Left Ventricular Dyssynchrony in Hypertensive Patients Without Congestive Heart Failure

Address for correspondence:
Jannet F. Lewis, MD
Department of Cardiovascular Science University of Michigan
Suite 4–414
Washington, DC 20037, USA
jlewis@mfa.gwu.edu

Benjamin Yang, MD, Dennis Chettiveettil, Fermon Jones, Millan Aguero, Jannet F. Lewis, MD
Division of Cardiology, Department of Medicine, George Washington University Medical Center, Washington DC, USA

ABSTRACT

Background: Normal left ventricular (LV) systolic function is present in as many as 50% of patients with congestive heart failure. The majority of such patients have systemic hypertension. Recent studies have demonstrated LV dyssynchrony among patients with heart failure and normal systolic function. However, it is unclear whether such abnormalities exist in hypertensive patients who have not developed clinical evidence of heart failure.

Methods: Hospitalized patients with established hypertension undergoing echocardiography who met the following criteria were eligible for the study: LV ejection fraction (EF) $\geq$50%, wall thickness $\geq$11 mm, absence of valvular or known ischemic disease, and normal QRS duration. Complete 2-Dimensional and Doppler echocardiography studies with tissue Doppler imaging (TDI) were performed in all patients. Dyssynchrony was measured using time from QRS to peak systolic velocity on TDI (T-P) in 3 apical views. Normal values for dyssynchrony were established in a group of normotensive patients with normal echocardiography studies.

Results: The study included 42 patients (19 women, 23 men with a, mean age of 59.6 y (range 32–96 y). Left ventricular dyssynchrony was common, occurring in 20 of 42 patients (47.6%). Dyssynchrony assessed with the maximum T-P (T-Pmax) was significantly related to LV mass ($r = 0.32$, $p = 0.036$), left atrial volume ($r = 0.59$, $p < 0.0001$), and LV sphericity index (0.32, $p = 0.037$). Dyssynchrony was not related to age or LV filling pressure calculated from the Doppler study.

Conclusions: Left ventricular dyssynchrony is common among hypertensive patients with normal LV systolic function and no evidence of congestive heart failure. The severity of LV dyssynchrony is related to the magnitude of LV hypertrophy, left atrial size, and LV remodeling.

Key words: hypertension, heart failure, left ventricular dyssynchrony

Introduction

Systemic hypertension is present in approximately 60 million individuals in the US.[1] Such individuals are predisposed to the development of major cardiovascular events, including congestive heart failure. Indeed, hypertension is a major cause of heart failure with normal left ventricular (LV) systolic function. Such individuals make up as many as 50% of patients treated for heart failure. Although the causes of systolic heart failure have been well examined, the mechanism of diastolic heart failure, or heart failure with normal systolic function, has been the subject of continued discussion.[2,3] Abnormal LV relaxation with elevated LV filling pressures secondary to a stiff, hypertrophied ventricle has been the most common explanation.[2] Recent studies have demonstrated significant LV dyssynchrony among patients with heart failure and preserved LV systolic function, providing further insight into the mechanism of heart failure with normal LV systolic function.[4,5] Whether LV dyssynchrony is only concomitant with heart failure or precedes the development of heart failure is unclear. The present study assessed LV dyssynchrony in hypertensive patients with normal systolic function and without the clinical syndrome of congestive heart failure.

Methods

The study group consisted of inpatients at George Washington University Hospital (Washington, DC, USA) undergoing clinically indicated transthoracic echocardiography studies and who met the following criteria: LV wall thickness $\geq$11 mm, LV ejection fraction (EF) $\geq$50%, and QRS duration $<$120 msec. Patients were excluded from the study if the following were present: congestive heart failure using Framingham criteria,[6] LV segmental wall motion abnormalities, evidence of valvular heart disease (regurgitation more than mild or any degree of stenosis), pulmonary hypertension, pericardial disease, atrial fibrillation, or renal insufficiency with creatinine $\geq$1.5.

Each patient had complete 2-Dimensional and Doppler echocardiography study using commercially available equipment (Philips Medical, Andover, Mass., USA). In addition, pulsed tissue Doppler imaging (TDI) recordings were obtained in basal and mid-LV segments from 3 apical views. Digital images were saved on magneto

Received: September 12, 2007
Accepted with revision: November 22, 2007

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20350

optical (MO) disc or network, and were analyzed off-line (Freeland System AccessPoint, Westminster, Colo., USA, and Encompass HeartLab, Westerly, RI, USA). Left ventricular measurements were made according to recommendations of the American Society of Echocardiography.[6] Left ventricular mass was calculated using a previously published formula[7] and indexed to both body surface area (BSA) (g/m^2) and height (g/m).[8] Left ventricular sphericity index was calculated as the ratio of LV end-diastolic diameter (in parasternal long-axis view) to diastolic longitudinal length obtained from an apical 4-chamber view. Left atrial volume was calculated from atrial area and length (L) in apical 2-chamber (A2) and 4-chamber (A1) views using the formula $[(0.85 \times A1 \times A2)/L]$.[6] Left atrial measurements were made at maximum atrial size just prior to mitral valve opening. Left atrial volume was indexed to BSA (g/m^2).

Pulsed wave tissue Doppler samples were obtained from basal and mid segments in 3 apical views: 4-chamber, 2-chamber, and apical long-axis. Gain and filter settings were adjusted to obtain optimal TDI images. The sonographer ensured that the electrocardiogram (ECG) recording during TDI samples was adequate for temporal measurement. The TDI measurements were made by a single reader. Left ventricular and left atrial measurements were made independently by a second observer.

Assessment of Left Ventricular Systolic Dyssynchrony

Left ventricular dyssynchrony was assessed from measurements of time intervals from onset of the QRS complex to the peak systolic velocity on the pulsed tissue Doppler waveform (T-P) in the 3 apical views. The maximum T-P was measured as the maximal difference of T-P between any 2 opposing LV walls. Additional LV dyssynchrony measurements included maximum interval between onset of QRS complex to onset of systolic velocity on pulsed tissue Doppler (T-Omax), and difference in T-P between the septal and lateral walls (i.e., septal-lateral delay).

A control group of 20 normotensive patients with normal echocardiography studies was used to establish normal values of LV synchrony. Controls were selected based on the presence of a normal echocardiography and Doppler study, normal ECG (QRS duration 84.8±9.6 msec), and absence of major medical problems including diabetes mellitus, hypertension, and coronary artery disease. Mean age of the controls was 50.7±12.7 y. Left ventricular wall thicknesses were normal (i.e., septal thickness 0.87±0.14 and posterior wall thickness 0.88±0.13). Left ventricular mass and mass index were within sex-specific normal limits (i.e., 142.1±46.2 g and 83.6±25.1 g/m, respectively).[8] A T-Pmax value of 50 msec was selected as the cut point for LV dyssynchrony. This value exceeded 2 standard deviations (SDs) of the mean value in the control group, 20.4±9.9 msec, and is comparable to previously published T-Pmax criteria for defining dyssynchrony.[9] The previously published LV dyssynchrony cut point of 40 msec was also assessed.[9] Similiarly, a cut point of 40 msec was selected for both T-Omax and septal-lateral delay based on mean control values (T-Omax 14.4±7.9; septal-lateral delay 10.7±8.5).

Data Analysis

Microsoft Excel with Analyse-it add-on software was used to analyze the data (Microsoft Corp., Redmond, Wash., USA). Continuous data are expressed as means±SDs. Pearson correlations with 2-tailed analysis were used to test associations between continuous data sets (e.g., between LV mass and dyssynchrony, and between left atrial size and dyssynchrony). Values were considered significant at $p < 0.05$.

Results

Baseline Characteristics

The study included 42 patients; 19 women and 23 men. Mean age was 59.6±13.6 y and ranging from 32–96 y. Mean LV mass/height was 124.3±42.3 g/m; 7 men and 13 woman met sex-specific criteria for LV hypertrophy.[8] Patient demographics are summarized in Table 1. Patients were on a variety of antihypertensive medications (Table 1), including 22 of 42 patients taking 2 or more drugs (52%) and 13 of 42 patients (31%) taking 3 or more antihypertensive medications. Mean systolic blood pressure performed within 6 h of the echocardiography study was 144±21 mm Hg. Mean systolic blood pressure on admission to the emergency department was 162±40 mm Hg. No patient was currently hospitalized for congestive heart failure or met Framingham criteria for prior episodes of heart failure. The QRS duration in hypertensive patients was 86.5±11.7 msec and did not differ from controls (84.8±9.6 msec, p = ns).

Left ventricular systolic dyssynchrony, using T-Pmax >50 msec, was commonly identified in patients in the hypertensive study; 20 of 42 patients (47.6%; Figure 1). The T-Pmax in hypertensives with dyssynchrony ranged from 51 to 217 msec. Using a 40-msec cut point, 22 of 42 patients (52.4%) met the criterion for LV systolic dyssynchrony, with T-Pmax ranging from 42 to 217 msec. Dyssynchrony based on septal–lateral delay identified 24 of 42 patients (57.1%), whereas T-Omax identified only 4 patients.

Correlates of Left Ventricular Dyssynchrony

Left ventricular dyssynchrony assessed by T-Pmax was significantly associated with LV mass/height, that is, greater LV dyssynchrony was observed with increasing LV mass/height ($r = 0.32$, $p = 0.036$) (Figure 2). A similar relationship was observed between T-Pmax and left atrial volume ($r = 0.59$, $p < 0.0001$) or left atrial volume index ($r = 0.51$, $p = 0.001$) (Figure 3). In addition, LV systolic dyssynchrony was significantly associated with LV remodeling. The T-Pmax showed positive correlation to increasing LV sphericity ($r = 0.32$, $p = 0.036$) (Figure 4).

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20350

TABLE 1: Characteristics of 42 hypertensive patients without heart failure

Age (y)	59.6±13.6
Gender (male/female)	23/19
BSA (m^2)	1.92±0.23
Height (m)	1.69±0.11
Systolic blood pressure (mm Hg)	147.4±22.5
Hyperlipidemia (%)	19 (45%)
Diabetes (%)	10 (24%)
Antihypertensive medications[a]	
ACEi or ARB	18 (43%)
β-blocker	15 (36%)
CCB	13 (31%)
Diuretic	18 (43%)
Alpha-2 agonist	3 (7%)
ECG Findings	
QRS duration (msec)	86.5±11.7
PR interval (msec)	165±23.5

[a]Twenty-two of 42 patients were on ≥2 anti-hypertensive medications; 13 of 42 patients were on ≥3. *Abbreviations*: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BSA = body surface area; CCB = calcium channel blocker; ECG = electrocardiogram.

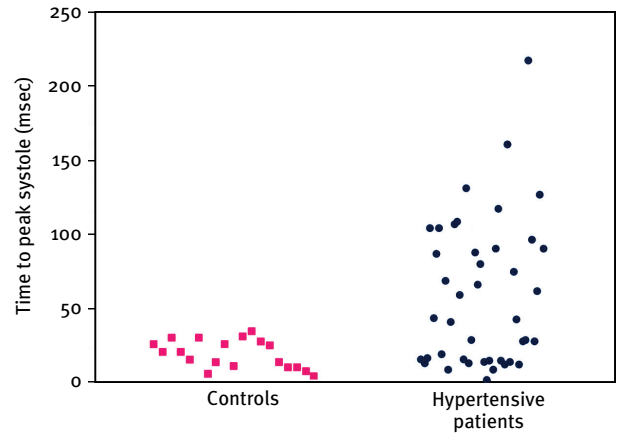

Figure 1: Scatter plot showing distribution of LV systolic dyssynchrony between controls (patients without hypertension or echocardiographic evidence of cardiac disease) and hypertensive patients. T-Pmax systole = maximal time difference from onset QRS to peak myocardial systolic velocity between any 2 LV segments.

TABLE 2: Echocardiographic findings in 42 hypertensive study patients

Ejection fraction (%)	65.7±9.3
LV mass (g)	211.4±78
LV mass indexed to BSA (g/m^2)	109.8±36.3
LV mass indexed to height (g/m)	124.3±42.3
LV septal thickness (mm)	1.36±0.24
LV posterior wall thickness (mm)	1.26±0.24
LA volume (mL)	54.7±19.4
LA volume indexed to BSA (mL/m^2)	28.6±9.6
Sphericity index	0.48±0.07
T-Pmax to Systole (msec)	58.2±49.6
Patients with dyssynchrony by T-Pmax >50 msec	20/42 (46%)
Patients with dyssynchrony by T-Pmax >40 msec	22/42 (52.4%)
Patients with dyssynchrony by septal–lateral delay	24/42 (57.1%)

Abbreviations: BSA = body surface area; EF = ejection fraction; LA = left atrial; LV = left ventricular; T-Pmax = maximum QRS to peak systolic velocity on TDI.

Left ventricular dyssynchrony assessed by septal–lateral delay showed nearly similar, but not superior, correlations to LV mass/height ($r = 0.29$, $p = 0.058$), left atrial volume ($r = 0.54$, $p<0.0003$), left atrial volume index ($r = 0.48$, $p = 0.0018$), and LV sphericity ($r = 0.31$, $p = 0.044$) (Table 2). The QRS duration did not differ among hypertensive patients with or without LV dyssynchrony (87.0±13.7 versus 85.7±9.6 msec, p = ns).

Discussion

The present study demonstrates that LV systolic dyssynchrony occurs frequently among hypertensive patients with normal systolic function and without clinical evidence of congestive heart failure. Left ventricular dyssynchrony among such patients is related to the magnitude of LV hypertrophy and left atrial size. These findings extend the findings of previous reports of LV dyssynchrony in diastolic heart failure, most commonly associated with hypertension.[6,7]

Patients with heart failure and preserved LV systolic function constitute as many as 50% of the heart failure population. The presence of this clinical entity is well recognized and appears to be related to age, sex, and the presence of systemic hypertension. The mechanism by which heart failure occurs in certain patients meeting this clinical profile but not in others is less clear.

In patients with heart failure because of decreased LV systolic function, dyssynchrony is a frequent finding[9–12] and is associated with poor clinical outcomes. In such patients, dyssynchrony appears to be related to abnormal

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20350

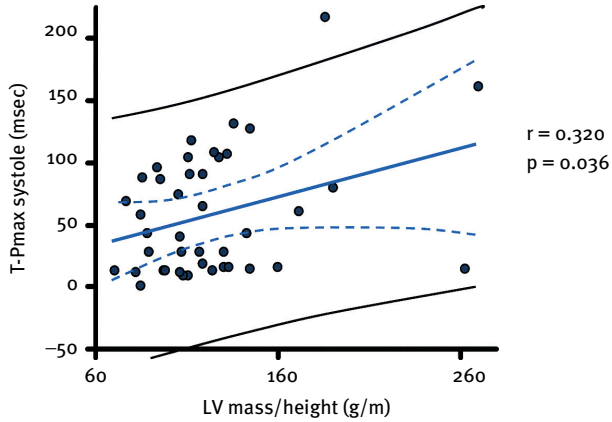

Figure 2: Scatter plot with linear regression analysis showing correlation between LV mass normalized by height and LV systolic dyssynchrony measured with T-Pmax systole. Abbreviation same as those in Figure 1.

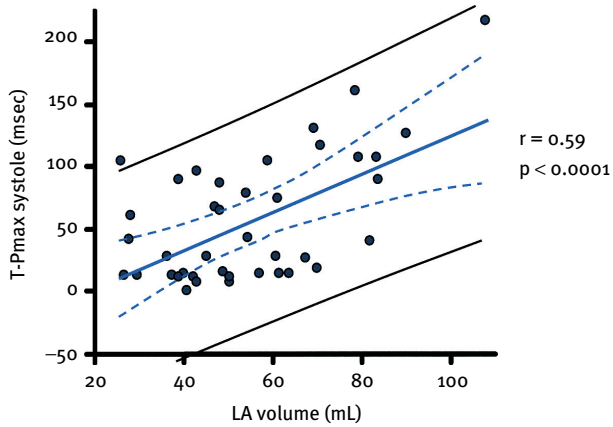

Figure 3: Scatter plot with linear regression analysis showing correlation between left atrial volumes and LV systolic dyssynchrony, or T-Pmax systole. Abbreviation same as those in Figure 1.

remodeling of the heart with consequent mitral regurgitation. Improvement of synchrony following biventricular pacemaker placement is associated with improved cardiac symptoms, favorable remodeling with reduced mitral regurgitation, and improved survival.[12–17]

Previous investigations have reported evidence of LV dyssynchrony in patients with normal systolic function and congestive heart failure. In a study by Yu et al.[5] of patients with diastolic and systolic heart failure, systolic asynchrony was observed in 39% of patients with normal LV systolic function. Hypertensive heart disease was found in 60% of the cohort studied. The study by Wang et al. also assessed Left vetnricular dyssynchrony in patients with heart failure and preserved systolic function, 66% of whom were hypertensive.[4] Left ventricular systolic dyssynchrony was observed in 33% of patients. These investigators

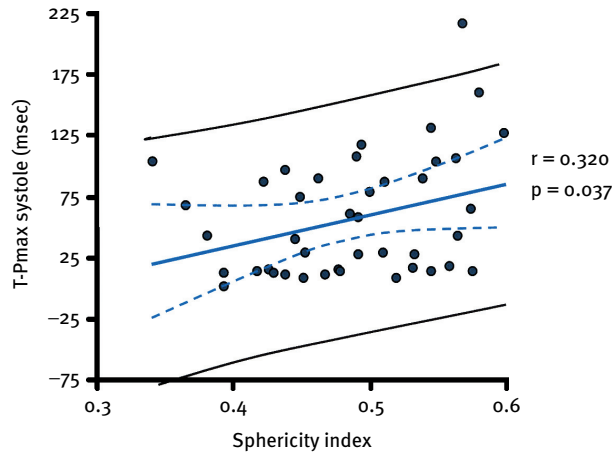

Figure 4: Scatter plot with linear regression analysis showing correlation between LV remodeling (measured with sphericity index) and LV systolic dyssynchrony, or T-Pmax systole. Abbreviations same as those in Figure 1.

TABLE 3: Pearson's Correlations of Left Ventricular Systolic Dyssynchrony with LV Mass, Left Atrial Size and LV Remodeling

	Pearson Correl.	p-value
LV Mass/Height index	0.320	0.036
LA volume	0.590	<0.0001
LA volume index	0.51	0.0007
LV remodeling (sphericity index)	0.320	0.037

also showed significant correlation to invasively measured pulmonary wedge pressure.

Our study extends the findings of these studies, and identifies LV dyssynchrony in hypertensive patients without clinically overt congestive heart failure or evidence of conduction abnormalities. The relationships observed in our study between dyssynchrony and LV mass, left atrial size, and ventricular sphericity provide further insight into the effects of hypertension on LV function and the potential mechanism for the development of clinical heart failure in patients with normal systolic function. Hypertension results in LV hypertrophy, increased LV filling pressure, and ultimately increased left atrial volume. The latter has been demonstrated to have important prognostic implications for cardiovascular events.[18–21] Left ventricular remodeling (abnormal LV sphericity) parallels the development of hypertrophy and changes in left atrial size. These changes are accompanied by changes in ventricular synchrony that may precede the development of clinical heart failure.

Conclusions

Patients with systemic hypertension but without clinical heart failure often demonstrate LV systolic dyssynchrony

by TDI. The severity of dyssynchrony is significantly related to LV mass, left atrial volume, and LV remodeling. Systolic dyssynchrony may identify hypertensive patients at risk for the development of congestive heart failure, and who may benefit from more intensive hypertension control at an earlier stage in their disease process. Follow-up study will be necessary to determine whether LV dyssynchrony in hypertensive patients is associated with the subsequent development of heart failure.

References

1. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, et al.: Heart disease and stroke statistics—2006 update. *Circulation* 2006;113:85–151
2. Zile MR, Baicu CF, Gaasch WH: Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;350:1953–1959
3. Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JG: Diastolic heart failure: neglected or misdiagnosed? *J Am Coll Cardiol* 2002;39:138–141
4. Wang J, Kurrelmeyer KM, Torre-Amione G, Nagueh SF: Systolic and diastolic dyssynchrony in patients with diastolic heart failure and the effect of medical therapy. *J Am Coll Cardiol* 2007;49:88–96
5. Yu C-M, Zhang Q, Yip GWD, Lee P-W, Kum LCC, et al.: Diastolic and systolic asynchrony in patients with diastolic heart failure. *J Am Coll Cardiol* 2007;49:97–105
6. McKee PA, Castelli WP, McNamara PM, Kannel WB: The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;285:1441–1446
7. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, et al.: members of the Chamber Quantification Writing Group: Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–1463
8. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, et al.: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57:450–458
9. Galderisi M, Lauer MS, Levy D: Echocardiographic determinants of clinical outcome in subjects with coronary artery disease (the Framingham Heart Study). *Am J Cardiol* 1992;70:971–976
10. Bader H, Garrigue S, Lafitte S, Reuter S, Jaïs P, et al.: Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. *J Am Coll Cardiol* 2004;43:248–256
11. 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
12. Burgess MI, Rozis E, Marwick TH: Prognostic value of intraventricular dyssynchrony according to clinical stage of left ventricular impairment. *Am J Cardiol* 2006;98:1439–1445
13. Yu CM, Fung JW, Zhang Q, Chan C-K, Chan Y-S, et al.: Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. *Circulation* 2004;110:66–73
14. Bax JJ, Bleeker GB, Marwick TH, Molhoedk SG, Boersma E, et al.: Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;44:1834–1840
15. Penicka M, Bartunek J, DeBruyne B, Vanderheyden M, Goethals M, et al.: Improvement of left ventricular function after cardiac resynchronization is predicted by tissue Doppler imaging echocardiography. *Circulation* 2004;109:978–983
16. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, et al.: for the Cardiac Resynchronization—Geart Faukyre (CARE-HF) Study Investigators: The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–1549
17. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, et al.: for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators: Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140–2150
18. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB: Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden *Am J Cardiol* 2002;90:1284–1289
19. Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, et al.: Diastolic dysfunction and left atrial volumes population-based study. *J Am Coll Cardiol* 2005;45:87–92
20. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, et al.: Left atrial size. Physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006;47:2357–2363
21. Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA: Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons 65 years of age (the Cardiovascular Health Study). *Am J Cardiol* 2006;97:83–89

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20350