Echocardiographic evaluation of systolic heart failure

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Abstract Echocardiography is the most commonly used modality for evaluating left ventricular size and function in the context of systolic heart failure. Traditional techniques, though extensively used, have their limitations and more recently several newer technologies have emerged that are more reproducible, provide prognostic information, guide therapies and have an important role in monitoring progress. This review will evaluate the traditional and more novel techniques used and briefly provide an overview of the role of echocardiography in guiding and monitoring therapies in patients with systolic heart failure.

Introduction
Heart failure (HF) is a global health problem, with an estimated 15 million symptomatic patients worldwide¹. In 2001, 300,000 Australians had chronic HF with 30,000 new cases diagnosed yearly ². HF was the third largest cause of death in 2002 ³ while deaths associated with HF accounted for 8.3% of circulatory deaths⁴. Current guidelines emphasise the importance of early identification of HF patients for initiation of therapy, thereby containing health care costs⁵. Echocardiography, according to ACC/AHA guidelines is “the single most useful diagnostic test in the evaluation of patients with HF” ⁶. This article addresses the utility of echocardiography in systolic HF, with discussion of traditional and newer techniques of assessment.

Traditional measurements

M mode
Left ventricular (LV) volumes, ejection fraction (EF) and fractional shortening can be measured by M-mode (Fig. 1) but are only applicable to a symmetrical heart without regional abnormality. Current American Society of Echocardiography (ASE) guidelines recommend two-dimensional (2D) LV volume and EF quantification discouraging M-mode measurements that rely on geometric assumptions to convert linear measurements to volumes⁷.

2-dimensional LV volumes
2D LV end systolic (LVESV) and end diastolic volumes (LVEDV), indexed LVESV (LVESVI) are important predictors of outcome. Current ASE guidelines recommend the modified biplane method of discs for LV volume and EF quantification from apical 4 and 2 chamber views ⁷ (Fig. 2), but measurements rely on image quality and inherently underestimate LV volume. However, the V-HeFT ⁸, SOLVD ⁹ and Val-HeFT ¹⁰,¹¹ trials have shown the close association of these parameters with morbidity and mortality.

White, et al.¹² showed that LVESVI was an independent predictor of survival and hospitalisation after acute myocardial infarction (AMI), while from the Heart and Soul study, LVESVI was an independent predictor of hospitalisation in patients with stable coronary heart disease (CHD)¹³. From the multicentre BEST study¹⁴, LVEDVI was a predictor of adverse outcome in advanced HF. Reproducibility of 2D measurements is a problem with a test-retest variability of 11%, inter-observer and intra-observer variability of 5% and 3% respectively¹⁵.
LV ejection fraction

LVEF is a parameter of global systolic function that provides a numeric interpretation for the diagnosis and therapeutic guidance in HF management and for device implantation. Despite the fact that LVEF does not correlate with HF symptoms, exercise capacity or myocardial oxygen consumption, it remains a powerful prognostic marker for future cardiac events, especially post AMI. Curtis, et al. examined the relationship of LVEF to clinical outcomes in 7,788 stable HF patients and a higher LVEF was associated with a linear decrease in mortality. Additionally, an LVEF < 35% was the benchmark for intra-cardiac defibrillator (ICD) implantation based on the MADIT II trial.

Wall motion abnormality

The ASE advocates the use of a 17 segment model, dividing the LV into three levels (basal, mid and apical) with further subdivision into six segments at the basal and mid level and 4 segments at the apical level and a single segment at the apex to produce 17 segments. A wall motion score index (WMSI) can be derived by grading segmental dysfunction severity (normal = 1, hypokinesis = 2, akinesis = 3, dyskinesis = 4). WMSI and LVEF for risk stratification after an AMI demonstrated that both were powerful predictors of all-cause mortality, with WMSI being an independent predictor of death and HF hospitalisation.

Ischaemic mitral regurgitation

Ischaemic mitral regurgitation (MR) is functional regurgitation consequent to infarction with structurally normal leaflets and subvalvar apparatus. Leaflet motion is restricted with apical displacement of the coaptation zone, causing incomplete systolic closure of the mitral valve or “systolic tenting”. Ischaemic MR results from complex alterations of spatial relationships between the LV and mitral apparatus and a recent study confirmed that MR severity is related to systolic tenting and not LV dysfunction. Ischaemic MR occurring early or late after AMI is associated with increased mortality, and severe MR portends poor prognosis. Transthoracic echocardiography (TTE) enables analysis of the mechanism and severity of MR, and transoesophageal echocardiogram (TOE) is only occasionally necessary. The quantification of ischaemic MR differs from organic MR with thresholds for severe ischaemic MR being 30 mL for regurgitant volume and 20 mm² for ERO, compared with 60 mL and 40 mm² respectively, in organic MR.

Tei Index

The myocardial performance index, or Tei index, reflects global performance incorporating both systolic and diastolic function. The Tei index is the ratio of the sum of isovolumic contraction and relaxation times to the ejection time, with these parameters obtained from Doppler assessment. The Tei Index is independent of heart rate, blood pressure, does not rely on geometric assumptions, is highly reproducible and correlates with invasively measured LV dP/dt. The Tei Index has prognostic value in various patient cohorts and an index > 0.77 proved superior to LVEF in predicting death. Other studies have shown its value in prediction of HF in an elderly cohort as well as predicting lack of treatment response in patients with HF.

Newer parameters and application

Newer echocardiographic techniques utilising tissue Doppler imaging (TDI) and strain (S) and strain rate (SR) imaging are more robust and reproducible, providing quantitative assessment of global and regional function.

Tissue Doppler imaging

TDI uses low-velocity, high amplitude myocardial velocity signals and is obtained by pulsed Doppler imaging (Fig. 4a) or colour Doppler (CTDI) (Fig. 4b) function. CTDI acquires tissue velocity information from the entire sector and thus multiple sites can be interrogated simultaneously and analysed offline. Pulsed Doppler measures peak velocity and
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is ~20–30% higher than the mean velocity measured by CTDI.

TDI has been validated extensively in a variety of cardiac pathologies including HF, AMI, hypertension, diabetes and in stress echocardiography where TDI systolic velocities are used as an adjunct to WMSI. The peak systolic septal annular (Sa) or basal septal segmental velocity (Sm) is a sensitive marker of impaired LV systolic function, even in those with a normal LVEF. Sm velocity is a predictor of outcomes and in patients with cardiac disease, mortality was higher when Sm was < 3 cm/s. In HF patients, CTDI Sm velocity and diastolic arterial pressure were independent predictors of outcome.

Strain and strain rate

Strain (S) is a measure of tissue deformation, defined as the change in length normalised to the original length, whilst strain rate (SR) measures the rate of deformation (Figs. 5a, 5b). Strain imaging is derived from TDI and more recently from 2D myocardial speckle-tracking. Unlike TDI measurements, S and SR are not subjected to cardiac tethering. Normal ranges for S and SR have been described, and while S is influenced by increasing age, pre-load and after-load, SR is less load dependent. S and SR can detect subclinical disease in hypertension and diabetes as well as infiltrative myocardial disease, correlates with myocardial fibrosis and has been used to evaluate therapeutic response. S and SR have been used in stress echocardiography. SR correlates with myocardial perfusion during dobutamine stress and is superior to TDI in detecting CAD. S and SR are reduced in ischaemia/infarction with augmentation in viable segments.

Diastolic parameters

Several diastolic parameters such as deceleration time and
restrictive filling and decreased diastolic TDI velocities are associated with poor prognosis in systolic HF. An E/Ea > 15 is a powerful prognosticator for adverse cardiac events and is an independent predictor of cardiac mortality and HF hospitalisation. However, these diastolic parameters will not be discussed in this current review.

Dyssynchrony

Uncoordinated ventricular motion or “mechanical dyssynchrony” is often present with LV dysfunction and is associated with a prolonged QRS complex. However, not all patients with a wide QRS complex exhibit dyssynchrony; 30–50% of patients with a narrow QRS complex may have echocardiographic dyssynchrony that benefits from cardiac resynchronisation therapy (CRT). Echocardiography is the most widely used modality for dyssynchrony and techniques include M-mode, TDI, speckle tracking, and real-time 3D echocardiography (RT3DE).

The simplest method for evaluating dyssynchrony is M-mode analysis of posterior wall to septal delay with ≥130 ms predicting HF improvement with CRT. Pulsed-wave TDI is performed on line and generally considered more difficult and time-consuming. CTDI is most commonly used and measures time from QRS onset to peak systolic velocity (TPSV). Bax and colleagues defined dyssynchrony as the maximum difference in TPSV between the four basal (anterior, inferior, septal, lateral) segments and TPSV difference of 65 ms had a sensitivity and specificity of 80% for predicting reduction in death and HF hospitalisation. Yu, et al. developed a 12-segment model involving six basal segments.

Table 1: Strengths and weaknesses of various echocardiographic techniques.

| Parameter                  | Utility                        | Strengths                                                                 | Limitations                                                                 |
|----------------------------|--------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| M-Mode                     | Part of standard TTE assessment | Easy to perform                                                           | Relies on geometrical assumptions                                          |
|                            | Available on all U/S systems   |                                                                           | Off axis imaging                                                            |
|                            |                                |                                                                           | Dependent on image quality                                                  |
| 2D volume (biplane modified | Assess global LV function      | Powerful prognostic marker of outcomes in HF and CAD                      | Underestimates volume due to inherent foreshortening                       |
| Simpsons method)           | Used to monitor therapy        |                                                                           | Dependent on image quality                                                  |
|                            |                                |                                                                           | Lacks reproducibility                                                       |
| Ejection fraction (        | Estimates global systolic      | Powerful prognostic marker for future cardiac events in HF and post AMI   | Poor correlation with HF symptoms or ex capacity                           |
| bipplane modified Simpsons | function                       |                                                                           | Load dependent                                                              |
| method)                    | Widely used                    |                                                                           | Dependent on image quality                                                  |
|                            | Guides medical, device therapy |                                                                           |                                                                            |
| Wall motion score index    | Semiquantitative score of      | Easy to perform                                                           | Requires adequate visualisation of all segments                             |
|                            | segmental dysfunction          |                                                                           | Visualisation of lateral segments problematic                               |
| Tei Index                  | Reflects global performance    | Independent of HR, BP                                                     |                                                                            |
|                            | Incorporates systolic and      | Highly reproducible                                                        |                                                                            |
|                            | diastolic function             | Prognostic value in HF                                                    |                                                                            |
| TDI                        | Estimates myocardic            | Independent of 2D quality                                                | Subject to cardiac tethering                                               |
|                            | velocity signals               | Prognostic in cardiac disease                                             | Less accurate in AF, pacing                                                |
|                            |                                | Detects subclinical LV dysfunction                                       | Partial preload dependence                                                 |
| Strain/ Strain rate        | Measures tissue deformation    | Independent of tethering                                                  |                                                                            |
|                            | and its time course            | Detects subclinical disease                                               |                                                                            |
|                            |                                | Correlates with fibrosis                                                  |                                                                            |
|                            |                                | Viability /ischaemia with stress echo                                     |                                                                            |
| Dyssynchrony               | Multiple techniques            | Quantitative monitor for CRT                                             | Modest correlation to CRT benefit                                          |
| Real time 3D               | Acquires full volume data set  | Eliminates geometrical assumptions                                       |                                                                            |
|                            | Global and regional            | Identifies true LV apex                                                   |                                                                            |
|                            | quantification                 | Low intra/inter observer variability                                      |                                                                            |
|                            |                                |                                                                            | Not readily available/ accessible                                         |
|                            |                                |                                                                            | Time consuming with offline analysis                                       |

AMI = acute myocardial infarction, AF = atrial fibrillation, BP = blood pressure, CAD = coronary artery disease, CRT = cardiac resynchronisation therapy, HR = heart rate, HF = heart failure, LV = left ventricular, TDI = tissue Doppler imaging, TTE = transthoracic echocardiogram, U/S = ultrasound.
and mid segments from the three apical views and deriving the standard deviation (SD) between the 12 measurements, thereby creating a dysynchrony index. A SD ≥ 32 msec identified dysynchrony and correlated with a favourable CRT response. Similarly, speckle tracking can assess dys synchrony as also RT3DE that examines the time to minimum systolic volume (TMSV). LV torsion LV twist or torsion describes the wringing motion of the LV and represents the net difference in clockwise and counterclockwise rotation of the LV apex and base. Torsion occurs because of the varying orientation of the myocardial fibres; subendocardial fibres have a longitudinal orientation (∼80°) relative to the mid-wall where the fibres are circumferentially orientated (0°), and changes to an oblique orientation (-60°) subependicularly.

During isovolumic contraction, the LV apex shows brief clockwise rotation that reverses rapidly and becomes counterclockwise during LV ejection, followed by untwisting (clockwise rotation) during early diastole. In contrast, rotation of the base is lower in magnitude and opposite in direction. Torsion is a function of LV contractility and varies linearly with EF while “untwisting” correlates with the relaxation time constant (τ). Both TDI and speckle tracking can measure torsion and correlate with MRI. Twist mechanics can be applied in disease states; in hypertension, diastolic LV untwisting was delayed and reduced in parallel to the severity of LV hypertrophy, while in AMI patients, apical LV twist was severely depressed.

Real time 3D echocardiography
RT3DE employs matrix array transducers that acquire real time full volume data sets. The recently validated RT3DE volumetric quantification of global and regional LV function overcomes limitations of 2D echocardiography as it eliminates geometric assumptions, identifies the true LV apex and evaluates wall motion encompassing all planes. Jenkins, et al. demonstrated the correlation of RT3DE to MRI with lower intra and inter observer variability, whilst comparing it to computed tomography. Sugeng, et al. have shown its superiority in LVEF and volume measurement. RT3DE can assess LV dysynchrony and demonstrated a greater improvement from CRT with RT3DE guided LV lead placement. RT3DE is superior in ischaemic MR quantification as it visualises the true vena contracta and proximal flow convergence especially with eccentric MR.

Role of echocardiography in therapeutic intervention
Echocardiography has a valuable role in guiding and monitoring HF therapies as discussed below.

Medical therapy
Current ACCF/AHA HF guidelines, recommend ACE inhibitors for patients with current or prior symptoms of HF and reduced LVEF while beta-blockers are recommended in stable patients (level A evidence). The addition of an aldosterone antagonist is recommended in patients with moderate to severe HF. In the SOLVD echo substudy, Enalapril significantly reduced LV volumes and mass while Carvedilol decreased LV volumes and increased LVEF in the ANZ HF Collaborative Group. The Val-HeFT echo substudy showed similar changes in LV dimension and LVEF with valsartan therapy. Aldosterone antagonists (Spironolactone and Elprenone) have shown mortality reduction in NYHA class III and IV HF patients with EF ≤ 35% and in post AMI patients with EF ≤ 40%.

By the same token, echocardiography can be used to monitor the deleterious effects of cardioactive medications such as anthracycline chemotherapy, and treatment can be discontinued based on reduction in LV function.

Cardiac resynchronisation therapy
Cardiac resynchronisation therapy (CRT) has emerged as a therapy for advanced HF patients on optimal medical treatment that favourably affects symptoms, hospitalisation and mortality rate. A meta-analysis confirmed a 30% decrease in hospitalisations and mortality benefit (24–36%) with LV reverse remodelling, improved EF and reduced MR predicting improved survival. Current guidelines recommend CRT for patients on optimal medical therapy with EF ≤ 35%, in NYHA class III or IV with QRS ≥ 120 ms although a subgroup of patients with QRS < 120 ms can benefit from CRT. Single centre studies of CRT response in HF found that improvement was more likely in patients with echocardiographic dyssynchrony at baseline. However, two multicenter studies, the PROSPECT and ReThiNQ trials, used echocardiographic criteria for patient selection and found only modest correlation between echocardiographic indices and CRT benefit. Additionally, a consistent finding from CRT trials, is a lack of benefit in approximately one third of patients (CRT nonresponders).

ICD implantation
In HF patients with reduced EF and previous cardiac arrest, ICD has shown mortality benefits despite optimal medical therapy. The AVID, CIDS and CASH trials established that ICD improved survival compared with antiarrhythmic agents for secondary prevention of sudden cardiac death (SCD). Other randomised, multicentre studies including MADIT I and II, MUSTT and the SCD-HeFT, established ICD therapy as effective for primary prevention of SCD in selected patient populations. The LVEF cut offs used in these trials were < 40% in MUSTT, < 35% in MADIT I and SCD-HeFT and < 30% in MADIT II. Based on these trials, present guidelines recommend an echocardiographic LVEF 30–40% for ICD implantation in specific patient groups.

Many patients eligible for CRT also meet criteria for ICD implantation. The COMPANION trial demonstrated the benefit of combined therapy with CRT and ICD over optimal medical therapy in patients with LVEF ≤ 35% with prior hospitalisation for HF.

Correction of ischaemic MR/ MV surgery
Ischaemic MR following an AMI is associated with increased mortality as demonstrated in the CADILLAC trial where those with MR had higher mortality rates at 30 days and at one year. A similar increase in mortality over the longer term (five years) with ischaemic MR was reported. Ischemic MR also predicts the development of HF in AMI patients with a little or no symptoms at base-
line\textsuperscript{11} and HF risk with moderate to severe MR was ~50% at two years in one series\textsuperscript{12,13}.

Evaluation of ischaemic MR is integral to post AMI assessment, particularly if surgical revascularisation is being considered\textsuperscript{14}. Echocardiography both peri- and intra-operatively can assess the mechanism and severity of MR and provide information as to the suitability for valvuloplasty or replacement. Intra-operative TOE tends to downgrade MR severity as a consequence of altered loading conditions under anaesthesia\textsuperscript{122}. Mitral valve repair rather than replacement should be attempted in experienced centres\textsuperscript{123,124}; however, the advantages of valve repair must be weighed against technical expertise and MR recurrence.

**Conclusion**

The evolving echocardiographic technologies have made it an indispensable modality of non-invasive cardiac imaging in the assessment of systolic HF providing information for diagnosis, quantification, therapeutic decision making and for monitoring treatment response. Newer echocardiographic modalities such as TDI, speckle tracking, twist mechanics, as well as RT3DE hold promise for improved accuracy of LV function assessment that would translate into benefits for HF patients by improved clinical care.

**References**

1. AHA. Heart disease and stroke statistics – 2004 update. Dallas Texas: American Heart Association, 2004.
2. NHF & CSANZ. Australian Institute of Health and Welfare. Issue 3 June 2003.
3. AIHW. Heart, stroke and vascular diseases: Australian facts 2004. Canberra: Australian Institute of Health and Welfare, 2004. Available online at www.aihw.gov.au/publications/cvd/hsvd04/hsvd04.pdf [verified June 2007].
4. Najafi F, Dobson AJ, Jamrozik K. Is mortality from heart failure increasing in Australia? An analysis of official data on mortality for 1997–2003. Ball World Health Oly 2006; 84: 722–8.
5. Hunt S, Abraham WT, Chin MH, et al. 2006 Focused Update: ACC/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2006; 114: e544–99.
6. Whellan DJ, Fonarow GC, Lee ET, et al. 2006 Focused Update: ACC/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119: e391–e479.
7. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused Update: ACC/AHA guidelines. J Am Coll Cardiol 2009; 23: 1002–1018.
8. Waller BF, Adams DF, Califf RM, et al. 2009 Focused Update: ACCF/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American Society of Echocardiography. J Am Coll Cardiol 2009; 43: 2263–319.
9. Waller BF, Adams DF, Califf RM, et al. 2009 Focused Update: ACCF/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American Society of Echocardiography. J Am Coll Cardiol 2009; 43: 2263–319.
10. Waller BF, Adams DF, Califf RM, et al. 2009 Focused Update: ACCF/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American Society of Echocardiography. J Am Coll Cardiol 2009; 43: 2263–319.
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29 Enriquez-Sarano M. Timing of mitral surgery. *Heart* 2002; 87: 79–85.
30 Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in heart failure. *J Am Coll Cardiol* 2007; 50 (5): 381–96.
31 Tei C, Nishimura RA, Seward JB, Tajik AJ. Non invasive Doppler derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterisation measurements. *J Am Soc Echocardiogr* 1997; 10: 169–78.
32 Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB. Value of a Doppler index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. *Am J Cardiol* 1998; 81: 1157–61.
33 Dujardin KS, Tei T, Yeo TC, Rossi AD, Seward JB. Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy. *Am J Cardiol* 1998; 82: 1071–6.
34 Amlov J, Ingelson E, Riserus U, Andreb L, Lind L. Myocardial performance index, a Doppler derived index of global left ventricular function, predicts congestive heart failure in elderly men. *Eur Heart J* 2004; 25: 2220–5.
35 Mikkelsen KV, Moller JE, Bie P, Ryde H, Vildebaek L, Haghfelt T. Tei index and neurohormonal activation in patients with incident heart failure: serial change and prognostic value. *Eur J Heart Fail* 2006; 8 (6): 599–608.
36 Sutherland GR, Bijens B, McDicken WN. Tissue Doppler echocardiography: historical perspective and technological considerations. *Echocardiography* 1999; 16: 445–53.
37 Gohrsan J, Gulati VK, Mandarino WA, Katz WE. Colour coded measures of myocardial velocity throughout the cardiac cycle by tissue Doppler Imaging to quantify regional left ventricular function. *Am Heart J* 1996; 131: 1203–13.
38 Abrahart TP, Dimanno VL, Liang HY. Role of tissue Doppler and strain echocardiography in current clinical practice. *Circulation* 2007; 116: 2597–609.
39 Wang M, Yip G, Yu CM, Zhang Q, Zhang Y, Tse D, et al. Independent and incremental prognostic value of early mitral annulus velocity in patients with impaired left ventricular systolic function. *J Am Coll Cardiol* 2005; 45 (2): 272–7.
40 Hillis GS, Moller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR, et al. Noninvasive estimation of left ventricular filling pressure by E/E’ is a powerful predictor of survival after acute myocardial infarction. *J Am Coll Cardiol* 2004; 43 (3): 360–67.
41 Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Tissue Doppler imaging provides independent prognostic value in patients with systemic hypertension and left ventricular hypertrophy. *J Hypertens* 2005; 23 (1): 183–91.
42 Fang ZY, Leano R, Marwick TH. Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. *Clin Sci (Lond)* 2004; 106: 53–60.
43 Sanderson JE, Wang M, Yu CM. Tissue Doppler imaging for predicting outcome in patients with cardiovascular disease. *Curr Opin Cardiol* 2004; 19: 458–63.
44 Marwick TH, Case C, Leano R, Short L, Baglin T, Cain P, Garrahy P. Use of tissue Doppler imaging to facilitate the prediction of events in patients with abnormal left ventricular function by dobutamine echocardiography. *Am J Cardiol* 2004; 93: 142–6.
45 Sanderson JE. Heart failure with a normal ejection fraction. *Heart* 2007; 93: 155–8.
46 Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. *J Am Coll Cardiol* 2003; 41: 820–6.
47 Nikitin NP, Loh PH, Silva R, Ghosh J, Khaleva OY, Goode K, et al. Prognostic value of systolic mitral annular velocity measured with Doppler tissue imaging in patients with chronic heart failure caused by left ventricular systolic dysfunction. *Heart* 2006; 92: 725–9.
48 Marwick TH. Measurement of Strain and Strain Rate by echocardiography: ready for prime time? *J Am Coll Cardiol* 2006; 47 (7): 1313–27.
49 Heimdal A, Stoylen A, Torp H, Skjærpe T. Real-time strain rate imaging of the left ventricle by ultrasound. *J Am Soc Echocardiogr* 1998; 11: 1013–19.
50 Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004; 17: 1021–9.
51 Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. *Circulation* 2000; 102: 1158–64.
52 Edvardsen T, Gerber BL, Garot J, Bluenkena DA, Lima JA, Smiseth OA. Quantitative assessment of intrinsic regional myocardial deformation by Doppler strain rate echocardiography in humans: validation against 3-dimensional tagged magnetic resonance imaging. *Circulation* 2002; 106: 50–6.
53 Sun JP, Popovic ZB, Greenberg NL, Xu XF, Asher CR, Stewart WJ, Thomas JD. Noninvasive quantification of regional myocardial function using Doppler-derived velocity, displacement, strain rate, and strain in healthy volunteers: effects of aging. *J Am Soc Echocardiogr* 2004; 17: 132–8.
54 Yuda S, Short L, Leano R, Marwick TH. Myocardial abnormalities in hypertensive patients with normal and abnormal left ventricular filling: a study of ultrasound tissue characterisation and strain. *Clin Sci (Lond)* 2002; 103: 283–93.
55 Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH. Echocardiographic detection of early diabetic myocardial disease. *J Am Coll Cardiol* 2003; 41: 611–17.
56 Sutherland GR, Di Salvo G, Claus P, D’hoooge J, Bijens B. Strain and strain rate imaging: a new clinical approach to quantifying regional myocardial function. *J Am Soc Echocardiogr* 2004; 17: 788–802.
57 Park TH, Nagahse SF, Khoury DS, Kopelen HA, Akrivakis S, Nasser K, et al. Impact of myocardial structure and function post infarction on diastolic strain measurements: implications for assessment of myocardial viability. *Am J Physiol Heart Circ Physiol* 2006; 290: H724–31.
58 Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. *Circulation* 2004; 110: 558–65.
59 Yip G, Khandheria B, Belohlavek M, Pislaru C, Seward J, Bailey K, et al. Strain echocardiography tracks dobutamine induced decrease in regional myocardial perfusion in non-obstructive coronary stenosis. *J Am Coll Cardiol* 2004; 44: 1664–71.
60 Weidemann F, Jamal F, Kowalski M, Kakuluki T, D’hooge J, Bijens B, et al. Can strain rate and strain quantify changes in regional systolic function during dobutamine infusin, beta blockade and atrial pacing? *J Am Soc Echocardiography* 2002; 15: 416–24.
61 Hoffmann R, Altiek E, Nowak B, Heussen N, Kühl H, Kaiser HJ, et al. Strain rate measurement by Doppler echocardiography allows improved assessment of myocardial viability in patients with depressed left ventricular function. *J Am Coll Cardiol* 2002; 39: 443–49.
62 Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. *J Am Coll Cardiol* 1994; 24: 132–9.
63 Wang M, Yip G, Yu CM, Zhang Q, Zhang Y, Tse D, et al. Independent and incremental prognostic value of early mitral annulus velocity in patients with impaired left ventricular systolic dysfunction. *J Am Coll Cardiol* 2005; 45: 272–7.
64 Nagahse SF, Middleton KJ, Kopelen HA, Zogbi WA, Quiñones MA. Doppler Tissue imaging: a non invasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997; 30: 1527–33.
65 Yamamoto T, Oki T, Yamada H, Tanaka H, Ishimoto T, Wakatsuki T, et al. Prognostic value of the atrial systolic annular motion velocity in patients with left ventricular systolic dysfunction. *J Am Soc Echocardiogr* 2003; 16: 333–9.
66 Fung JW, Yu CM, Yip G, Zhang Y, Chan H, Kunn CC, Sanderson JE. Variable left ventricular activation pattern in patients with heart failure and left bundle branch block. *Heart* 2004; 90: 17–19.
67 Bleeker GB, Schalij MJ, Molhoek SG, Holman ER, Verwey HF.
Steendijk P, et al. Frequency of left ventricular dysynchrony in patients with heart failure and a narrow QRS complex. *Am J Cardiol* 2005; 95 (1): 140–142.

Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart* 2003; 89: 54–60.

Pitzalis MV, Iacovelli M, Romito R, Massari F, Rizzon B, Luzzi G, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol* 2002; 40: 1615–22.

Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, et al. Left ventricular dysynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004; 44: 1834–40.

Yu CM, Zhang Q, Fung JW, Chan HC, Chan YS, Yip GW, et al. A novel tool to assess systolic dysynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging. *J Am Coll Cardiol* 2005; 45: 677–84.

Yu CM, Fung JW, Zhang Q, Chan CK, Chan YS, Lin H, et al. Tissue Doppler imaging is superior to strain rate imaging and post systolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. *Circulation* 2004; 110: 66–73.

Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. *Am J Cardiol* 2003; 91: 684–88.

Suffoletto MS, Dohi K, Camessoni M, Saba S, Gorcsan J 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dysynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006; 113 (7): 960–68.

Mor-Avi V, Sugeng L, Lang RM. Contemporary Reviews in Cardiovascular Medicine: Real-Time 3-Dimensional Echocardiography an Integral Component of the Routine Echocardiographic Examination in Adult Patients? *Circulation* 2009; 119: 314–29.

Kapetanakis S, Kearney MT, Siva A, Gall N, Cooklin M, Monaghan MJ. Real-time three-dimensional echocardiography—a novel technique to quantify global left ventricular mechanical dyssynchrony. *Circulation* 2005; 112 (7): 992–1000.

Sengupta P, Jamil Taje A, Chandrasekaran K, Khandheria BK. Twist mechanics of the left ventricle. *J Am Coll Cardiol Cardiaccvasc Im* 2008; 1 (3): 366–76.

Smiseth OA, Remme EW. Regional left ventricular electric and mechanical activation and relaxation. *J Am Coll Cardiol* 2006; 47: 173–4–

Ingels NB Jr, Hansen DE, Daughters GT 2nd, Stinson EB, Alderman EL, Miller DC. Relation between longitudinal, circumferential, and oblique shortening and torsional deformation in the left ventricle of the transplanted human heart. *Circ Res* 1989; 64: 915–27.

Narula J, Vannan MA, DeMaria AN. Of that Waltz in my heart. *J Am Coll Cardiol Cardiovasc Imag* 2007; 20: 558–65.

Kahlert P, Plicht B, Erbel R, Buck T. Direct assessment of proximal jet area in mitral regurgitation using real time three dimensional colour Doppler echocardiography: comparison with two dimensional proximal jet width and function: side by side comparison of real time three dimensional echocardiography and computed tomography with magnetic resonance reference. *Circulation* 2006; 114: 654–61.

Soliman OI, Geleijnse MJ, Theuns DAMJ. Effects of left ventricular pacing site and outcome after CRT using novel real-time three dimensional echocardiography technique to define site of latest activation (abstr). *J Am Soc Echocardiogr* 2007; 20: 558.

Greenberg B, Quinones MA, Koipillai C, Limacher M, Shindler D, Benedict C. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: results of SOLVD echocardiographic substudy. *Circulation* 1995; 91: 2573–81.

Dougherty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N, Australia-New Zealand Heart Failure Research Collaborative Group. Left ventricular remodelling with carvedilol in patients with congestive heart failure due to ischaemic heart disease. *J Am Coll Cardiol* 1997; 29: 1060–6.

Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomised Aldactone Evaluation Study Investigators. *New Engl J Med* 1999; 341: 709–17.

Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Eplerone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators, et al. Epleronone, a selective aldosterone blocker, in patients with left ventricular dysfunction: results of SOLVD myocardial infarction. *New Engl J Med* 2003; 348: 1309–21.

Youssef G, Links ML. The prevention and management of cardiovascular complications of chemotherapy in patients with cancer. *Am J Cardiovasc Drugs* 2005; 5: 233–43.

Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, DeMarco T. Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators, et al. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *New Engl J Med* 2004; 350: 2140–50.

Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators, et al. The effect of cardiac resynchronization therapy on morbidity and mortality in heart failure. *New Engl J Med* 2005; 352: 1539–49.

Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003; 289: 730–40.

Yu CM, Fung JWH, Lin H, Zhang Q, Sanderson JE, Lau CP, et al.
Left ventricular reverse remodelling but not clinical improvement predicts long-term survival after cardiac resynchronisation therapy. *Circulation* 2005; 112: 1580–6.

103 ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. A report of the ACC/AHA Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008; 51 (21): e1–62.

104 Leclercq C, Faris O, Tunin R, Johnson J, Kato R, Evans F, et al. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle-branch block. *Circulation* 2002; 106: 760–63.

105 Penicka M, Bartunek J, De Bruyne B, Vanderheyden M, Goethals M, De Zutter M, et al. Improvement in left ventricular function after cardiac resynchronisation s predicted by tissue Doppler imaging echocardiography. *Circulation* 2004; 109 (8): 978–83.

106 Mele D, Pasanisi G, Capasso F, De Simone A, Morales MA, Poggio D, et al. Left intraventricular myocardial deformation dysynchrony identifies responders to cardiac resynchronisation therapy in patients with heart failure. *Eur Heart J* 2006; 27 (9): 1070–8.

107 Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the predictors of Response to CRT (PROSPECT) Trial. *Circulation* 2008; 117: 2608–16.

108 Beshai JF, Grimm R, Rethin Q Investigators. Cardiac-resynchronisation therapy in heart failure with narrow QRS complexes. *New Engl J Med* 2007; 357: 2461–71.

109 Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. *J Am Coll Cardiol* 2005; 46: 2183–92.

110 The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997; 337: 1576–83.

111 Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; 101: 1297–302.

112 Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; 102: 748–54.

113 Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannon DS, Multicenter Automatic Defibrillator Implantation Trial II Investigators, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *New Engl J Med* 2002; 346: 877–83.

114 Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; 341: 1882–90.

115 Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *New Engl J Med* 2005; 352: 225–37.

116 Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. Executive Summary. *J Am Coll Cardiol* 2008; 51 (21): 2085–105.

117 Bristow MR, Saxon LA, Boehmer J, Knueger S, Kass DA, De Marco T. Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators, et al. Cardiac-resynchronisation therapy with or without an implantable defibrillator in advanced chronic heart failure. *New Engl J Med* 2004; 350: 2140–50.

118 Pellizzon GG, Grines CL, Cox DA, Stuckey T, Tcheng JE, Garcia E, et al. Importance of mitral regurgitation in patients undergoing percutaneous coronary intervention for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *J Am Coll Cardiol* 2004; 43: 1368.

119 Grigioni F, Detaint D, Avierinos JF, Scott C, Tajik J, Enriquez-Sarano M. Contribution of ischaemic mitral regurgitation to congestive heart failure after myocardial infarction. *J Am Coll Cardiol* 2005; 46: 260–7.

120 Aronson D, Goldsher N, Zukermonds R, Kapelowich M, Lessick J, Mutlak D, et al. Ischaemic mitral regurgitation and risk of heart failure after myocardial infarction. *Arch Intern Med* 2006; 166: 2362–8.

121 Gillinov AM, Wierup PN, Blackstone EH, Bishay ES, Cosgrove DM, White J, Lytle BW, et al. Is repair preferable to replacement for ischaemic mitral regurgitation? *J Thorac Cardiovasc Surg* 2001; 122: 1125.

122 Aklog L, Filsoufi F, Flores KQ, Chen RH, Cohn LH, Nathan NS, et al. Does coronary artery bypass grafting alone correct moderate ischaemic mitral regurgitation? *Circulation* 2001; 104 (suppl 1): I-68–75.

123 Lavie CJ, Gersh BJ. Mechanical and electrical complications of acute myocardial infarction. *Mayo Clin Proc* 1990; 65: 709.

124 David TE. Techniques and results of mitral valve repair for ischaemic mitral regurgitation. *J Card Surg* 1994; 9: 274.