finding is surprising since physiologically systole and diastole are closely intertwined (4).

In patients undergoing permanent RV pacing. To determine the effects of chronic RV pacing on LV synchrony and function, Tops et al. (5) studied 58 patients before and at 3.8 ± 2.0 years after His bundle ablation and RV pacemaker insertion for intractable atrial fibrillation. At baseline there was no evidence of DYS. In contrast, at follow-up DYS (>130 ms time delay between the septum and lateral wall) was found in 33 patients (57%). In patients with DYS, the time to septal and antero-septal peak strain was shorter than baseline while the time to peak strain for the lateral and posterior segments was longer. In patients without DYS, both times were slightly longer but similar. In 38 patients, echocardiography was performed 1 day after pacemaker insertion, and DYS was present in 14 (37%). In patients with DYS, New York Heart Association (NYHA) functional class deteriorated from 1.8 ± 0.7 to 2.4 ± 0.7, whereas NYHA class improved in patients without DYS. In addition, there was a significant increase in LV EDV, LV end-systolic volume (ESV) and decrease in left ventricular ejection fraction (LVEF) in patients with DYS compared with those without DYS. In 11 patients, the permanent RV pacemaker was upgraded to a biventricular pacemaker at a mean of 4.1 years after the original pacemaker insertion. Upgrading to a biventricular pacemaker eliminated the DYS in all cases and was associated with an increase in LVEF, and the deleterious effect on LV volumes was partially reversed. In all patients, a decrease in ESV >15% was noted. The reason that some patients with RV pacing develop DYS while others do not remains to be determined.

In another study relating DYS to outcomes, Mollema et al. (6) studied 178 consecutive patients with acute myocardial infarction undergoing percutaneous transluminal coronary angioplasty and found that baseline (within 48 h of admission) DYS (ST-maximal difference between 6 basal segments) was the strongest multivariate predictor of remodeling (decrease in LV ESV >15%) at 6 months compared with other echo-Doppler parameters. Using a cutoff of >130 ms, DYS had a sensitivity and specificity of 82% and 95%, respectively, for the detection of remodeling (decrease in LV ESV >15%) (6).

CRT

Effects on atrial function. Although CRT is of established benefit for patients with severe systolic LV dysfunction and prolonged QRS duration improving LV systolic function and associated LV reverse remodeling, little is known about the effects of CRT on atrial size and function. Yu et al. (7)

studied 107 patients with SHF who received CRT and were followed for 3 months. In responders (n = 62) to CRT (>10% reduction in LV ESV), there was a significant increase in LA fractional area change and volume emptying fraction compared with that seen in nonresponders. Responders also had a significant decrease in LA volume both before and after atrial systole, and an increase in atrial contraction velocity and strain (measured at end systole, early diastole, and late diastole) in both the left and right atrium. Maximal LA area and volume at end systole remained unchanged despite the increase in active atrial contractile function. The increase in strain at a constant LA volume suggests an increase in atrial compliance. Although the authors note that change in MR was similar in the 2 groups and thus not a factor in these changes, most reports note a decrease in MR in responders to CRT.

Effects of papillary muscle (PM) resynchronization on degree of MR. Ypenburg et al. (8) examined the relationship of cardiac resynchronization to reduction in MR in 25 patients with an acute decrease in MR after CRT. Initiation to CRT caused resynchronization (ST) of the PMs with a decrease in anterior PM to posterior PM DYS from 169 ± 69 ms to 25 ± 26 ms accompanied by a decrease in PM-fibrosa distance, a decrease in tenting area, and improved annular contraction. This degree of CR was maintained at 6 months. However, with interruption of CRT, PM DYS increased acutely together with an acute deterioration in the degree of MR.

Effects on exercise-induced MR. Chronic LV dysfunction is associated with functional MR due to LV dilation, PM displacement, and leaflet tethering. Functional MR is characteristically dynamic during exercise, and the change in MR severity during exercise is unrelated to the severity at rest. An increase in MR during exercise has been shown to identify a subgroup at high risk for cardiac events (9). To test the effects of CRT on exercise-induced MR, Madaric et al. (10) studied 28 patients with SHF (LVEF 25 ± 7%), a broad QRS complex (171 ± 27 ms), and at least mild MR (effective regurgitation orifice area [EROA] 0.25 ± 0.12 cm^2) with quantitative exercise echocardiography and cardiopulmonary exercise testing before and at 1 week and 3 months after CRT. Functional MR at rest decreased significantly immediately after CRT and was further reduced 3 months later. In contrast, the extent of exercise-induced MR remained unchanged early after CRT and was proportional to the extent of persistent exercise-induced DYS. At 3 months, exercise-induced MR was significantly reduced as evidenced by a decrease in EROA, regurgitant volume, and regurgitant fraction. This decrease occurred in parallel with absence of exercise-induced DYS. The early improvement in resting MR was related to the extent of exercise-induced LV DYS and contractile reserve before CRT while the extent of improvement in exercise-induced MR late after CRT was related to changes in the LV sphericity index and reduction in tenting area. There was a greater improvement in cardiopulmonary performance in patients with a smaller increase in exercise-related MR (10). This study confirms that both MR and LV synchronicity are dynamic and can vary substantially during exercise independent of ischemia and contribute to the limitation in stroke volume adaptation during exercise and, therefore, contribute to exercise-related symptoms that are out of proportion to resting LV function or degree of MR (9).

The relationship of DYS to functional MR in patients with a narrow QRS. D'Andrea et al. (11) examined the relationship of DYS and functional MR in 60 patients with dilated cardiomyopathy (mean LVEF 30.1%) and narrow QRS (<120 ms) at rest and at peak bicycle exercise using TDI. Dyssynchrony (tissue doppler [TD], standard deviation of 12 segments >34.4 ms) was present in 20 patients (33%) at rest and in 35 patients (58.3%) at peak exercise. There was an exercise-induced increase in MR in 78.3% of patients with a strong relationship ($r = 0.78$, $p < 0.00001$) between the change in DYS and the change in MR (EROA). The increase in DYS was also inversely related to the change in LV stroke volume at peak exercise ($r = -0.74$) and impaired exercise capacity. Since all of the patients in this study had normal coronary arteries, the change in degree of DYS appears unrelated to ischemia (11).

Relationship of baseline DYS to degree of resynchronization and response to CRT. While a number of studies have reported that selection of patients for CRT based on mechanical DYS is superior to the use of electrocardiogram (ECG) criteria alone, some patients still fail to respond, and it is unclear whether a reduction in LV DYS or CR is necessary for a positive response. To address this question, Bleeker et al. (12) studied a group of 100 patients with dilated SHF (EF <35%, NYHA functional class III to IV), and QRS >120 ms (mean 168 ms) who had baseline evidence of DYS (Ts-diff-4, >65 ms) by TD at baseline, immediately after CRT and at 6 months. Immediately after CRT, LV DYS decreased from a mean of 114 to 40 ms (65%). At 6 months, this decrease was sustained (mean 35 ms, 69% reduction). The percent reduction was not different between patients in sinus rhythm and those with atrial fibrillation or between those with ischemic versus nonischemic cardiomyopathy. There were 85 responders to CRT (reduction in LV ESV >10%) at 6 months follow-up. At baseline, there were no significant differences between responders and nonresponders. Although the prevalence of patients with ischemic cardiomyopathy was higher in the nonresponder group, this did not reach statistical significance. Responders showed a significant decrease in LV ESV (mean 190 to 130 ml) and increase in EF (mean 23% to 34%). In a multivariate logistic analysis, including clinical, ECG, and echocardiographic variables, only immediate LV CR was predictive of response to CRT at 6 months. Patients with a <20% improvement in CR did not respond to CRT while 85 of 91 patients (93%) with >20% CR were responders (positive predictive value 100%, negative predictive value 93%). The nonresponders either had an anterior

pacemaker lead placement or a posterior or lateral lead placement with ischemic cardiomyopathy. Although linear regression analysis showed a significant correlation between immediate reduction in DYS and the reduction in LVESV at 6 months, as pointed out in the accompanying editorial (13), the correlation was driven by the patients with <30% change in synchronization. For the nearly 90% of patients above this level, there was little relationship between degree of resynchronization and the degree of reverse remodeling. It was further noted that in a prior report the same group found that using a >65-ms delay, one achieved a 92% specificity and sensitivity for a >15% long-term decline in ESV. Using this criterion for response in this study, ~30% of patients would be nonresponders (13).

CRT in patients with normal QRS intervals. While CRT has proven benefit in patients with SHF and a P-QRS interval, there is limited data on its efficacy in patients with QRS intervals <120 ms. Preliminary data suggest that between 20% and 50% of patients with N-QRS complexes may exhibit DYS and may benefit from CRT. To evaluate the effects of CRT in patients with heart failure and N-QRS, Bleeker et al. (14) compared the results of CRT in a group of 33 SHF patients with N-QRS and evidence of DYS (TDI-Ts-diff >65 ms) to a comparable group of patients with SHF, DYS, and a QRS >120 ms. To identify the 33 patients with N-QRS and DYS, the authors screened 105 heart failure patients with N-QRS (31%). After CRT, patients with N-QRS showed a mean increase in QRS interval (110 to 129 ms, $p < 0.001$) and an immediate mean decrease in LV DYS (102 to 35 ms, $p < 0.001$), which remained unchanged at 6 months. There was a significant improvement in all clinical and echocardiographic parameters including mean NYHA functional class (3.1 to 2.2), Minnesota quality of life score (39 to 25), 6-min walk distance (274 to 370 m), LVEF (22% to 30%), LV EDV (216 to 189 ml), and LV ESV (174 to 134 ml): all changes were significant ($p < 0.001$). There was no correlation between baseline LV DYS and percent change in LV ESV at 6 months. At follow-up, there was no difference in the magnitude of improvement in clinical or echocardiographic parameters between patients with DYS and narrow or prolonged QRS intervals. Eighty-eight percent of patients with N-QRS showed a clinical response to CRT (defined as an improvement >1 NYHA functional class) compared with 91% of patients with a P-QRS. There was no correlation between baseline QRS interval and baseline degree of DYS in either group (14).

In a similar study, Yu et al. (15) examined 102 patients with SHF (EF <40%), 51 patients with an N-QRS (<120 ms), and 51 with a P-QRS. Approximately one-half of the patients with N-QRS had evidence of DYS (TDI, Ts-SD-12, >32.6 ms). In both groups CRT resulted in significant improvement in NYHA functional class, 6-min walk, and maximum metabolic equivalents by exercise testing. There was a significant correlation between baseline DYS index and change in LV ESV for both groups (in contrast to Bleeker et al. (14) who found no correlation). The prevalence of responders (reduction in LV ESV >15%) was 62.7% in the wide QRS group and 45.1% in the narrow QRS group. In the narrow QRS group, the change in LV EDV, LV ESV, and LVEF was significantly greater for those with baseline DYS. For a similar extent of baseline DYS, the degree of cardiac improvement was similar in both groups. Interestingly, when pacing was withheld for 4 weeks after 3 months of CRT, the clinical parameters remained unchanged while the echocardiographic benefits disappeared (15).

Relationship of acute changes in dP/dT to clinical long-term clinical outcome. To determine the relationship of acute changes in dP/dT to clinical outcome, Tournoux et al. (16) studied 53 patients with SHF, QRS >120 ms, and MR sufficient to record a continuous wave Doppler MR velocity profile (55% of patients screened). The slope (between 1 and 3 m/s) of the MR velocity profile was used to determine the change in dP/dT with CRT-on versus CRT-off (separated by a 10-min recovery period). After CRT, DYS and dP/dT were significantly improved with no difference between the ischemic and nonischemic groups and a significant correlation between change in dP/dT and change in asynchrony ($r = -0.574$, $p < 0.0001$). Patients were divided into 3 groups based on the percent change in dP/dT (>25% = high responders [HR, n = 28], 0% to 25% low responders [LR, n = 17], and <0% = nonresponders [NR, n = 8]). At follow-up (1 year), 89.2% of the HR group were event-free (death or rehospitalization for worsening heart failure) compared with 58.9% of the LR and 37.5% of the NR group (16). Overall, there was no difference in MR with CRT-off or -on; however, there was wide variation between patients, but this was not predictive of outcome.

The potential of a combination of longitudinal (TDI) and radial (ST) measures of DYS to define response of CRT was examined in 159 patients with SHF (EF <35%) and a prolonged QRS. Dyssynchrony was measured by TD based on a septal lateral delay (>60 ms) in all patients and by a maximal opposing wall delay (>65 ms) and Ts-SD in 12 segments in a subgroup of 67 patients (17). Radial DYS was defined by ST analysis of a midventricular short-axis plane with DYS defined as an antero-septal to posterior wall delay of >130 ms in time to peak strain. Responders were defined by an EF increase >15%. Sixty-six percent of patients were EF responders at 6 ± 3 months. The sensitivity and specificity for a positive response were 72% and 77%, 84% and 76%, and 80% and 78%, respectively for the 2-site, 12-site, and Ts-SD methods. When DYS was present by both TD and ST, 95% had a positive EF response, while when both were negative 21% were responders. Nonresponders were more likely to have ischemic heart disease, a lower EF, and a wider QRS compared with responders. Combined longitudinal and radial DYS predicted EF response with 88% sensitivity and 80% specificity, which was significantly better than either technique alone.

Perspective. These studies, in general, support the concept that mechanical DYS (variably defined) is bad and that resynchronization causes improvement in clinical and/or echocardiographic parameters (in some percentage of patients) termed responders, which is good. Unfortunately, beyond these general conclusions, the issues become less clear. Lack of clarity occurs for a number of reasons. First, it is difficult to define the percent of patients with DYS or the number who respond because different authors use different systems for dividing the ventricle, different methods for defining mechanical activation, different criteria for defining DYS, and different criteria for defining responders. This is further complicated by the fact that the same authors use different criteria for response in different studies suggesting that individual criteria yield inconsistent results. Second, beyond the binary distinction between responders and nonresponders, one would expect some correlation between the degree of resynchronization and improvement in parameters of LV function (e.g., LV ESV), but in many studies this did not appear to be the case. Third, while the goal of therapy is to improve symptoms either acutely or to delay/prevent their occurrence in the future, the relationship between resynchronization and clinical recovery were not always tightly coupled. For example, in the study of Yu et al. (15), biventricular pacing improved echocardiographic and clinical parameters at 3 months; however, when pacing was discontinued for 4 weeks the echocardiography parameters deteriorated while the clinical parameters were unchanged. Finally, preliminary data presented at the European Heart Association meeting in Vienna from the core laboratories for the multicenter PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) (18) trial, designed to clarify some of these issues, revealed varying yields for different measures and relatively high core lab variability (coefficients of variation [standard deviation/mean × 100] of 33.7% and 72.1% for Ts-SD and septal-posterior wall motion delay, respectively) emphasizing the need for some agreed upon standardization in this area.

MCE

Molecular imaging of acute ischemia. The diagnosis of ischemia in patients presenting with chest pain without ECG changes or acute enzyme elevations can be extremely difficult. Ischemia is known to trigger the activation of endothelial leukocyte adhesion molecules that persist after the ischemia has resolved. The adhesion molecule P-selectin is rapidly mobilized to the endothelial surface from preformed cytoplasmic stores within minutes of ischemia-reperfusion. This initial activation is followed by delayed transcription-dependent endothelial overexpression of E-selectin, more P-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule. Once activated, these markers persist on the endothelial surface for hours. Because these molecules are located on the luminal surface, Villanueva et al. (19) using a rat model of acute ischemia tested whether acoustically active gas-filled microbubbles bearing a selectin-specific ligand on their surface would bind to post-ischemic endothelium and thus permit the echocardiographic detection of recent ischemia. After a 15-min occlusion followed by reperfusion, nontargeted bubbles showed homogeneous myocardial enhancement indication restoration of flow. Subsequent injection of targeted microbubbles revealed persistent contrast enhancement in the region of previous ischemia. A significant linear relationship was found between risk area size and the size of the region of contrast enhancement by the targeted microbubbles. Although the duration of selectin expression after ischemia is unclear, large animal studies suggest that it can be present for many hours. Of note, selectin expression is not specific for ischemia but is found in inflammation of any type, and other clinical causes of inflammation could be confounding. As the authors point out, it remains to be determined whether similar data would be obtainable in patients with less favorable windows and at lower imaging frequencies (19).

Clinical toxicity. Recent reports of several deaths in extremely unstable patients after administration of contrast for LV opacification have caused the Food and Drug Administration to require that a black box warning be added to the cautions concerning use of these agents. A number of experimental studies in small animals have shown the microbubble destruction in high intensity sound fields can cause local adverse effects including ventricular ectopy, increased vascular permeability, and even cell death in exposed tissues. To determine the clinical relevance of the microscale bio-effects seen in animals during prolonged high intensity imaging, Vancraeynest et al. (20) studied the effects of low and high mechanical index (MI) contrast-enhanced (perfluorocarbon-enhanced Sonicated Dextrose Albumin infusion for 15 min) imaging in 20 stable patients undergoing routine coronary angiography. Myocardial cell damage was assessed using a coronary sinus catheter in patients after low MI (n = 6, MI = 0.2 with 10 consecutive high MI = 1.7 frames on demand every minute) or high MI imaging ([n = 7] MI = 1.5 triggered [1 frame every other beat or ~450 high MI frame at a heart rate of 60 beats/min] for 15 min compared with control subjects [n = 7]). Markers of cell injury included lactate, myoglobin, creatine kinase (CK), CK-MB, troponin I, and oxygen content. Creatine kinase-MB, myoglobin, and troponin I remained stable in the control and low MI groups, while CK-MB and troponin I increased significantly in the high MI group during coronary sinus but not arterial blood sampling. Although the actual increase in biomarkers was small, these findings suggested microscale damage to cardiomyocytes during high MI contrast imaging. These finding appear specific for the combination of contrast agent and high MI imaging since they did not appear in patients with high MI imaging without contrast or in patients receiving contrast with low MI imaging. The authors conclude that the observed microscale toxicity was clinically irrelevant in their

stable patients with largely normal LV function but could not exclude the possibility that microscale myocyte damage might contribute to serious complications in hemodynamically unstable patients or those with ongoing myocardial infarction or ischemia (20). In interpreting these data it is important to note that the use of a 15-min continuous infusion, prolonged high MI imaging, and a single constant examining plane represent significantly more exposure than would occur in normal clinical practice.

RT3D

The accuracy of RT3D imaging in assessing LV size and function has been reported in a number of studies; however, the utility of RT3D for the evaluation of the more complex RV is still being defined. Several recent studies have looked at this issue. Gopal et al. (21) compared 2-dimensional and RT3D measures of RV volume, stroke volume, and EF with cardiac magnetic resonance imaging in 71 healthy individuals. The RT3D volumes were calculated using both the disc summation method (RT3D-DS) using endocardial contours from 3 orthogonal views and from boundaries obtained from 8 equiangular planes obtained by apical rotation (RT3D-AR). The RT3D-DS showed less volume underestimation compared with RT3D-AR and 2-dimensional (EDV −1.2 vs. −16.0 vs. 19.5 ml; ESV −0.02 vs. −8.3 vs. 14.7 ml; stroke volume −1.2 vs. −7.6 vs. −4.8 ml; EF −0.7% vs. −1.7% vs. 11.1% respectively). Test-retest variability for RT3D-DS EDV, ESV, stroke volume, and EF were 3.3%, 8.7%, 10%, and 10.3%, respectively. Normal values for men and women were derived.

In another study, Grison et al. (22) calculated 3-dimensional RV volumes in 18 pediatric patients with secundum atrial septal defects in the operating room (anesthetized, intubated, and ventilated) before surgery and compared them with the directly measured volume at surgery (injected volume of saline required to completely fill the RV and close the tricuspid valve). Three-dimensional volumes were derived from either transthoracic or transesophageal rotation of the imaging plane at 2-degree intervals over 180 degrees and calculated using the disc summation method (30 cross sections of known width). In an additional 5 patients, images were derived using a matrix array transducer; RV diastolic pressures were measured, and saline infused until the previously measured RV EDP was reached. Remarkable correlations were found between measured and echocardiography volumes for both the rotation ($Y = 1.0292x + 3.3737$, $r^2 = 0.9908$) and for the RT3D acquisition ($Y = 0.9914x + 4.6118$, $r^2 = 0.9919$) methods.

Prognosis of normal exercise echocardiography. Exercise echocardiography has prognostic value independent of the information provided by clinical factors and the exercise ECG. In a meta-analysis by Metz et al. (23), examining the negative predictive value of exercise echocardiography, 4 studies including 3,021 subjects (mean age 56 years and 46% women) without resting or exercise-induced wall motion abnormalities, the estimated annualized rate of cardiac death or myocardial infarction was 0.54%. In 2 of these studies (380 subjects), which included data on rates of unstable angina or revascularization, the annualized event rate was 0.95%. In studies stratified by gender, the annualized event rate after a normal test was <1% in women and approximately 1% in men. Metz et al. (23) did not include analyses of positive predictive values as they note that these values are particularly subject to referral bias due to differing patient risk profiles, and the effect of positive tests on subsequent revascularization and medical management. Although many studies attempt to deal with referral bias by excluding subjects with early revascularization, this bias persists in unadjusted results.

Dobutamine stress echocardiography (DSE). Although a normal exercise echocardiogram is associated with an excellent prognosis, DSE is generally reserved for patients who are unable to exercise and, therefore, have a generally poorer prognosis and more comorbid conditions. While the short- and intermediate-term prognosis of DSE is good, less is know about the long-term prognosis. Chaowalit et al. (24) studied 3,014 patients (1,200 men, 68 ± 12 years) with a normal DSE during a median follow-up of 6.3 years. All-cause mortality and cardiac events (myocardial infarction or coronary revascularization) occurred in 920 patients (31%) and 271 (7.7%) patients, respectively. Survival and cardiac event-free probabilities were 95% and 98% at 1 year, 78% and 93% at 5 years, and 56% and 89% at 10 years. Age, diabetes, and failure to achieve 85% of maximal age-predicted heart rate were independent predictors of death and cardiac events. Patients with all 3 characteristics had a 13% probability of an event within 1 year. Thus, although prognosis after a normal DSE is good, the annual mortality and cardiac event rate are higher than for a normal exercise echocardiograph (24).

In other stress echocardiography studies: 1) Park et al. (25) reported that imaging at intermediate stages during supine bicycle exercise improved the sensitivity for detection of ischemia without changing specificity by highlighting the contrast between the transient increase in contraction at lower loads with the decrease in contraction with the onset of ischemia. This approach also permitted definition of the rate pressure product at the onset of ischemia, which correlated with percent stenosis ($r = -0.61$, $p < 0.001$); 2) Bangalore et al. (26) reported that a patient with a LA size of >2.4 cm/m^2 at the time of a stress echo had a 2.9 times higher event rate (death or nonfatal myocardial infarction) than those with a normal LA size during a mean follow-up of 2.7 years).

Epidemiology

The prevalence and prognostic significance of wall motion abnormalities in adults without clinical cardiovascular disease was examined in 2,864 participants in the Strong Heart study (age 60 ± 8 years, 64% women) (27). Echocardio-

graphic assessment revealed segmental wall motion abnormalities in 140 (5%) and global hypokinesis in 42 (1.5%). During 8 ± 2 years of follow-up, segmental wall motion abnormalities were associated with a 2.5-fold higher risk of cardiovascular events (CVEs) and a 2.6-fold higher risk of cardiovascular death (CVD) after adjustment for age, gender, waist/hip ratio, systolic blood pressure, and diabetes. In a similar model, global hypokinesis was associated with a 2.4-fold increase in CVE and a 3.4% increase in CVD.

Effect of afterload on diastolic function. The effects of load and load sequence on LV TDI E'-wave velocities were studied by Borlaug et al. (28) in 48 subjects. Afterload was measure by effective arterial resistance and systemic vascular resistance; loading sequence was quantified by early (carotid characteristic impedance) and late systolic loads (augmentation index; late pressure time-integral). Vascular stiffness was measured by carotid-femoral pulse wave velocity and total arterial compliance. Diastolic and systolic tissue velocities were found to vary inversely with arterial afterload, with late systolic load (related to arterial stiffness) having the greatest influence on E'. These findings may partly explain the decrease in early relaxation velocity noted with aging, hypertension, and DHF. The E/E' ratio also varied directly with afterload. The observation that S' velocity also shows a significant afterload dependence suggests that it may not be an optimal measure of contractility but that indexing for afterload may improve utility (28).

Association of Aortic Atheroma to Long-Term Mortality in Patients Undergoing Cardiac Surgery

Although several studies have shown a correlation between aortic atheroma and long-term mortality in high-risk patients, the relationship in the general population and the effects of associated clinical variables remain unknown. Thambidorai et al. (29) studied 8,581 patients undergoing first time cardiac surgery. Transesophageal echocardiography imaging of the ascending aorta, arch, and descending aorta was used to detect atheroma, which were subclassified as absent, mild (<4 mm without complex features), moderate (>4 mm without complex features), and severe (any size with protruding or mobile elements). There were 2,878 (34%) patients with no atheroma; 4,129 (48%) with mild atheroma; 1,215 (14%) with moderate atheroma; and 359 (4%) with severe atheroma. Compared with those with no atheroma, patients with severe atheroma were older, had more severe coronary artery disease, were more likely to have had a prior myocardial infarction, had a lower EF, were more likely to have a remote cerebrovascular accident, had a higher creatinine, and were more likely to be undergoing a coronary artery bypass grafting. Survival rates for none, mild, moderate, and severe atheroma were 90%, 86%, 76%, and 66% at 5 years. After adjusting for clinical characteristics including age, gender, diabetes, hypertension, smoking, renal function, EF, and multiple other confounders, severe atheroma remained modestly predictive of risk (adjusted relative risk 1.50, 95% confidence interval [CI] 1.10 to 2.04, $p = 0.01$). However, using a propensity analysis, matching patients with no atheroma with those with severe atheroma, severe atheroma was no longer predictive. These data suggest that severe atheroma may be a marker for mortality associated with known complications of atherosclerosis rather than the mortality being due to the atheroma itself (29).

Natural History of RV Dysfunction After Acute Pulmonary Embolism

Large pulmonary emboli are associated with acute RV dilation, RV dysfunction (RV strain), and an increase in pulmonary artery pressure. However, these changes are generally described qualitatively or semiquantitatively. To provide a more quantitative measure of RV function in acute pulmonary emboli, Chung et al. (30) measured tricuspid annular velocity and TD-derived measures of myocardial velocity, strain and strain rate in 35 patients with documented pulmonary emboli. The ratio of Sm at the basal and apical segments of the RV free wall was taken as the systolic velocity gradient. The extent of pulmonary emboli was defined as the percent of the total lung volume showing ventilation perfusion mismatch with a large pulmonary emboli defined as involvement of >30% of the lung. Of the conventional 2-dimensional echo parameters, RV percent area change ($r = -0.58$), RV:LV end-diastolic area ratio ($r = -0.54$), and RV end-systolic area ($r = -0.49$) showed the strongest correlation with extent of pulmonary emboli. Of the measures of RV longitudinal function, the RV systolic velocity gradient ($r = 0.66$), tricuspid annular motion (TAM) ($r = -0.61$), and RV midsystolic strain ($r = -0.57$) showed the strongest correlation. Multivariate analysis showed that TAM and RV basal Am were the strongest independent predictors of the extent of pulmonary emboli. Tricuspid annular motion was the most useful in predicting large pulmonary emboli with a TAM <2.0 cm had a sensitivity and specificity of 75% and 84%, respectively (all patients with a TAM <1.7 cm had a large pulmonary embolism). When patients with medical comorbidities known to affect RV function were excluded, the correlations between pulmonary emboli size and parameters of RV function improved. Most parameters improved within 5 days after presentation; however, the RV:LV end-diastolic area ratio and RV ejection area returned to normal after 6 weeks, whereas the TAM and systolic velocity gradient normalized after 3 to 6 months.

PFO and Stroke

The risk of stroke in patients with PFO remains unclear. Although case control studies suggest an increased risk particularly in younger patients, a prior prospective population study of 577 patients failed to find an association (31). To explore this question further, Di Tullio et al. (32) followed a prospective, multiethnic cohort of 1,100 stroke-

free patients >39 years of age (mean 68.7 years) for a mean of 79.7 months. There were 164 patients (14.9%) with PFO and 27 patients (2.5%) with an atrial septal aneurysm. An ischemic stroke occurred in 68 subjects (6.2%), but after adjustment for demographics and risk factors, PFO was not found to be significantly associated with stroke (hazard ratio 1.64, 95% CI 0.87 to 3.09). The same trend was present in all age, gender, and race-ethnic subgroups. The coexistence of PFO and atrial septal aneurysm did not increase stroke risk; however, the presence of an isolated atrial septal aneurysm was associated with increased risk (2 of 8 patients). The prevalence of PFO in the population is lower than previously reported despite the use of contrast to detect shunt flow (32). This study, together with the study of Meissner et al. (31), suggests that the risk of stroke in patients with PFO is quite low and would likely require much larger studies to be accurately defined.

Aortic Stenosis

Some patients with severe aortic stenosis on the basis of aortic valve area may have a relatively low gradient despite the presence of a preserved LVEF. In a retrospective study of 512 consecutive patients with severe aortic stenosis (indexed aortic valve area <0.6 cm^2/m^2) and preserved LVEF (>50%), Hachicha et al. (33) found that 181 (35%) had paradoxically low flow (stroke volume index <35 ml/m^2). When compared with normal flow patients, the paradoxically low flow group had markedly increased global LV afterload as evidenced by the valvulo-arterial impedance (Zva) (Zva = systolic arterial pressure + mean aortic gradient/stroke volume index) values 29% higher than those with normal flow and had transvalvular flow rates comparable with those observed in patients with low flow aortic stenosis associated with low EF. Despite the normal LVEF, these patients had reduced midwall fractional shortening and stroke work index suggesting significant impairment in intrinsic myocardial function. Patients with paradoxically low flow also had smaller LV cavities, greater concentric remodeling, were older, and more often women. These patients also had a markedly lower survival with medical rather than surgical treatment (33).

MR

Calculation of the EROA using the proximal flow convergence region (proximal isovelocity surface area) traditionally assumes a hemispheric velocity profile with flow approaching the orifice in a series of concentric shells. Previous studies have challenged this assumption and suggested that a hemielliptical approximation would be more appropriate. Using real time 3-dimensional echo, Yosefy et al. (34) examined the shape of the proximal flow convergence region using both 2- and 3-dimensional echo in 40 patients and attempted to derive a practical clinical method for MR quantitation. The majority of patients (39 of 40 [97.5%]) had a hemielliptic-appearing proximal flow convergence region contour with a mean ratio of medial-lateral to antero-posterior diameter of 1.4 ± 0.17 (viewed en-face from the LV). When compared with the quantitative Doppler method for assessing MR (mitral inflow-aortic outflow), the 2-dimensional method based on a hemispheric assumption underestimated EROA (0.34 ± 0.14 vs. 0.48 ± 0.25, $p < 0.001$). Real-time 3-dimensional EROA was not significantly different from the quantitative Doppler method. The difference between the 2-dimensional D and RT3D measures was more striking for eccentric MR jets than for central jets. Based on the quantitative Doppler method (inflow-outflow), 33 patients had moderate/severe MR (EROA >0.3 cm^2) based on American Society of Echocardiography guidelines. Of these, 15 of 33 (45%) were underestimated as having mild-to-moderate MR (EROA <0.3 cm^2) by the 2-dimensional method whereas only 1 was classified as mild/moderate by RT3D.

The question of whether ischemic MR causes excess LV remodeling and whether repairing it reverses the process remains controversial. Beeri et al. (35) examined this question in an ovine model (n = 18) of acute antero-apical myocardial infarction with controlled flow from the LV to LA simulating moderate MR. The animals were divided into 3 groups: myocardial infarction plus shunt for 90 days (MR+, n = 6), myocardial infarction with shunt ligated at 30 days (MR repair), and myocardial infarction alone (n = 6). The MR+ and MR repair groups had similar LV EDVs at 1 month, but the LV EDV was significantly reduced in the MR repair group at 3 months. A similar pattern was noted with LV ESV. Peak positive dP/dT was similar in the 3 groups at 1 month but decreased significantly in the MR+ group at 3 months while remaining relatively constant in the MR repair and myocardial infarction only groups. Preload-recruitable stroke work were also depressed in the MR+ compared with the MR repair and myocardial infarction groups. Molecular markers also differed between the MR+ and MR repair groups with adverse molecular events that typify remodeling being suppressed after MR repair to levels seen with myocardial infarction alone, whereas compensatory mechanisms including matrix stabilization remained activated after repair (35).

Reprint requests and correspondence: Dr. Arthur E. Weyman, Massachusetts General Hospital, Yawkey 5E, Boston, Massachusetts 02114. E-mail: aweyman@partners.org.

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