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Feasibility of Diastolic Function Assessment With Cardiac CT

Feasibility Study in Comparison With Tissue Doppler Imaging

Mark J. Boogers, MD,*† Jacob M. van Werkhoven, MSc,*† Joanne D. Schuijf, PhD,* Victoria Delgado, MD,* Heba M. El-Naggar, MD,* Eric Boersma, PhD,‡ Gaetano Nucifora, MD,* Rob J. van der Geest, MSc,§ Bernard P. Paelinck, MD, PhD,‖ Lucia J. Kroft, MD, PhD,§ Johan H. C. Reiber, PhD,§ Albert de Roos, MD, PhD,§ Jeroen J. Bax, MD, PhD,* Hildo J. Lamb, MD, MSc, PhD§

Leiden, Utrecht, and Rotterdam, the Netherlands; and Antwerp, Belgium

OBJECTIVES This study aimed to demonstrate the feasibility of multidetector row computed tomography (CT) for assessment of diastolic function in comparison with 2-dimensional (2D) echocardiography using tissue Doppler imaging (TDI).

BACKGROUND Diastolic left ventricular (LV) function plays an important role in patients with cardiovascular disease. 2D echocardiography using TDI has been used most commonly to evaluate diastolic LV function. Although the role of cardiac CT imaging for evaluation of coronary atherosclerosis has been explored extensively, its feasibility to evaluate diastolic function has not been studied.

METHODS Patients who had undergone 64-multidetector row CT and 2D echocardiography with TDI were enrolled. Diastolic function was evaluated using early (E) and late (A) transmitral peak velocity (cm/s) and peak mitral septal tissue velocity (Ea; cm/s). Peak transmitral velocity (cm/s) was calculated by dividing peak diastolic transmitral flow (ml/s) by the corresponding mitral valve area (cm^2). Mitral septal tissue velocity was calculated from changes in LV length per cardiac phase. Subsequently, the estimation of LV filling pressures (E/Ea) was determined.

RESULTS Seventy patients (46 men; mean age 55 ± 11 years) who had undergone cardiac CT and 2D echocardiography with TDI were included. Good correlations were observed between cardiac CT and 2D echocardiography for assessment of E ($r = 0.73$; $p < 0.01$), E/A ($r = 0.87$; $p < 0.01$), Ea ($r = 0.82$; $p < 0.01$), and E/Ea ($r = 0.81$; $p < 0.01$). Moreover, a good diagnostic accuracy (79%) was found for detection of diastolic dysfunction using cardiac CT. Finally, the study showed a low intraobserver and interobserver variability for assessment of diastolic function on cardiac CT.

CONCLUSIONS Cardiac CT imaging showed good correlations for transmitral velocity, mitral septal tissue velocity, and estimation of LV filling pressures when compared with 2D echocardiography. Additionally, cardiac CT and 2D echocardiography were comparable for assessment of diastolic dysfunction. Accordingly, cardiac CT may provide information on diastolic dysfunction. (J Am Coll Cardiol Img 2011;4:246–56) © 2011 by the American College of Cardiology Foundation

From the *Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; †Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands; ‡Department of Epidemiology and Statistics, Erasmus University, Rotterdam, the Netherlands; §Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands; and the ‖Department of Cardiology, Antwerp University Hospital, Antwerp, Belgium. Dr. Boogers is supported by the Dutch Heart Foundation (grant 2006T102). Dr. van Werkhoven is financially supported by the Netherlands Society of Cardiology. Dr. Delgado has consulted for St. Jude Medical. Dr. Nucifora received a research grant from the European Society of Cardiology. Dr. van der Geest is a consultant for Medis Medical Imaging Systems. Dr. Bax received research grants from Medtronic, Boston Scientific, Biotronik, Edwards Lifesciences, Bristol-Myers Squibb Medical Imaging, St. Jude Medical, and GE Healthcare. All other authors have reported that they have no relationships to disclose.

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Diastolic left ventricular (LV) function plays an important role in the evaluation of clinical symptoms, therapeutic options, and prognosis in patients with cardiovascular disease (1,2). More specifically, it has been shown that diastolic dysfunction represents an important pathological condition in patients with coronary artery disease (CAD) (3,4).

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Doppler echocardiography represents the most commonly used approach for evaluation of diastolic function (5–10). For the evaluation of diastolic function, transmitral velocity has been used frequently as a noninvasive alternative to directly measured LV filling pressures (5,7). However, it is important to note that several confounding factors may influence transmitral velocity, and consequently, transmitral velocity alone may not be the best marker for diastolic LV dysfunction (6,7,11). Combined assessment of early (E) peak transmitral velocity and early peak mitral septal tissue velocity (Ea) may be more accurate for the evaluation of diastolic LV function, predominantly in patients with depressed or increased LV filling pressures (6,10,11). Cardiac computed tomography (CT) has emerged as a potent noninvasive imaging modality for the evaluation of coronary atherosclerosis (12,13). In specific subsets of patients, multiphase CT imaging may be indicated to ensure diagnostic image quality for visualization of the coronary arteries.

Thus far, multiphase CT studies have been restricted to LV systolic function analysis (14), and no information is available on the feasibility of cardiac CT imaging to assess diastolic LV function. Accordingly, the present study aimed to evaluate the feasibility of cardiac CT for assessment of diastolic function in a direct comparison with 2-dimensional (2D) echocardiography using tissue Doppler imaging (TDI).

METHODS

Patient population and study design. Seventy consecutive patients who had been referred for 64-CT imaging were retrospectively selected from our clinical registry. Cardiac CT imaging had been performed to evaluate known or established CAD, and 2D echocardiography with TDI had been performed to evaluate therapeutic options. Both examinations had been performed sequentially, in random order. Known CAD was defined as previous myocardial infarction, revascularization, or evidence of CAD on previous diagnostic tests. Patients without evidence of CAD on previous diagnostic tests were suspected to have CAD (and therefore referred for CT angiography).

Patients were chosen from our ongoing clinical registry if they met the following selection criteria: 1) presence of multiphase CT imaging (information acquired of the entire cardiac cycle); 2) availability of multiphase CT and 2D echocardiography with TDI within 3 months; 3) diagnostic image quality of multiphase CT and 2D echocardiography with TDI; 4) sinus rhythm; and 5) absence of valvulopathy (aortic or mitral valvulopathy, grade ≥I). Additionally, patients with unstable angina pectoris or acute coronary syndrome were excluded from further analysis.

Our institutional review board does not require approval for retrospective technical analyses of clinically obtained data, as was the case in this study.

Cardiac CT data acquisition and analysis. Multidetector row CT imaging was performed with a 64-slice CT scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan). Before MDCT imaging, patients were monitored for blood pressure and heart rate. Patients with heart rates ≥65 beats/min were given metoprolol 50 or 100 mg orally, unless contraindicated. Patients did not receive nitroglycerin before cardiac CT imaging.

For the contrast-enhanced helical scan, collimation was 64 × 0.5 mm with a rotation time of 400 ms. Tube current and voltage were 350 mA and 120 kV, respectively. At an injection rate of 5 ml/min, 95 to 130 ml of nonionic contrast medium (Iomeron 400, Bracco, Milan, Italy) was infused in the antecubital vein. After the start of contrast infusion, recurrent low-dose examinations were performed to monitor contrast arrival within the region of interest, in the descending aorta. An electrocardiogram (ECG) was started simultaneously for retrospective gating of the data. The entire cardiac cycle was scanned without dose modulation. The ECG-gated helical scan was automatically triggered once the pre-determined threshold level of baseline + 100 Hounsfield units was reached. After a preset delay of 2 s, scanning was performed during an inspiratory breath hold of 8 to 12 s.

Data were reconstructed with a slice thickness of 1 mm and reconstruction interval of 1 mm. With

ABBREVIATIONS AND ACRONYMS

A = peak transmitral velocity at atrial contraction

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CT = computed tomography

E = peak transmitral velocity in early diastole

Ea = peak mitral septal tissue velocity in early diastole

LV = left ventricle/ventricular

TDI = tissue Doppler imaging

the use of half reconstruction algorithms, the actual temporal resolution was 200 ms. Segmented reconstruction algorithms yielded a temporal resolution of up to 50 ms, depending on the actual imaging acquisition conditions (pitch, rotation time, and heart rate). An ECG-gated post-processing software was used to reconstruct data in short-axis orientation. Images were reconstructed at 20 intervals (0% to 95% of the R-R interval) and transferred to a separate workstation with dedicated cardiac function analysis software (Mass V2008-EXP, LKEB, Leiden, the Netherlands) (15). Contrast-enhanced scans were analyzed by an independent observer who was blinded to all other data. Significant coronary artery stenosis was defined as ≥50% luminal narrowing, whereas nonsignificant stenosis was defined as <50% luminal narrowing.

The evaluation of LV diastolic function was based on the assessment of transmitral velocity (15 min per patient) and mitral septal tissue velocity (5 min per patient). Accordingly, the assessment of LV diastolic function was performed within 20 min per patient.

Cardiac CT transmitral velocity. Peak transmitral velocity (cm/s) was measured in E and late (A) diastole. The peak value represents the highest mean value of the measurements obtained during E and A diastole. Late peak transmitral velocity was measured at atrial contraction. Transmitral velocity measurements were based on several processing steps (Fig. 1). At first, LV volumes were calculated for 20 cardiac phases (each phase represented 5% of the cardiac cycle). For each phase, automatic contour detection was performed on 1-mm sliced reconstructed short-axis images ranging from mitral valve annulus to the apex (Fig. 1A, left panel). Manual corrections could be made to improve contour detection. Papillary muscles were regarded as part of the LV cavity and were included in the LV volume analyses (16). Automatic contour detection was performed using dedicated in-house developed Mass research software package (Mass V2008-EXP, LKEB, Leiden, the Netherlands) (15). Next, LV volumes were plotted in a volume versus time curve (Fig. 1A, right upper curve). In addition, changes in LV volumes between 2 consecutive phases (first derivative) were derived and used to calculate the transmitral flow (ml/s) per phase (Fig. 1A, right lower curve). Subsequently, the maximal transmitral flow in E and A diastole was derived using the transmitral flow versus time curve. To allow direct comparison with 2D echocardiography, the maximal transmitral flow in E and A diastole was divided by their corresponding mitral valve area (which was measured during E and A diastole, as described below), yielding E and A peak transmitral velocities and the E/A.

Cardiac CT mitral septal tissue velocity. Myocardial tissue velocity (cm/s) was measured at the septal level of the mitral valve annulus attachment. Measurements of Ea (cm/s) are illustrated in Figure 1B. For 20 phases, LV length (mm) was calculated as the distance between 2 anatomic markers: 1) mitral septal annulus (annular attachment of septal mitral valve leaflet) and 2) cardiac apex (Fig. 1B, left panel). Anatomic markers were positioned at reconstructed 4-chamber views. Reconstruction of a 4-chamber view was based on several reconstruction steps. At first, a 2-chamber view was reconstructed from axial slices, directing the image slice (cardiac axis) through the cardiac apex. Consecutively, a 4-chamber view was reconstructed by positioning the image slice at two-thirds of the mitral valve annulus (perpendicular to the interventricular septum) using the 2-chamber view.

The LV length per phase was plotted in an LV length versus time curve (Fig. 1B, right upper panel). Changes in LV length between 2 consecutive phases were calculated and used to generate a velocity versus time curve (Fig. 1B, right lower panel). In this curve, mitral septal tissue velocities were plotted against time. For each phase, mitral septal tissue velocity was computed using changes in LV length and heart rate. The maximal tissue velocity during E diastole represented Ea. Measurements were performed using Mass software (15). Finally, the estimation of LV filling pressures (E/Ea) was calculated by dividing early transmitral velocity by mitral septal tissue velocity.

Cardiac CT mitral valve area. Mitral valve area was measured to enable direct comparison of volumetric indexes derived from cardiac CT with velocity-based parameters as assessed with 2D echocardiography. In Figure 1C, the processing steps involved in mitral valve area measurements are illustrated. Images were reconstructed with a slice thickness of 0.5 mm and a reconstruction interval of 0.3 mm.

Mitral valve area measurements were determined on the basis of different steps: the LV axis was positioned perpendicular to mid–mitral valve annulus on sagittal and coronal views, yielding a 2-chamber view (Fig. 1C, panel 1). Subsequently, a 4-chamber view (Fig. 1C, panel 2) was reconstructed, and manual contour detection was performed at the most distal level of the mitral valve leaflets in short-axis views (Fig. 1C, panels 3 and 4).

Figure 1. Diastolic LV Function Assessed With MDCT

(A) Transmitral flow: left ventricular (LV) volumes (ml) were measured for 20 phases per cardiac cycle, using short-axis images by outlining endocardial contours in each phase. The volumes were plotted in a volume versus time curve **(right upper)**. These curves were used to define the diastole, ranging from end-systolic (ES) to end-diastolic (ED) phase. Changes in LV volumes between 2 consecutive phases were plotted against time (transmitral flow vs. time curve) **(right lower)**. Subsequently, early and late peak transmitral flows (ml/s) were derived. **(B)** Mitral septal tissue velocity: anatomic markers were positioned at the mitral septal annulus (MS) and cardiac apex (AP). The LV length (mm; distance between anatomic markers) was calculated for each phase **(left)** and plotted in a LV length versus time curve **(right upper)**. Next, changes in LV length between 2 consecutive phases were calculated. Based on these numbers, mitral septal tissue velocities (cm/s) were calculated for each phase (velocity vs. time curve) **(right lower)**. The early peak mitral septal tissue velocity (cm/s) represented the maximal tissue velocity during early diastole. **(C)** Mitral valve area: measurements were taken at the most distal level of the mitral valve leaflets (smallest mitral valve area) using reconstructed images at peak early and late transmitral velocities. The LV axis was positioned perpendicular to mid–mitral valve annulus on sagittal and coronal views, yielding a 2-chamber view **(panel 1)**. Then the 4-chamber view was reconstructed **(panel 2)**, and the mitral valve area was measured at the tip of the leaflets **(panels 3 and 4)** on short-axis views. For direct comparison, transmitral velocity (cm/s) was calculated using the following formula: peak diastolic transmitral flow divided by the corresponding mitral valve area. MDCT = multidetector row computed tomography.

Measurements were taken during early and late peak transmitral flow using a dedicated workstation (Vitrea 2, Vital Images, Minnetonka, Minnesota).

The mitral valve area was calculated to enable direct comparison with 2D echocardiography. Transmitral velocity was calculated by dividing transmitral flow by corresponding mitral valve area (Fig. 1).

Intraobserver and interobserver reproducibility. Intraobserver and interobserver reproducibility for assessment of transmitral velocity was evaluated in a subset of 15 patients who were randomly selected from the patient population. Transmitral velocity was measured twice by the same observer in these 15 patients. Subsequently, transmitral velocity measurements were performed by a second independent observer in the same subset of patients.

In addition, intraobserver and interobserver reproducibility for assessment of mitral septal tissue velocity was evaluated in another random sample of 15 patients. Mitral septal tissue velocity was measured twice by the same observer in these patients according to the standardized protocol, as described earlier. Additionally, a second independent observer performed the mitral septal tissue velocity measurements in the same subset of patients.

Finally, the intraobserver and interobserver reproducibility of the mitral valve area measurements was evaluated in a subset of 20 patients who were randomly selected from the patient population. In these patients, the mitral valve area was measured twice by the same observer using the same processing steps, as described earlier. Furthermore, a second blinded observer performed the mitral value measurements in the same subset of 20 patients.

Transthoracic 2D echocardiography using TDI acquisition. Transthoracic 2D echocardiography was performed in left lateral decubitus position using a commercially available system (Vingmed Vivid-7, General Electric, Horten, Norway). Standard parasternal (long- and short-axis) and apical views (2- and 4-chamber) were obtained. In addition, continuous-wave and pulsed-wave Doppler examinations were performed. From the 4-chamber view, TDI was obtained with color Doppler frame rates exceeding 115 frames/s, depending on the sector width of the range of interest. Aliasing velocities varied between 16 and 32 cm/s and resulted from pulse repetition frequencies ranging from 500 to 1,000 Hz. The echocardiographic analyses were performed by an independent and blinded observer.

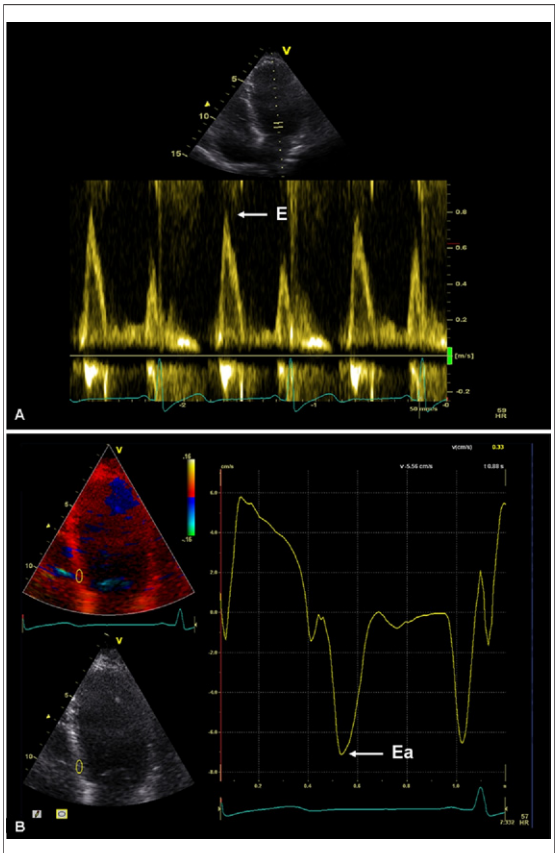

Figure 2. Evaluation of Diastolic Function With 2D Echocardiography Using TDI

(A) Two-dimensional (2D) echocardiographic assessment of pulsed-wave Doppler of early (E) transmitral velocity (cm/s) **(white arrow)**. **(B)** Early diastolic peak mitral septal tissue velocity (Ea) (cm/s) **(white arrow)** at basal septal segment by tissue Doppler imaging (TDI).

2D echocardiography transmitral velocity. Transmitral velocity was recorded at the end of respiratory expiration (Fig. 2, upper panel). Transmitral velocity measurements were taken using dedicated offline software (EchoPAC 7.0.0, General Electric). Standard pulsed-wave Doppler imaging was performed to assess E and A peak transmitral velocities. E and A peak transmitral velocities were used to calculate the E/A. Doppler sample volume was placed at the tip of the mitral valve leaflets, on a 4-chamber view (17). Subsequently, E and A peak transmitral velocities were obtained in diastole.

2D echocardiography mitral septal tissue velocity. Early peak mitral septal tissue velocity was assessed using color-coded TDI on a 4-chamber view. Images were obtained in end-expiration in a patient in left lateral decubitus position. Doppler velocities were measured from the apical 4-chamber view using a 6 × 6 mm sample volume positioned at the

basal septal mitral valve annulus, as illustrated in Figure 2 (lower panel) (17).

Color-coded images from 3 consecutive heartbeats were analyzed using dedicated offline software (EchoPAC 7.0.0., General Electric). Reliable TDI curves were obtained in 67 patients.

Detection of diastolic dysfunction. For evaluation of the accuracy of cardiac CT to detect diastolic dysfunction, diastolic function was graded in 4 categories using the following criteria: 1) normal diastolic function (≥1 E/A <2 and E/Ea ≤8); 2) impaired relaxation pattern (diastolic dysfunction grade I; E/A <1 and E/Ea ≤8); 3) pseudonormal pattern (diastolic dysfunction grade II; ≥1 E/A <2 and ≥9 E/Ea ≤12); and 4) restrictive filling pattern (diastolic dysfunction grade III; E/A ≥2 and E/Ea ≥13) (18). Based on these criteria, the patient population was divided into 2 groups: patients with normal diastolic function and patients with diastolic dysfunction (including impaired LV relaxation and pseudonormal and restrictive LV filling patterns).

Statistical analysis. Continuous data are presented as mean ± SD, and categoric data are presented as absolute numbers or percentages. Kolmogorov-Smirnov tests were used to evaluate the distribution of the data. All variables were normally distributed except for the estimation of LV filling pressures (E/Ea) on cardiac CT and 2D echocardiography with TDI. Data for E/Ea were presented as medians and 25th and 75th percentiles. When appropriate, paired *t* tests or Wilcoxon signed rank tests were used to compare diastolic function parameters as derived from cardiac CT and 2D echocardiography with TDI.

Comparison of cardiac CT and 2D echocardiography with TDI was performed using Pearson linear regression analysis or the Spearman rho correlation. The 95% limits of agreement were calculated using Bland-Altman analysis that plotted the mean value of differences of each pair against the average value of a similar pair of data. Cardiac CT was subtracted from 2D echocardiography with TDI because the latter was considered the clinical standard. Reproducibility was evaluated by calculating the intraclass correlation coefficients (ICC), and an excellent agreement was defined as ICC > 0.8. Diagnostic accuracy of cardiac CT for detection of diastolic dysfunction was assessed using a binary approach; normal diastolic function and diastolic dysfunction (including impaired LV relaxation and pseudonormal and restrictive LV filling patterns). Corresponding sensitivity and specificity values were calculated. For these values, the 95% confidence intervals (CIs) were calculated using the following formula: $p \pm 1.96 \times SE$. The SE was estimated by $\sqrt{(p[1-p]/n)}$. Statistical analyses were performed with SPSS (version 16.0, SPSS Inc., Chicago, Illinois). A value of $p < 0.05$ was considered statistically significant. Bland-Altman analyses were performed with GraphPad Prism software (version 5.01, GraphPad Software Inc., San Diego, California).

Table 1. Baseline Characteristics of Study Population (N = 70)

Men	46 (66)
Age (yrs)	55 ± 11
Suspected CAD	58 (83)
Known CAD	12 (17)
Significant coronary stenosis	21 (30)
Cardiovascular risk factors	
Diabetes mellitus	35 (50)
Systemic hypertension	43 (61)
Hypercholesterolemia	40 (57)
Current smoking	11 (16)
Positive family history	27 (39)
Medication use	
Beta-blockers	24 (34)
ACEI/AT II antagonists	35 (50)
Statins	29 (41)
Diuretics	15 (21)
Anticoagulants	30 (43)
Cardiac CT	
Heart rate (beats/min)	58 ± 10
LV end-systolic volume (ml)	70 ± 50
LV end-diastolic volume (ml)	149 ± 52
LV ejection fraction (%)	56 ± 13

Data are presented as mean ± SD or n (%).
ACEI = angiotensin-converting enzyme inhibitor; AT = angiotensin; CAD = coronary artery disease; CT = computed tomography; LV = left ventricular.

RESULTS

Patient population. A total of 80 patients had undergone multiphase CT imaging and 2D echocardiography with TDI within 3 months. Of these 80 patients, 10 patients were excluded owing to the absence of sinus rhythm (n = 2) or the presence of nondiagnostic image quality of either cardiac CT (n = 7) or 2D echocardiography with TDI (n = 1). Accordingly, 70 patients (46 men [66%]; mean age 55 ± 11 years) were included. Baseline characteristics of the patient population are listed in Table 1. Cardiac CT and 2D echocardiography were performed within 3 months, during which no acute coronary events or worsening of angina occurred. No changes in the use of medication occurred between both examinations. The mean duration

Table 2. Diastolic Function Parameters for Cardiac CT and 2D Echocardiography

	Cardiac CT	2D Echocardiography
Transmitral velocity		
E (cm/s)	59.0 ± 16.6	61.8 ± 14.5*
A (cm/s)	56.2 ± 17.4	64.8 ± 18.2*
E/A	1.1 ± 0.4	1.1 ± 0.5*
Mitral septal tissue velocity		
Ea (cm/s)	6.6 ± 2.7	6.2 ± 2.3*
E/Ea	8.8 (6.4–13.1)	9.7 (7.5–14.0)**

Data are presented as mean ± SD or median (25th–75th percentiles). Data for E/Ea are presented as medians and corresponding 25th and 75th percentiles. *Paired *t* test showed a value of $p < 0.05$. **Wilcoxon signed rank test showed a value of $p < 0.05$.
A = peak transmitral velocity at atrial contraction; CT = computed tomography; E = peak transmitral velocity in early diastole; Ea = peak mitral septal tissue velocity in early diastole; 2D = 2-dimensional.

between cardiac CT and 2D echocardiography was 34.1 ± 25.0 days. Clinical referral for cardiac CT was based on suspected CAD in 58 patients and known CAD in 12 patients. Patients with known CAD included patients with previous myocardial infarction (n = 10), percutaneous coronary intervention (n = 7), and indications of CAD on earlier diagnostic tests (n = 3). Significant coronary artery stenosis (≥50% luminal narrowing) was reported in 21 patients (30%). In total, 31 (44%) patients received beta-blocking therapy before cardiac CT imaging.

Transmitral velocity. Transmitral flow versus time curves were obtained in all patients. Mean LV end-systolic and end-diastolic volumes were 70 ± 50 ml and 149 ± 52 ml, respectively, on cardiac CT. Accordingly, the mean LV ejection fraction was 56% ± 13% (Table 1). Mean values for E and A peak transmitral velocities are shown in Table 2. The mean diastolic transmitral velocity was 24.3 ± 8.5 cm/s. Pearson correlation showed a good correlation for E ($r = 0.73$; $p < 0.01$) and E/A ($r = 0.87$; $p < 0.01$) (Figs. 3A and 4A). Bland-Altman analysis for E showed a mean difference of 2.4 ± 12.0 cm/s, with 95% limits of agreement ranging from −21.2 to 26.0 cm/s, whereas the mean value of difference was −0.1 ± 0.2 cm/s for E/A, with 95% limits of agreement ranging from −0.5 to 0.4 cm/s (Figs. 3B and 4B).

A low intraobserver and interobserver variability was observed for assessment of E (ICC: 0.97, 95% CI: 0.91 to 0.99, and ICC: 0.93, 95% CI: 0.78 to 0.97, respectively) and A (ICC: 0.98, 95% CI: 0.94 to 0.99, and ICC: 0.91, 95% CI: 0.51 to 0.98, respectively) peak transmitral velocities. Moreover, the assessment of E/A showed a low intraobserver and interobserver variability (ICC: 0.95, 95% CI: 0.84 to 0.98, and ICC: 0.95, 95% CI: 0.85 to 0.98, respectively).

Finally, the intraobserver and interobserver reproducibility of mitral valve area measurements was evaluated. In a subset of 20 patients, an excellent intraobserver and interobserver reproducibility was observed for assessment of mitral valve area (ICC: 0.94, 95% CI: 0.83 to 0.98, and ICC: 0.92, 95% CI: 0.80 to 0.97, respectively).

Mitral septal tissue velocity. Velocity versus time curves were obtained for all patients. Mean values for Ea are shown in Table 2. In addition, the medians and corresponding 25th and 75th percentiles for E/Ea are shown in Table 2. A good correlation ($r = 0.82$; $p < 0.01$) (Fig. 5A) for Ea was found. Bland-Altman analysis showed a mean value of difference of −0.5 ± 1.6 cm/s, with 95% limits of agreement ranging from −3.6 to 2.5 cm/s (Fig. 5B). In addition, good correlation ($r = 0.81$;

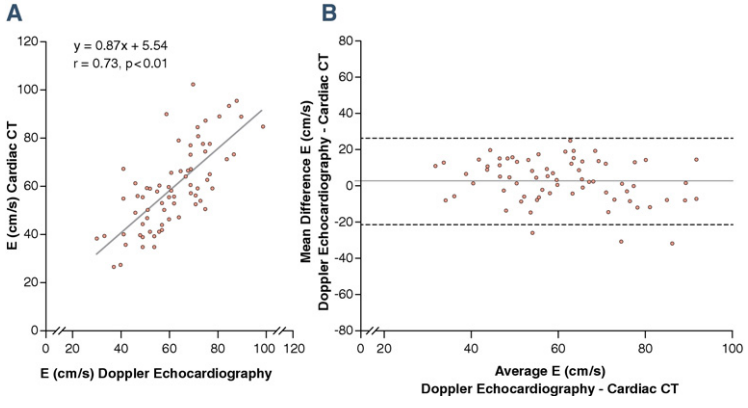

Figure 3. Comparison Between 2D Echocardiography and MDCT for Assessment of Early Maximal Diastolic Transmitral Velocity

(A) Good correlation was observed between both techniques. **(B)** Bland-Altman analysis showing the difference of each pair plotted against the average value of the same pair of values. **Dotted lines** represent 95% limits of agreement. Abbreviations as in Figures 1 and 2.

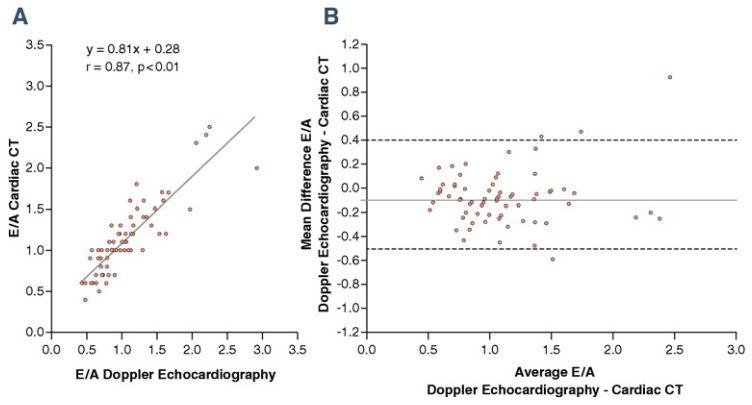

Figure 4. Comparison Between 2D Echocardiography and MDCT for E/A

(A) Good correlation was observed between both techniques. **(B)** Bland-Altman analysis showing the difference of each pair plotted against the average value of the same pair of values. **Dotted lines** represent 95% limits of agreement. A = peak transmitral velocity at atrial contraction; other abbreviations as in Figures 1 and 2.

$p < 0.01$) (Fig. 6A) was reported for E/Ea, with a mean value of difference of 1.0 ± 2.9 cm/s and 95% limits of agreement ranging from −4.6 to 6.7 cm/s (Fig. 6B).

An excellent intraobserver and interobserver reproducibility was observed for assessment of mitral septal tissue velocity (ICC: 0.95, 95% CI: 0.85 to 0.98, and ICC: 0.89, 95% CI: 0.69 to 0.96, respectively) and estimation of LV filling pressures (E/Ea; ICC: 0.96, 95% CI: 0.87 to 0.99, and ICC: 0.93, 95% CI: 0.80 to 0.98, respectively).

Detection of diastolic dysfunction. The diagnostic accuracy of cardiac CT to detect diastolic dysfunction in comparison with 2D echocardiography with TDI was calculated (18). In total, 19 patients (27%) showed normal diastolic function, whereas 51 patients (73%) showed diastolic dysfunction using 2D echocardiography. Of the patients with diastolic dysfunction on 2D echocardiography, 40 patients were scored similarly using cardiac CT, yielding a sensitivity of 78% (95% CI: 67% to 89%). Normal diastolic function was found in 15 of the 19 patients using cardiac CT, yielding a specificity of 79% (95% CI: 61% to 97%). Overall, diagnostic accuracy for assessment of diastolic dysfunction was 79% (95% CI: 69% to 89%).

DISCUSSION

This study demonstrated good correlations for transmitral velocity (E and E/A) and mitral septal tissue velocity (Ea). Additionally, combined assessment of transmitral and mitral septal tissue velocity

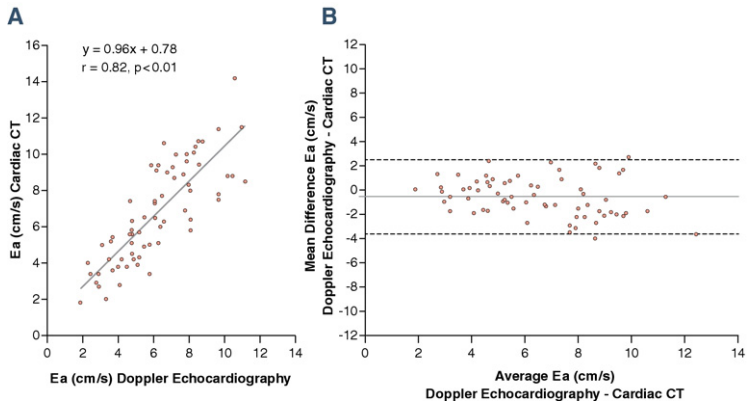

Figure 5. Comparison Between 2D Echocardiography and MDCT for Assessment of Ea

(A) Good correlation was observed between both imaging techniques. **(B)** Bland-Altman analysis showing the difference of each pair plotted against the average value of the same pair of values. **Dotted lines** represent 95% limits of agreement. Abbreviations as in Figures 1 and 2.

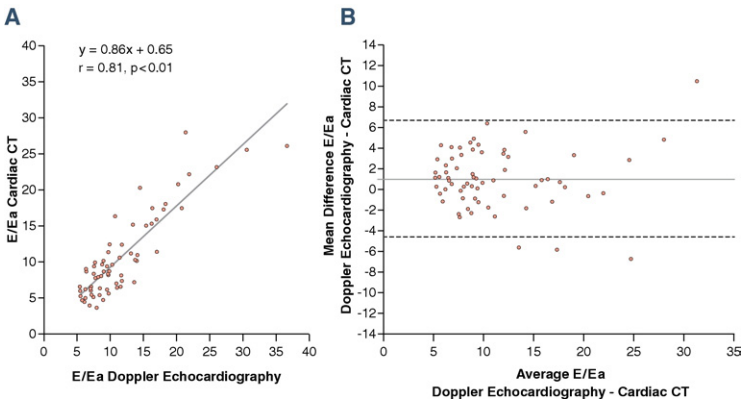

Figure 6. Comparison Between 2D Echocardiography and MDCT for E/Ea

(A) Good correlation for E/Ea was observed between both techniques. **(B)** Bland-Altman analysis showing the difference of each pair plotted against the average value of the same pair of values. **Dotted lines** represent 95% limits of agreement. Abbreviations as in Figures 1 and 2.

(E/Ea), representing an estimation of LV filling pressures, showed good correlation between cardiac CT and 2D echocardiography with TDI. Finally, the study showed that cardiac CT and 2D echocardiography were comparable for assessment of diastolic dysfunction. Accordingly, cardiac CT may provide information on diastolic dysfunction.

The importance of diastolic function in patients with coronary atherosclerosis has been demonstrated in several studies (3,4). A recent meta-analysis pooled 3,396 patients with documented myocardial infarction from 12 prospective studies and demonstrated that patients with a restrictive LV filling pattern had a significantly higher mortality rate than patients with a nonrestrictive LV filling pattern (28.7% vs. 11.3%, respectively; $p < 0.01$) (3,4). Although invasive measurements of LV filling pressure are considered the most accurate approach for evaluation of diastolic LV function, they are not ideal for widespread application and follow-up examinations. Consequently, several cardiac imaging techniques (particularly 2D echocardiography) have been used to assess transmitral velocity as a noninvasive alternative (5,7). Even though complex interacting pathophysiologic mechanisms may underlie diastolic dysfunction, evaluation of diastolic LV function is most frequently based on transmitral velocity measurements alone (5,7,11).

Transmitral velocity. Doppler echocardiography has been validated for the assessment of transmitral velocity as a noninvasive alternative of direct LV filling pressures (5). Additionally, Doppler echocardiography has been compared with cardiac magnetic resonance (CMR) for assessment of transmitral velocity (9,10). The present study demonstrated that cardiac CT can be used for assessment of LV diastolic function, as was indicated by good correlations between cardiac CT and Doppler echocardiography for E transmitral velocity ($r = 0.73$; $p < 0.01$) and E/A ($r = 0.87$; $p < 0.01$). In line with the study by Hartiala et al. (9), a systematic underestimation of transmitral velocity was observed when compared with Doppler echocardiography (Table 2). One of the potential explanations of this underestimation could be related to the sampling rate of cardiac CT. Because the datasets were sampled in 20 cardiac phases, each sampling took place in 5% steps of the R-R interval. Accordingly, the sampling rate of cardiac CT was markedly lower as compared with 2D echocardiography, and this may have resulted in an underestimation of transmitral velocity on CT because the peak transmitral velocity as derived from 2D echocardiography could be present between 2 sampled cardiac phases.

In both studies, correlations were not excellent for transmitral velocity, and this may be related to other parameters that could influence transmitral velocity measurements, including filling pressures, degree of LV relaxation, and myocardial elastic recoil and stiffness (7,8). For overcoming these limitations, additional measurements have been proposed, including the evaluation of pulmonary venous velocity, M-mode echocardiography flow velocity curves, and altering pre-load and afterload conditions (Vasalva maneuver or nitroglycerin administration) (19,20). In the current study, however, these measurements were not performed because this study was only conducted to evaluate the feasibility of cardiac CT.

Additionally, it has been suggested to combine transmitral velocity and mitral septal tissue velocity measurements when evaluating diastolic heart function. Importantly, the combined assessment of trans-

mitral velocity and mitral septal tissue velocity represents a better estimate of LV filling pressures because it is a normalization of LV filling gradient for filling LV volume (6,10,11).

Mitral septal tissue velocity. Ommen et al. (6) studied the clinical use of TDI for evaluation of diastolic LV function in 100 patients. Comparison between invasive LV filling pressures and combined assessment of E transmitral velocity and Ea showed improved correlation ($r = 0.64$) as compared with transmitral velocity ($r = 0.59$) or mitral septal tissue velocity ($r = 0.36$) alone (6). In addition, CMR has been compared with TDI for assessment of tissue velocities. Paelinck et al. (10) used phase-contrast CMR and Doppler echocardiography to measure transmitral and mitral septal tissue velocities in 18 patients with hypertrophic cardiomyopathy. Importantly, combined assessment of E transmitral velocity and Ea (E/Ea) showed a good correlation between Doppler echocardiography and CMR ($r = 0.89$; $p < 0.01$). Moreover, invasive measurements were well correlated to E/Ea derived from Doppler echocardiography ($r = 0.85$; $p < 0.01$) and CMR ($r = 0.80$; $p < 0.01$). Likewise, the current study reported good correlations for transmitral velocity (E/A; $r = 0.87$; $p < 0.01$) and E/Ea ($r = 0.81$; $p < 0.01$). Furthermore, both studies showed that mitral septal tissue velocity was slightly overestimated when compared with 2D echocardiography with TDI. With tissue Doppler echocardiography, tissue velocities are quantified using changes in Doppler signal over time. Doppler patterns are only displayed for the region of interest (sample volume), located at the basal septal mitral valve annulus. With cardiac CT, however, tissue velocities are measured using a different region of interest, ranging from the basal septal mitral valve annulus to the apex. The different regions of interest may have caused a slight overestimation of tissue velocity using cardiac CT.

Diastolic LV function. Cardiac CT and 2D echocardiography with TDI were comparable for detection of diastolic dysfunction. This represents an important finding because the assessment of diastolic dysfunction provides important diagnostic, therapeutic, and prognostic information in patients with cardiovascular disease, and more specifically, in patients with coronary atherosclerosis (1–4). Additionally, it has been shown that patients with coronary atherosclerosis and normal LV systolic function may already exhibit diastolic dysfunction (21). Accordingly, additional postprocessing for diastolic dysfunction may have the potential to enhance the clinical evaluation derived from cardiac CT, particularly in patients with evidence of coronary atherosclerosis but with normal LV systolic function. Moreover, the feasibility of cardiac CT for assessment of diastolic function is of particular interest because the number of patients referred for noninvasive evaluation of known or suspected coronary atherosclerosis with cardiac CT imaging has increased substantially over recent years.

At present, prospective triggering techniques are commonly used in patients referred for cardiac CT, particularly for ruling out the presence of significant CAD in young patients. However, cardiac CT is also used in patients with advanced CAD or elderly patients for detailed characterization of coronary and cardiac anatomy. In these patients, multiphase CT images may still be acquired using retrospective ECG gating to ensure diagnostic image quality for coronary visualization. The additional information derived from this examination can be used for other purposes, including the retrospective evaluation of systolic, and as demonstrated in the current study, diastolic function. Accordingly, the information that is needed for evaluation of diastolic function can be derived from conventional multiphase CT, without additional image acquisition or radiation dose.

Moreover, with the recent developments in acquisition and reconstruction algorithms, multiphase imaging may be performed at considerably lower radiation dose as compared with the currently available imaging protocols.

Study limitations. Some limitations of this study need to be considered. This was a retrospective study, and a prospective study design would be preferable. Secondly, transmitral velocity parameters were assessed with Doppler echocardiography and cardiac CT as a noninvasive alternative to directly measured LV filling pressures. Although direct measurements of LV filling pressures would have been preferred, they are not ideal for routine clinical examination. Furthermore, patients with valvular regurgitation were excluded. Severe valvular regurgitation may disturb accurate velocity measurements, leading to an inaccurate diastolic LV function analysis. Future studies are needed to evaluate this potential confounding effect. Additionally, cardiac CT and 2D echocardiography with TDI were performed within a period of 3 months maximum. However, to ensure optimal comparability between both examinations, the study only included patients with stable hemodynamic conditions; patients with unstable angina pectoris or acute coronary syndromes were excluded. Also, in the current study, diastolic function indexes were derived from multiphase CT datasets acquired without tube current modulation. To what extent

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tube modulation may influence the measurements of the mitral valve area and other diastolic function parameters needs to be addressed in additional studies. Finally, it is important to note that the effect of intravenous infusion of contrast media during cardiac CT angiography on diastolic function indexes is currently unknown (22).

CONCLUSIONS

Good correlations were observed for transmitral velocity, mitral septal tissue velocity, and estimation of LV filling pressures when compared with 2D echocardiography using TDI. Accordingly, cardiac CT may provide information on diastolic dysfunction in selected patients imaged by retrospectively ECG-gated CT.

Reprint requests and correspondence: Dr. Hildo J. Lamb, Department of Radiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands C2-S. *E-mail: h.j.lamb@lumc.nl.*

REFERENCES

1. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387–93.
2. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260–9.
3. Perrone-Filardi P, Bacharach SL, Dilsizian V, Bonow RO. Impaired left ventricular filling and regional diastolic asynchrony at rest in coronary artery disease and relation to exercise-induced myocardial ischemia. Am J Cardiol 1991;67:356–60.
4. Moller JE, Whalley GA, Dini FL, et al. Independent prognostic importance of a restrictive left ventricular filling pattern after myocardial infarction: an individual patient meta-analysis: Meta-Analysis Research Group in Echocardiography acute myocardial infarction. Circulation 2008; 117:2591–8.
5. Nishimura RA, Appleton CP, Redfield MM, et al. Noninvasive Doppler echocardiographic evaluation of left ventricular filling pressures in patients with cardiomyopathies: a simultaneous Doppler echocardiographic and cardiac catheterization study. J Am Coll Cardiol 1996;28:1226–33.
6. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.
7. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol 1997;30:8–18.
8. Oh JK, Appleton CP, Hatle LK, Nishimura RA, Seward JB, Tajik AJ. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 1997;10:246–70.
9. Hartiala JJ, Mostbeck GH, Foster E, et al. Velocity-encoded cine MRI in the evaluation of left ventricular diastolic function: measurement of mitral valve and pulmonary vein flow velocities and flow volume across the mitral valve. Am Heart J 1993;125:1054–66.
10. Paelinck BP, de Roos A, Bax JJ, et al. Feasibility of tissue magnetic resonance imaging: a pilot study in comparison with tissue Doppler imaging and invasive measurement. J Am Coll Cardiol 2005;45:1109–16.
11. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–33.
12. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. J Am Coll Cardiol 2005; 46:552–7.
13. Mollet NR, Cademartiri F, van Mieghem CA, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. Circulation 2005;112:2318–23.
14. Henneman MM, Bax JJ, Schuijf JD, et al. Global and regional left ventricular function: a comparison between gated SPECT, 2D echocardiography and multi-slice computed tomography. Eur J Nucl Med Mol Imaging 2006;33:1452–60.
15. van der Geest RJ, Reiber JH. Quantification in cardiac MRI. J Magn Reson Imaging 1999;10:602–8.
16. Pattynama PM, Lamb HJ, van der Velde, van der Wall EE, de Roos A. Left ventricular measurements with cine and spin-echo MR imaging: a study of reproducibility with variance component analysis. Radiology 1993; 187:261–8.
17. Lester SJ, Tajik AJ, Nishimura RA, Oh JK, Khandheria BK, Seward JB. Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. J Am Coll Cardiol 2008;51:679–89.
18. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–33.
19. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Relation of pulmonary vein to mitral flow velocities by transesophageal Doppler echocardiography. Effect of different loading conditions. Circulation 1990;81:1488–97.
20. Takatsuji H, Mikami T, Urasawa K, et al. A new approach for evaluation of left ventricular diastolic function: spatial and temporal analysis of left ventricular filling flow propagation by color M-mode Doppler echocardiography. J Am Coll Cardiol 1996;27:365–71.
21. Garcia-Fernandez MA, Azevedo J, Moreno M, et al. Regional diastolic function in ischaemic heart disease using pulsed wave Doppler tissue imaging. Eur Heart J 1999;20:496–505.
22. Stern L, Firth BG, Dehmer GJ, et al. Effect of selective coronary arteriography on left ventricular volumes and ejection fraction in man. Am J Cardiol 1980;46:827–31.

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