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Validation of Real-Time 3d Echocardiography Left Ventricular Volume-Time Curves with Cardiac MRI and Clinical Utilization of Emptying and Filling Rates

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Abstract

Background: 3D echocardiography derived volumetric data can be used to generate left ventricular volume-time curves and has the potential to elucidate aspects of contractility, systolic and diastolic function in normal and disease states. We sought to establish the validity and reproducibility of these volume-time curves and apply novel parameters derived from these curves to a clinical population.

Methods: Consecutive patients, who underwent cardiac MRI and echocardiography within 12 hours, were used to compare volume-time curves. Inter- and intra observer variability of the 3D echocardiography volume-time curves was assessed. Peak emptying rates, peak filling rates, and peak systolic acceleration were measured in a normal population (normal Ejection Fraction (EF) and no significant valvular disease) and their change with age was evaluated.

Results: 16 patients with an average EF of 55% ± 10% underwent cardiac MRI and 3D echocardiography. There was no significant difference between the systolic and diastolic slopes of the volume-time curves derived by the two methods with good correlation for both systole (r=0.62, p < 0.0001) and diastole (r=0.43, p=0.0025). In 50 normal patients aged 19-91, peak emptying rate, peak filling rate, and peak systolic acceleration all decreased with age.

Conclusion: 3D echocardiography volume-time curves correlate well with the gold standard of cardiac MRI. The novel 3D parameters of peak emptying rate, peak filling rate, and peak systolic acceleration may prove to be helpful in the assessment of systolic and diastolic function and provide insight into ventricular performance.

Abbreviations: LV: Left Ventricle; EF: Ejection Fraction; 2D: Two Dimensional; 3D: Three Dimensional; CAD: Coronary Artery Disease; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; EDV: End Diastolic Volume; ESV: End Systolic Volume; SV: Stroke Volume

Introduction

Echocardiographic assessment of Left Ventricular (LV) function, both systolic and diastolic, is important for the management of patients but is currently limited. Systolic function is derived by providing a global number (Ejection Fraction (EF)) based on single or bi-plane slices, and diastolic function is assessed by sampling small volumes (tissue Doppler) or single thin slices (2D strain). Real time transthoracic 3D echocardiography, may overcome 2D limitations by imaging the entire volume of the left ventricle and providing volumetric data rather than single plane or sample area data. 3D volumetric data has the potential to assess ventricular function using novel systolic and diastolic performance parameters. 3D datasets can be used to generate change in global LV volume over time curves which have the potential to elucidate aspects of contractility, systolic function, and diastolic function in normal and disease states. Analysis of these volume-time curves includes deriving: peak systolic emptying rates (ml/s), peak diastolic filling rates (ml/s), and peak systolic acceleration (ml/s^2) (Figure 1).

Previous work on peak filling and emptying rates has used gated blood pool scans, cineangiography, invasive hemodynamics, and cardiac MRI [1-8]. These studies demonstrated a distinct separation in peak emptying between patients with normal and abnormal EF's and peak filling rates were abnormal in a high percentage of patients with Coronary Artery Disease (CAD), both with normal and abnormal EF's [1,2]. Peak emptying and filling rates correlated well with invasive hemodynamic measurements such as EF, + dP/dt, - dP/dt, and LV end diastolic pressure [5]. Several small studies have also investigated using 3D echocardiography to generate volume-time curves along with peak emptying and filling rates [9-11]. 3D echocardiography has several advantages compared to gated blood pool scans, cineangiography, and cardiac MRI. It is non-invasive, portable, involves no radiation exposure, has short image acquisition time, better spatial resolution, and images the entire ventricular volume not counts or single/bi-plane slices.

The novel 3D systolic and diastolic performance parameters of peak filling and emptying rates have the potential to contribute to

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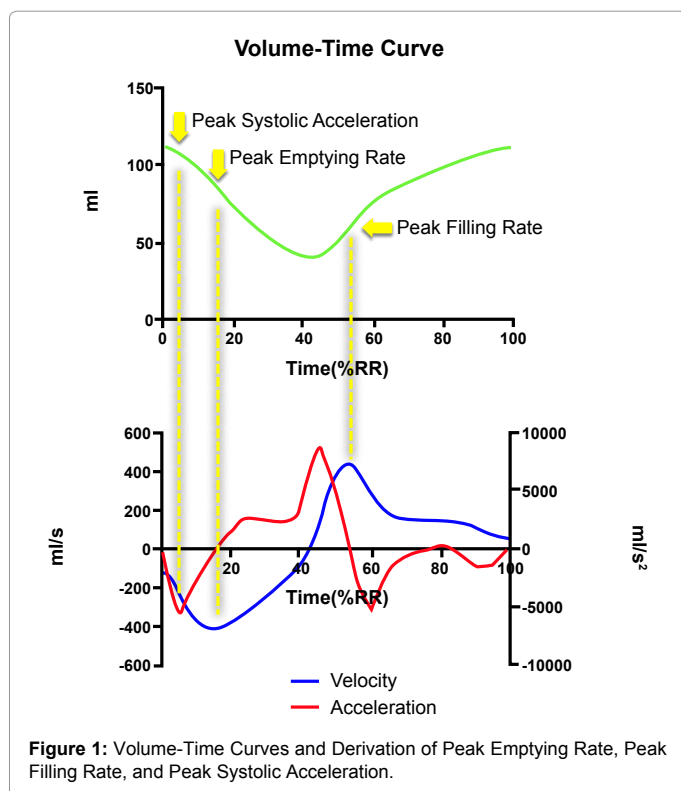
Figure 1: Volume-Time Curves and Derivation of Peak Emptying Rate, Peak Filling Rate, and Peak Systolic Acceleration.

the current assessment of left ventricular function in patients with subclinical disease or heart failure with normal EF's. The current diagnosis of diastolic dysfunction is based on Doppler derived diastolic filling parameters whose diagnostic accuracy was established as a result of these conventional echocardiographic parameters worsening with age [12-14]. Normal aging has been shown to result in reduced LV filling in early diastole and increased filling at atrial contraction and in most individuals the peak E and A wave velocities become approximately equal during the sixth and seventh decade of life [15-18]. Studies of the general population have shown the prevalence of diastolic dysfunction by Doppler measurements to be as high as 28-38% with the prevalence increasing with age [14,19]. These novel 3D performance parameters may be able to add to the assessment of diastolic function by augmenting the number of tools available to make the diagnosis.

We set out to establish 3D echocardiography derived volume-time curves as a valid measurement and a potential clinical tool. First, we sought to validate 3D echocardiography derived volume-time curves, and second we applied them to a clinical population. To establish the validity and reproducibility of this novel volumetric approach, we compared 3D echocardiography derived volume-time curves with those obtained from cardiac MRI. We also assessed the inter- and intra-observer variability of the 3D echocardiography volume-time curves and the derived peak emptying and filling rates. To clinically evaluate these novel 3D performance parameters as a potential diagnostic tool, we chose a normal population and assessed changes in the parameters with age.

Methods

Study design

In a study design approved by the Mount Sinai Medical Center's

Institutional Review Board, we studied two groups of subjects to both prospectively validate the 3D echocardiography derived volume time curves with a gold standard and retrospectively demonstrate possible clinical applications.

Validation cohort

We studied 16 consecutive patients over the age of 18 who consented to the study protocol with acceptable 3D echocardiography images who underwent a 1.5 Tesla (Magnetom Sonata*, Siemens Medical Solutions, Erlangen, Germany) or a 3.0 Tesla (Achieva*, Philips Medical Systems, Best, The Netherlands) cardiac MRI followed by a 3D echocardiogram (Philips IE-33, Andover, MA) within 12 hours.

Clinical cohort

The first 50 patients with adequate acoustic windows presenting for a clinically indicated transthoracic echocardiogram over a three month period from June 2008 through August 2008 who were imaged on the Philips IE-33 platform were included for analysis. Patients with an EF of <45%, significant (moderate or greater) valve disease, and atrial fibrillation were excluded. Patients were divided into four age groups (< 40, 41-59, 61-79, and > 80 years old) for analysis.

3D Image acquisition and processing

A standard transthoracic echocardiogram was performed and then high-resolution real time transthoracic 3D echocardiography images in the apical view were acquired with an X3-1 Philips transthoracic probe during a breath hold. 3D processing and volume-time curves were generated with commercially available software (Philips Q-Lab 5.0). From the volume-time curves exported from Philips Q-Lab, peak emptying rates (ml/s), peak filling rates (ml/s), and peak systolic acceleration (ml/s^2) were generated using custom written software. Left ventricular EF, presence and severity of valvular disease, and common measures of diastolic function including trans-mitral pulse wave E/A, tissue Doppler e'/a' at the mitral annulus, E/e' ratio were recorded from the 2D images. Left ventricular 3D EF, End Diastolic Volumes (EDV), End Systolic Volumes (ESV), and Stroke Volumes (SV) were recorded from the standard 3D processing.

Cardiac MRI image acquisition and processing

Patients in the validation cohort were imaged in the supine position using dedicated multi-element surface coils and retrospective electrocardiographic gating. Multiple short-axis cine views covering the left ventricle from base to apex were acquired over 5-7 minutes with a standard segmented steady-state free precession sequence during limited end-expiratory breath-holds. Typical imaging parameters included repetition time 3.2 ms, echo time 1.6 ms, maximized flip angle, field of view adjusted to patient body size, matrix 256 x 125, lines per segment 11-15 (resulting in a temporal resolution of 35-50 ms), reconstructed cardiac phases 25-30; receiver bandwidth 930 Hz/pixel). Images were then analyzed with dedicated software (Argus*, Siemens Medical Solutions, Erlangen, Germany; or Extended MR Workspace*, Philips Medical Systems, Best, Netherlands). Left ventricular endocardial contours were traced from base to apex throughout the cardiac cycle. For each phase, LV volumes were obtained by Simpson's method and combined to generate volume-time curves.

3D echocardiography inter- and intra-observer variability

For inter-observer variability assessment, two level 3 echocardiographers (WLD and MEG) independently and blindly processed the 3D datasets from the 16 patients in the validation cohort

to generate volume-time curves. From the volume-time curves peak emptying rates and peak filling rates were generated using custom written software. For intraobserver variability assessment, two weeks after the initial 3D processing one of the echocardiographers, blindly and in random order, re-processed the 3D datasets. These volume-time curves were again used to generate peak emptying rates and peak filling rates.

Statistical analysis

The volume-time curves derived from cardiac MRI and 3D echocardiography were compared after dividing the curves into six segments, three each for both systole and diastole. Comparisons between MRI and 3D echocardiography-derived slope segments were made using paired t-tests and Pearson correlation coefficients, respectively. Inter- and intra-observer variability for peak emptying and peak filling rates was determined using Pearson's correlation coefficient.

Novel performance parameters of peak emptying rates, peak filling rates, and peak systolic acceleration in the normal clinical cohort were analyzed by age, E/e' Ratio, EF, EDV, and SV. Continuous variable were analyzed using a two-tailed paired Student's t-test and categorical variables using Chi-squared analysis. Independent associations between variables were assessed by linear regression.

Results

Validation with cardiac MRI

The 16 patients had a mean age of 50.7 ± 13.1 years, 56% were male, and the average EF was 54.9% ± 10.3% (Table 1). There was no significant difference between the systolic and diastolic slopes of the volume-time curves derived using 3D echocardiography and cardiac MRI (Figure 2). There was good correlation between the two methods for both systole (r - 0.62, p<0.0001) and diastole (r - 0.43, p - 0.0025).

Inter- and intra-observer variability

Inter-observer correlation for 3D echocardiography derived slopes was excellent: r - 0.8 for systole, r - 0.98 for diastole, p<0.0001. Interobserver variability on the 16 patients in the validation cohort was low for both the peak emptying rate and the peak filling rate (r - 0.88 and r - 0.93 respectively, p<0.0001) (Figure 3). Intraobserver variability on these patients was also good with r - 0.71 for peak emptying rate (p - 0.0019) and r - 0.76 for peak filling rate (p - 0.0006) (Figure 4).

Clinical cohort

We studied 50 normal clinical patients for age related cardiac changes who had a mean age of 58.6 ± 18.6 years, 54% of whom were male (Table 1). The average left ventricular EF was 61.1% ± 7.5%.

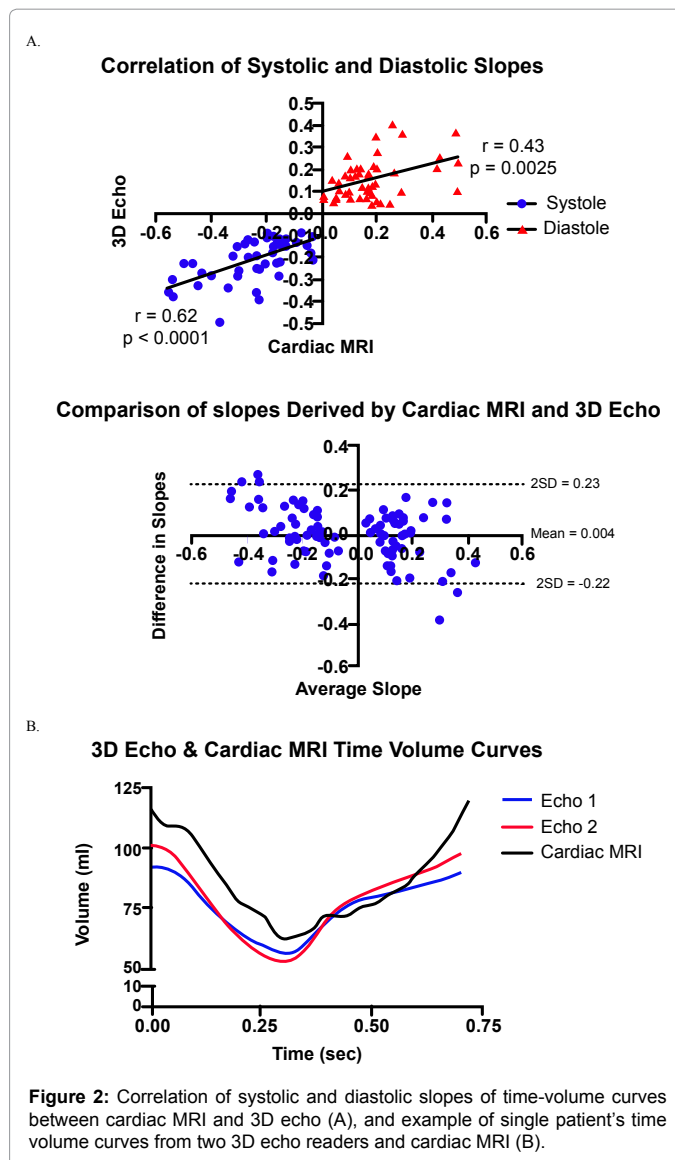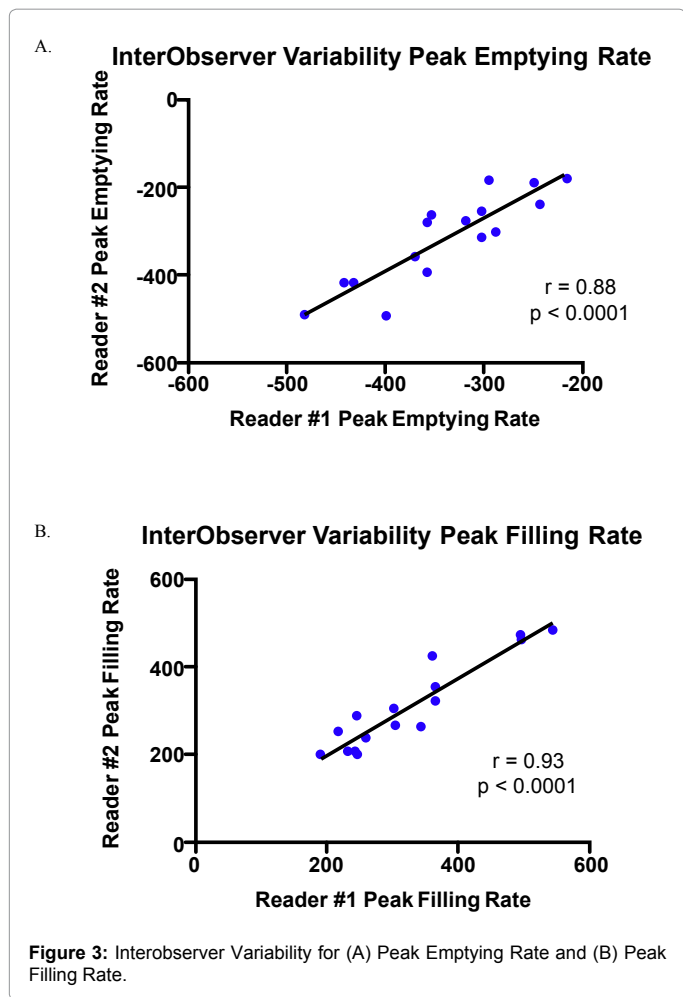Despite having a normal left ventricular EF, peak emptying rates,

Figure 2: Correlation of systolic and diastolic slopes of time-volume curves between cardiac MRI and 3D echo (A), and example of single patient's time volume curves from two 3D echo readers and cardiac MRI (B).

systolic acceleration, and peak filling rates all decreased with age. When these patients were divided based on age range, compared to patients in the oldest group, patients in the youngest group had significantly faster peak emptying rate (p - 0.02), peak filling rate (p - 0.02), and peak systolic acceleration (p - 0.04) (Figure 5). When taken as a continuous variable, peak emptying rates (p - 0.0007) and peak filling rates (p - 0.0031) both significantly decreased with age and peak systolic acceleration (p - 0.059) showed a trend towards slowing with age (Figure 6).

As potential novel measures of diastolic function, we compared them to common echocardiographic Doppler measures of diastolic function. All three novel parameters derived from 3D echocardiography had as strong or stronger association with age than E/e' ratio did (Figure 6 and 7). Peak diastolic filling rates poorly correlated with the E/e' ratio (r - -0.35, p - 0.019) (Figure 7).

The novel 3D parameters of peak emptying rate, peak filling rate, and peak systolic acceleration were assessed for their association to EF and ventricular volumes such as EDV and SV (Table 2). While univariate analysis showed significant correlation between the 3D parameters and

	Validation Cohort N = 16	Clinical Cohort N = 50
Age (yrs)	50.7 ± 13.1	58.6 ± 18.6
Gender		
Male	9 (56%)	27 (54%)
Female	7 (44%)	23 (46%)
3D Ejection Fraction (%)	54.9% ± 10.3%	61.1% ± 7.5%
End Diastolic Volume (ml)	110.7 ± 26.2	89.4 ± 30.9
End Systolic Volume (ml)	50.7 ± 19.0	34.1 ± 13.9
Stroke Volume (ml)	60.0 ± 15.6	55.3 ± 20.5

Table 1: Patient Characteristics.

Figure 3: Interobserver Variability for (A) Peak Emptying Rate and (B) Peak Filling Rate.

the left ventricular variables, the association lost statistical significance in a multivariate model (consisting of age, EF, EDV, SV, and E/e' ratio) for all variables except peak emptying rate and stroke volume.

Discussion

This work demonstrated that real time 3D echocardiography generated volume-time curves correlated well with cardiac MRI generated curves and were not significantly different. The 3D echocardiography generated curves also had low inter-observer variability of measurements of derived slopes. The reproducibility of these novel parameters was good with minimal inter- and intraobserver variability for peak emptying rates and peak filling rates. For the most part, the novel 3D parameters provided information beyond of traditional measures of left ventricular function and volume based on multivariate analysis. These novel parameters were associated (weakly) with EF but had a stronger association with LV volumes (EDV and ESV). However in multivariate analysis, most associations to EF and volumes were lost.

In a small clinical cohort we also demonstrated that despite preserved LVEF, aging hearts manifested progressive changes in these novel systolic and diastolic performance variables. All three novel parameters, peak emptying rate, peak filling rate, and peak systolic acceleration, declined with age and had a stronger association with age than E/e' ratio. These novel systolic parameters worsen with age despite patients having normal left ventricular ejection fraction suggesting

that the ventricular aging process involves both systole and diastole. This study demonstrates that 3D echocardiography is a feasible way to measure these novel parameters.

The parameters we derived from 3D echocardiography volume time curves have been derived from other modalities in the past. The initial work on left ventricular emptying and filling rates dates back to the 1970's and studied 113 patients and 29 normal subjects using single-plane cineangiograms [3,4]. Peak emptying rate correlated well with peak aortic flow rates and was not closely related to EF but to LV volume (EDV and SV) [3]. Peak diastolic filling rate was abnormal in patients with coronary disease and chronic valvular disease but was also related to volume characteristics of the LV (EDV & SV) [4]. Subsequent work with first pass radionuclide angiocardiograms in 22 patients without valvular regurgitation found that peak emptying rates correlated well with EF by angiography and allowed complete separation of normal and abnormal EF patients [1]. In addition, peak emptying rates increased eight-fold more than EF after isoproterenol infusion. In the largest study of 231 patients, radionuclide angiography derived peak filling rates were abnormal in a high percentage of patients at rest with coronary artery disease, both with normal and abnormal EF's [2]. And in a study of 28 patients using gated radionuclide angiography and intracardiac pressure recordings peak ejection and filling rates correlated well with invasive hemodynamic measurements (EF, +dP/dT, -dP/dT, and LV end diastolic pressure) [5].

Older 3D echocardiography platforms have been used to generate
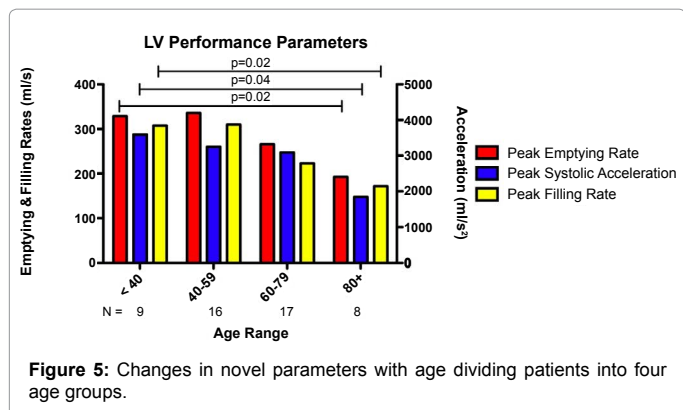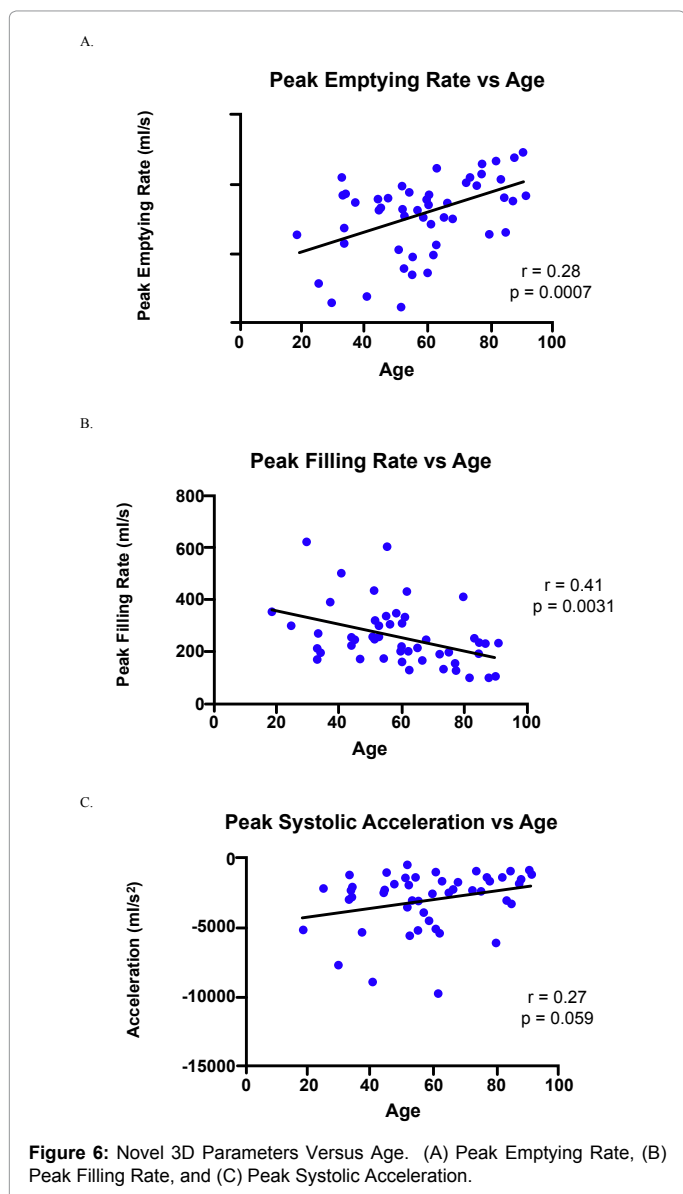

Figure 4: Intraobserver Variability for (A) Peak Emptying Rate and (B) Peak Filling Rate.
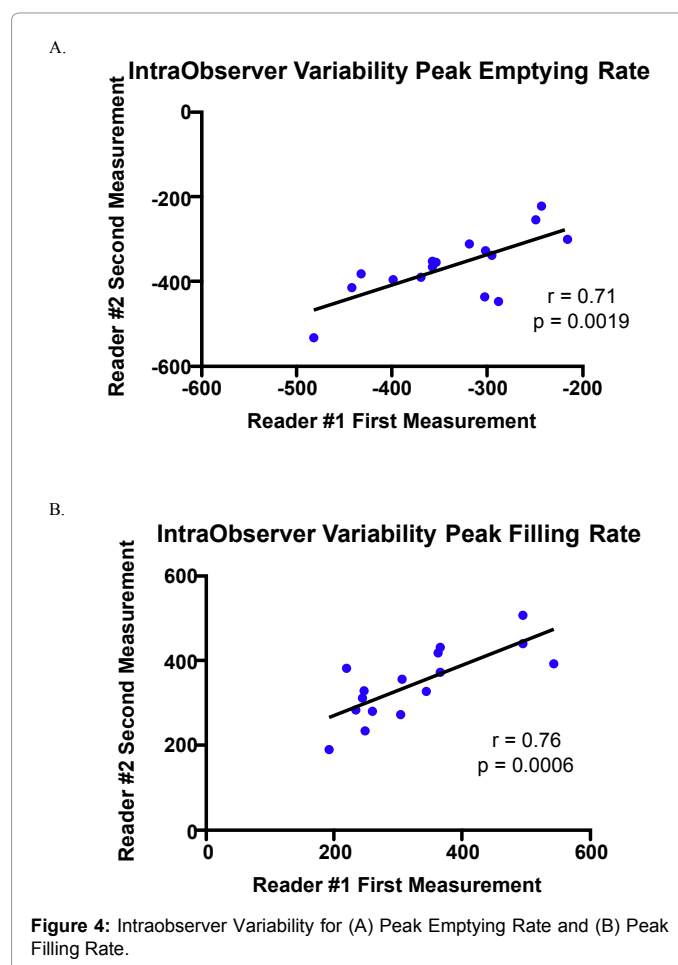
Figure 5: Changes in novel parameters with age dividing patients into four age groups.

Figure 6: Novel 3D Parameters Versus Age. (A) Peak Emptying Rate, (B) Peak Filling Rate, and (C) Peak Systolic Acceleration.

cardiac MRI. Differences were found in peak filling rates and peak emptying rates between small groups of patients without cardiovascular disease and those with heart failure, hypertension, and coronary artery disease [10,11]. Our study supports 3D echocardiography's ability to noninvasively assess left ventricular emptying and filling rates and finds differences in these parameters with increasing age in place of based on normal patient's age. 3D echocardiography has advantages over other imaging techniques including portability, improved spatial resolution (gated blood pool scans and myocardial perfusion imaging), fast image acquisition and analysis time (cardiac MRI), lack of ionizing radiation (nuclear cardiology and cardiac CT), and independence from potentially nephrotoxic agents (cardiac CT).

The rate of peak systolic emptying, the systolic ejection phase derived parameter may be affected by intrinsic factors (aging, ischemia, myocardial disease) and extrinsic factors (loading conditions, valve disease). In our group of otherwise normal subjects, ventricular

Figure 7: Correlation of E/e' Ratio with Age (A) and Difference in E/e' Ration by Age Group (B). The Correlation of Peak Filling Rate to E/e' Ratio (C).

volume-time curves and peak emptying and filling rates calculated [9-11]. While these echocardiography systems are no longer, or never were commercially available, they also showed good correlation with
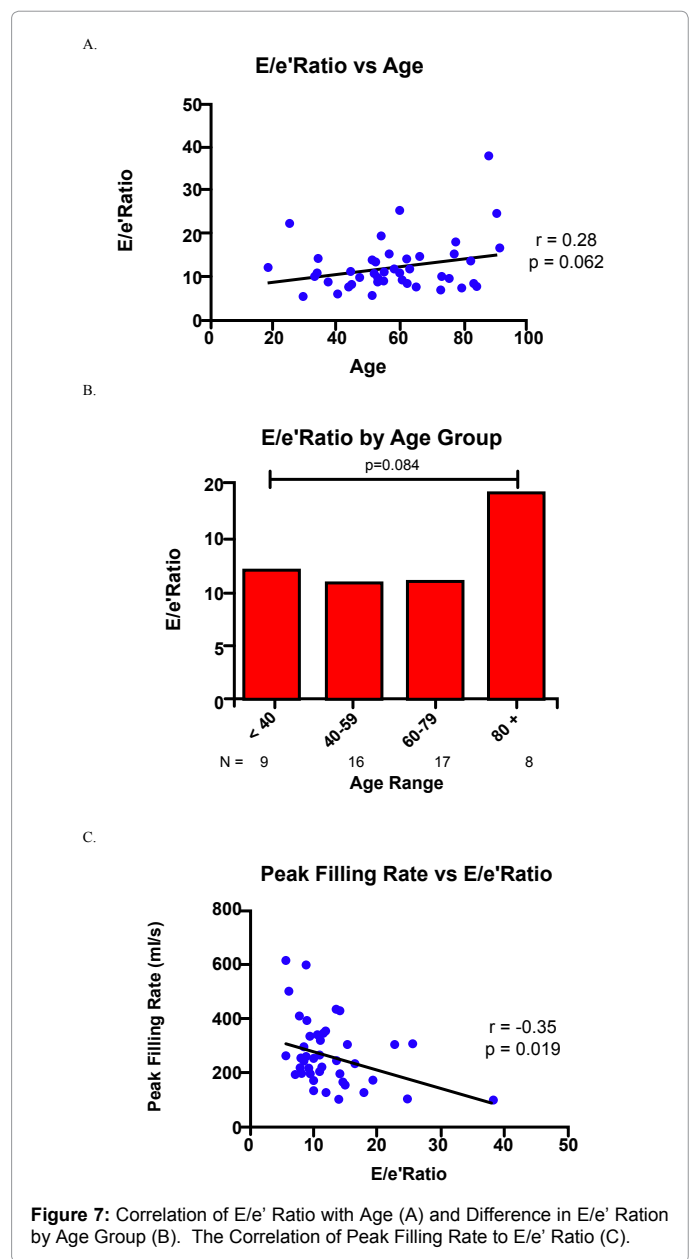
Peak Emptying Rate

Characteristic	Univariate P value	Multivariate P Value
Age	0.0007	0.044
EF	0.044	0.64
EDV	<0.0001	0.76
SV	<0.0001	0.027
E/e' Ratio	0.093	-

Peak Filling Rate

Characteristic	Univariate P value	Multivariate P Value
Age	0.0031	0.76
EF	0.042	0.23
EDV	<0.0001	0.31
SV	<0.0001	0.83
E/e' Ratio	0.019	0.21

Peak Systolic Acceleration

Characteristic	Univariate P value	Multivariate P Value
Age	0.059	0.81
EF	0.123	-
EDV	<0.0001	0.93
SV	<0.0001	0.14
E/e' Ratio	0.036	0.20

Table 2: Univariate and Multivariate Analysis of the Association of Novel 3D Parameters to Age, E/e' Ratio, EF, and Ventricular Volumes.

systolic performance as determined by peak emptying rates was slower in the older patients compared to younger subjects. This was in addition to a reduction in peak diastolic filling rates. The abnormalities in systolic ventricular performance were present despite a normal ejection fraction. While patients with diastolic heart failure virtually always exhibit normal indices of LV systolic performance, function, and contractility previous echocardiography Doppler studies have suggested that diastolic heart failure may be caused by subtle systolic dysfunction or exhibits a coexistence with systolic dysfunction [20-23]. In this current study, a subtle but measureable decline in ventricular systolic function as well as diastolic function was present in the aging heart and these novel parameters may in the future be able to aid in the diagnosis of normal EF heart failure.

Limitations

This study is limited by its small sample size and single center experience. 3D echocardiography is currently limited by image quality and the inability to acquire diagnostic images in a majority of patients. New technology may improve these shortcomings. The uni- and multivariate analysis may have been limited due to the narrow range of EF's (>45%) since we were evaluating a group who by definition had normal LVEF.

Conclusions

These novel real time 3D echocardiography volume time curve derived parameters may, with further study, prove to be helpful in the assessment of systolic and diastolic function. They correlate well with the gold standard of cardiac MRI and yet are quicker and easier to obtain. Novel systolic and diastolic parameters derived from volumetric data may provide insight into ventricular performance not available by other imaging modalities. Further work in various disease states might demonstrate that these parameters could provide a more detailed noninvasive assessment of systolic function, may prove to be early markers of latent disease, and might simplify the evaluation of diastolic dysfunction.

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