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Impact of medical therapy for cardiovascular disease on left ventricular diastolic properties and remodeling☆,☆☆

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ABSTRACT

Background: Left ventricular (LV) remodeling and diastolic properties are affected by both underlying cardiovascular disease/cardiovascular disease risk factors (CVDRFs) and corresponding medication therapy. However, these effects may not be apparent in patients with multiple CVDRFs. We evaluated the effect of medication classes on hemodynamics in a patient cohort with normal LV dimensions and systolic function.
Methods: In 38 participants (61 ± 7 years, 64 ± 9% LV ejection fraction) undergoing coronary angiography, LV pressure measurement and cardiac magnetic resonance imaging was performed. The effects of coronary artery disease (CAD), CVDRFs and their corresponding medication therapy on LV parameters were analyzed considering the number of CAD/CVDRFs and 'adequacy' of medication therapy to address each existing condition with specific indication-based medication classes.
Results: Of the patients studied, 68% had CAD, 87% had hypertension, 87% had dyslipidemia, and 45% had diabetes. Neither individual or total number of CAD/CVDRFs were associated with overall differences in LV diastolic parameters. However, those without (n = 20) and with (n = 18) 'adequate' medication therapy for underlying CAD/CVDRFs differed in values of LV end diastolic pressure (17 ± 4 vs. 11 ± 5 mm Hg, $P < 0.001$), wall stress (3.9 ± 1.6 vs. 2.2 ± 1.2 x1000 N/m^2, $P < 0.001$), pressure/volume ratio (0.13 ± 0.04 vs. 0.08 ± 0.03 mm Hg/ml, $P < 0.01$), and mass/volume ratio (0.77 ± 0.20 vs. 0.92 ± 0.24 g/ml, $P < 0.05$), but not in systolic blood pressure or LV mass index.
Conclusions: Our results suggest an association between the degree of LV diastolic impairment and LV remodeling with the intensity of treatment for CAD/CVDRFs. Comprehensive treatment of all identified CAD/CVDRFs may be an important factor for the preservation of diastolic function.

1. Introduction

Heart failure is a major clinical problem [1]. Patients with left ventricular (LV) ejection fraction (EF) ≥50% in the appropriate clinical context are considered to have diastolic dysfunction and heart failure with preserved LVEF. LV remodeling is central to the pathogenesis of cardiac dysfunction with characteristic changes in response to pressure or volume overload or both [2]. It is well accepted that LV mechanical properties are closely associated with LV structural remodeling [3]. In patients with hypertension (HTN), who are predisposed to diastolic dysfunction, increased LV wall stress due to elevated systolic blood pressure leads to LV concentric remodeling and hypertrophy associated with increased chamber stiffness [4,5], which are considered important features of diastolic dysfunction [2,3]. In contrast, in other situations, including post myocardial infarction, eccentric LV remodeling may develop [2,3,6]. These patients may demonstrate systolic dysfunction [2,3,6]. It has been suggested that with advancing heart failure, concentric LV remodeling may eventually transform to a dilated LV and systolic dysfunction [7]. However, this conventional concept of HTN-associated LV remodeling has been challenged [8].

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In a recent study, we reported that participants with advanced LV diastolic hemodynamic abnormalities (increased LV end diastolic pressure, LVEDP, and the time constant of LV relaxation, τ,) and increased chamber stiffness surprisingly revealed relatively more eccentric LV geometry, versus more concentric LV geometry in those with better LV hemodynamic measurements and less chamber stiffness [9]. This prompted us to test the hypothesis that such a contradiction to the expected relationship between LV concentricity and diastolic properties may be due to the effects of concomitant cardiovascular diseases, major cardiovascular disease risk factors (CVDRFs) and the corresponding medication therapy. This hypothesis relies on accumulated evidence that coronary artery disease (CAD) and all major CVDRFs including HTN, dyslipidemia (DL), and diabetes mellitus (DM) can be associated with impaired LV diastolic hemodynamic and mechanical properties [10]. Therefore, using our well-characterized patient cohort, we undertook a detailed analysis of the relationship between concomitant CAD and major cardiovascular disease risk factors (CVDRFs) and corresponding medications with LV diastolic properties.

2. Methods

2.1. Study Population

The study participants (n = 38, 61 ± 7 years, 87% male) were recruited among patients with chest pain and/or dyspnea undergoing diagnostic cardiac catheterization for the evaluation of coronary artery disease with LVEF ≥50% and no evidence of acute infarction, and those who agreed to participate in research cardiovascular magnetic resonance imaging (CMR) for new diagnostic imaging parameters [9]. To the present analysis, two additional participants excluded from our previous study due to the lack of tagging scans necessary for the torsional measurements during CMR were added. Major exclusion criteria included primary coronary intervention during cardiac catheterization, presence of hypertrophic cardiomyopathy or myocarditis, or significant valve disease, presence of pacemaker or defibrillator or contraindication to CMR. All participants gave written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by the University of Alabama at Birmingham and U.S. Department of Veterans Affairs Institutional Review Board.

2.2. LV measurement of diastolic hemodynamic and mechanical properties

After diagnostic left heart catheterization, comprehensive hemodynamic assessment was performed using a high-fidelity manometer (Millar Instruments, TX, USA or St Jude, MN, USA). Multiple LV pressure tracings were acquired. LV EDP was quantified from median measurement obtained from 5 to 7 tracings (~25–30 beats) in a blinded fashion. The time constant of LV relaxation (τ) was assessed by Weiss method [11]. LV EDP >12 mm Hg and τ >48 ms were considered as abnormal [12]. Participants with both abnormal LVEDP and τ were considered as having advanced diastolic hemodynamic abnormalities [9]. LV ED wall stress was calculated as previously described [13]. The chamber stiffness constant β was calculated from a single beat ED pressure-volume relationship as described [14–16]. Additionally, LV ED pressure/volume ratio was calculated as a surrogate estimate of LV chamber stiffness [16].

2.3. Cardiac magnetic resonance imaging

Cine CMR was performed a median one day after cardiac catheterization on a 1.5-T CMR scanner (Signa, GE Healthcare, Milwaukee, Wisconsin) [9]. ECG-gated breath-hold steady-state free precision technique was used to obtain short- and long-axis LV views prescribed in a circular orientation at 30° intervals to allow for comprehensive LV coverage [9]. The CMR parameters were: slice thickness of the imaging planes at 8 mm with zero inter-slice gap, field of view 40 cm, scan matrix 256 × 128, flip angle 45°, repetition/echo times 3.8/1.6 ms and number of reconstructed cardiac phases 20. LV geometric parameters were measured from endocardial and epicardial contours manually traced on cine images acquired near end-diastole and propagated throughout the cardiac cycle using in-house software [17]. LV volumetric variables were computed as previously described, with papillary muscles included as part of the LV volume [18,19]. LV concentricity was evaluated based on LV mass/volume ratio.

2.4. CAD & CVD RFs, medications, and assessment of CAD & CVD RFs treatment with medications

The following CVD RFs were evaluated (Table 1): HTN, DM and dyslipidemia. CAD was defined as presence of moderate-severe luminal stenosis (>40%) in major epicardial arteries and/or prior coronary intervention/coronary artery bypass grafting (CABG) [9]. Adequate medical therapy for CAD and CVD RFs was defined based on a simplified evidence-based approach as described: HTN: angiotensin-converting enzyme inhibitor/Angiotensin II type-1 receptor blockers (AI/AT1RB), and/or diuretic, and/or beta blocker and/or calcium channel blocker (no aldosterone antagonists or vasodilators were reported in this cohort; 2 patients received alpha-blockers but together with AI/AT1RB); DL: statin; DM: oral hypoglycemic/insulin; and CAD: nitrates or alternatively nitrates and calcium channel blockers since participants had symptoms of chest pain, as these classes of medications may increase myocardial blood flow. If participants were treated with respective drug classes, they were considered adequately treated.

2.5. Other potential risk factors

Other potential risk factors including age, gender, history of smoking, systolic blood pressure, and obesity that could affect LV diastolic hemodynamic and mechanical parameters were also considered. Patients were divided based on either median age (younger vs. older) or gender type (males vs. females), or history of smoking (current, former smokers vs. never smokers), values of systolic blood pressure (normal, ≤130 mm Hg, vs. elevated, >130 mm Hg), or obesity (not obese vs. obese, defined as body mass index ≥ 30 kg/m^2). Due to a limited patient size, interaction effects of age, gender, history of smoking, systolic blood pressure, and obesity on relation of CAD, HTN, DL, DM and corresponding CAD&CVDRFs medication with LV function and properties was not analyzed. Clinical duration of CAD, HTN, DL, DM was not available for analysis.

2.6. Data and statistical analysis

Data are mean ± SD for normally distributed variables or median (interquartile range) for non-normally distributed variables. The effect of CAD & CVD RFs in the subgroups was evaluated based on 1) the presence or absence of specific CAD & CVD RFs; 2) total number of CAD & CVD RFs per participant; 3) number of CAD & CVD RFs that were not 'adequately' treated with medications. For normally distributed variables, characteristics of groups were compared using either unpaired *t*-test (two groups) or unpaired one-way ANOVA (three groups). For non-normally distributed variables, characteristics of groups were compared using either Mann-Whitney test (two groups) or Kruskal-Wallis test (three groups). Differences in proportions were evaluated by Fisher's exact test (two groups) or by Chi-square test (three groups). Effects of CAD and major CVD RFs without 'adequate' medication therapy as sources of variation in groups were evaluated by 2-Way ANOVA. Statistical analysis was performed using GraphPad Prism v.4.01. A 2-tail P-value <0.05 was considered statistically significant.

Table 1
Distribution of CAD, major cardiovascular disease risk factors and medication classes in the study subjects.

Subject number	CAD and CVD RFs				Medication classes							Statistics per subject	
	CAD	HTN	DL	DM	Nitrates (CAD/HTN)	Ca^{2+} channel blockers (HTN/CAD)	AI/AT1RBs (HTN/CAD)	Beta-blockers (HTN/CAD)	Diuretics (HTN)	Statins (DL/CAD)	Hypoglycemics (DM)	Number of CAD and CVD RFs	Number of CAD/CVD RFs without adequate treatment
1	●	●	●					●				3	2
2	●	●	●	●								4	4
3	●	●	●	●			●	●		●	●	4	1
4	●	●	●	●				●	●	●	●	4	1
5	●	●	●	●			●	●		●		4	2
6	●	●	●				●	●		●		3	1
7	●	●	●	●			●			●	●	4	1
8	●	●	●	●				●		●	●	4	1
9	●	●	●					●		●		3	1
10	●	●					●		●			2	1
11	●			●								2	2
12	●	●	●		●	●		●	●			3	1
13	●	●	●	●	●			●				4	2
14	●	●	●	●	●		●	●	●	●	●	4	0
15	●	●	●	●		●	●		●	●	●	4	1
16	●	●	●	●		●	●	●		●	●	4	1
17	●	●	●		●		●	●	●	●		3	0
18	●	●	●		●		●	●	●	●		3	0
19	●	●	●	●	●		●	●		●	●	4	0
20	●	●	●	●	●			●	●	●	●	4	0
21	●	●	●		●		●	●		●		3	0
22	●	●	●		●			●	●	●		3	0
23	●	●	●			●	●			●		3	1
24	●	●				●	●	●	●			2	1
25			●		●			●	●			1	1
26		●	●									2	2
27		●	●									2	2
28		●	●	●			●	●	●	●	●	3	0
29		●	●	●		●	●		●	●	●	3	0
30		●	●	●			●	●		●	●	3	0
31		●	●		●			●	●	●		2	0
32		●	●			●	●			●		2	0
33		●	●					●	●	●		2	0
34		●	●	●					●	●	●	3	0
35		●	●					●		●		2	0
36			●							●		1	0
37												0	0
38												0	0

CAD: coronary artery disease (defined based on moderate-severe luminal stenosis (>40%) on the coronary angiogram or prior angioplasty performed); HTN: hypertension; DL: dyslipidemia; DM: diabetes mellitus; CVD RFs: cardiovascular disease risk factors; AI/AT1RB: angiotensin-converting enzyme inhibitor/Angiotensin II type-1 receptor blockers. Black circle indicates the presence of indicated disease and/or use of indicated medication class. No aldosterone antagonists or vasodilators were reported in this cohort, 2 patients had alpha-blockers but together with AI/AT1RB.

3. Results

3.1. Study population

Table 1 shows the distribution of CAD & CVD RFs and medication classes in study participants. Table 2 (Grouping: all subjects) presents the basic clinical characteristics and overall prevalence of CAD (63%), HTN (87%), DL (87%), and DM (45%) as well as overall use of different medication classes. The majority of the study subjects had chest pain (89%) and almost half (42%) experienced NYHA class II dyspnea.

3.2. CMR and hemodynamic measurements

Average LV ejection fraction and LV volumetric indices were within the normal range (Table 2; Grouping: all subjects) [20]. Average LVEDP and τ were above normal values (14.3 $\pm$ 5.6 mm Hg and 58 $\pm$ 10 ms, respectively). All but 4 participants had either abnormal LVEDP (>12 mm Hg) and/or LV relaxation time (τ >48 ms). Nineteen (50%) participants had both abnormal LVEDP and τ, suggesting advanced diastolic hemodynamic abnormalities in these subjects. Average values of LV mass/volume ratio was 0.86 $\pm$ 0.26 g/ml (n = 38), which is midway between healthy controls and uncontrolled HTN as reported by us previously [21].

3.3. Effect of CAD & CVD RFs on LV concentricity and diastolic hemodynamic and mechanical properties

We evaluated the association of LV concentricity, hemodynamic and mechanical properties with the prevalence of CAD & CVD RFs. We grouped the study subjects based on the presence or absence of CAD or any of specific CVD RFs. We found no significant differences in LV hemodynamic and mechanical properties between the groups (*Supplementary Table S1*). As most of participants had HTN, we separately evaluated the cumulative effect of having CAD or DM on LV properties in hypertensive subjects. The presence of CAD in hypertensive subjects did not significantly affect LV structural, hemodynamic or mechanical characteristics (*Supplementary Table S2*). The effect of DM in hypertensive subjects did not reach statistical significance although there was a trend towards increased LV mass/volume ratio and LV mass index and decreased LV wall stress and τ (*Supplementary Table S3*). In a separate analysis, we evaluated whether increasing number of CAD & CVD RFs, per se, plays a major role in differences in the hemodynamic and mechanical properties and found no such effect

Table 2
Clinical characteristics in entire study cohort and in comparator groups.

Variables	All subjects	Grouping 1: Number of CAD & CVD RFs				Grouping 2: Number of CAD & CVDRFs without 'adequate' medications			
Group value (n = subjects in group)	(n = 38)	0–2 (n = 13)	3 (n = 13)	4 (n = 12)	*P-value*	2–4 (n = 7)	1 (n = 13)	0 (n = 18)	*P-value*
Clinical characteristics									
Age, year	61 ± 7	60 ± 7	61 ± 6	64 ± 6	*>0.1*	59 ± 6	64 ± 6	61 ± 7	*>0.1*
Body surface area, m^2	2.1 ± 0.2	2.1 ± 0.2	2.0 ± 0.2	2.1 ± 0.2	*>0.1*	2.0 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	*>0.1*
Body mass index, kg/m^2	29.4 ± 5.1	29.2 ± 4.4	27.5 ± 4.6	31.7 ± 5.8	*>0.1*	27.3 ± 4.3	29.8 ± 5.2	30.0 ± 5.4	*>0.1*
Systolic blood pressure, mm Hg	131 ± 17	129 ± 17	126 ± 15	137 ± 18	*>0.1*	128 ± 20	137 ± 15	127 ± 16	*>0.1*
Diastolic blood pressure, mm Hg	74 ± 10	74 ± 13	76 ± 9	72 ± 9	*>0.1*	73 ± 8	76 ± 10	74 ± 12	*>0.1*
Heart rate, beats/min	68 ± 11	65 ± 9	68 ± 11	71 ± 12	*>0.1*	66 ± 8	68 ± 13	69 ± 11	*>0.1*
Chest pain, %	89	92	83	92	*>0.1*	100	85	88	*>0.1*
Dyspnea, %	66	46	69	83	*>0.1*	86	69	56	*>0.1*
Hemoglobin, g/dl	13.6 ± 1.7	14.2 ± 1.3	14.0 ± 1.5	12.7 ± 1.9	*0.06*	13.6 ± 1.5	13.5 ± 1.3	13.7 ± 2.0	*>0.1*
Creatinine, mg/dl	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	*>0.1*	1.1 ± 0.3	0.9 ± 0.2	1.0 ± 0.3	*>0.1*
Total bilirubin, mg/dl	0.5 ± 0.2	0.4 ± 0.1	0.6 ± 0.2	0.5 ± 0.1	*>0.1*	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	*>0.1*
Glucose, mg/dl	108 (98–146)	100 (95–108)	101 (96–136)	145 (124–179)	†	126 (95–145)	117 (98–136)	104 (98–169)	*>0.1*
Total cholesterol, mg/dl	174 ± 45	195 ± 49	174 ± 35	149 ± 41	*	185 ± 42	171 ± 58	174 ± 36	*>0.1*
Triglycerides, mg/dl	130 (104–196)	130 (86–223)	132 (96–196)	125 (101−221)	*>0.1*	152 (106–384)	124 (98–216)	131 (82–214)	*>0.1*
Blood urea nitrogen, mg/dl	16.3 ± 5.3	15.3 ± 6.6	17.2 ± 4.4	16.3 ± 5.3	*>0.1*	16.9 ± 4.7	16.0 ± 4.9	16.2 ± 6.1	*>0.1*
Concomitant CAD & CVDRFs and medications									
Coronary artery disease, (%)	63	23	69	100	‡‡‡	71	92	39	‡‡
Without 'adequate' medication, (%)	39	23	31	67	*0.06*	57	92	0	‡‡‡
Hypertension, (%)	87	62	100	100	‡‡	86	92	83	*>0.1*
Without 'adequate' medication, (%)	8	15	0	9	*>0.1*	43	0	0	‡‡‡
Dyslipidemia, (%)	87	62	100	100	‡‡	86	85	89	*>0.1*
Without 'adequate' medication, (%)	18	23	15	17	*>0.1*	71	15	0	‡‡‡
Diabetes, (%)	45	8	31	100	‡‡‡	57	46	39	*>0.1*
Without 'adequate' medication, (%)	10	8	0	25	*>0.1*	57	0	0	‡‡‡
AI/AT1RB, (%)	47 (42/5)	23	62	58	*0.1*	14	62	50	*>0.1*
Beta blockers, (%)	63	38	77	75	*0.07*	43	69	67	*>0.1*
Calcium channel blockers, (%)	18	15	23	17	*>0.1*	0	31	11	*>0.1*
Diuretics, (%)	42	38	54	33	*>0.1*	0	46	56	‡
Nitrates, (%)	29	15	38	33	*>0.1*	14	15	44	*>0.1*
Statins, (%)	68	38	85	83	‡	14	69	89	‡‡
Hypoglycemic drugs, (%)	34	0	31	75	‡‡‡	0	46	39	*0.1*
CAD & CVDRFs per subject, n	3 (2–4)	2 (1–2)	3	4	††	3 (2–4)	3 (2.5–4)	3 (2–3)	*>0.1*
Medication classes per subjects, n	3 (2–4.5)	2 (0–3)	4 (3–5)	4 (3–5)	†	0 (0–2)	3 (3–4)	4 (2.5–5)	†
Antihypertensive medications, n	2 (1–2.5)	1 (0–2)	2 (1.5–3)	2 (1–2.5)	*0.06*	0 (0–1)	2 (1.5–3)	2 (1–3)	†
CAD & CVDRFs without 'adequate' medications, n	1 (0–1)	0 (0–1.5)	0 (0–1)	1 (0.5–1.5)	*>0.1*	2 (2–2)	1 (1–1)	0 (0–0)	††

Data are mean ± SD or median (interquartile range). CAD: coronary artery disease; CVD RFs: cardiovascular disease risk factors; AI/AT1RB: angiotensin-converting enzyme inhibitor/Angiotensin II type-1 receptor blocker.
* P < 0.05 by One-Way ANOVA.
† P < 0.01.
†† P < 0.001 by Kruskal-Wallis.
‡ P < 0.05.
‡‡ P < 0.01.
‡‡‡ P < 0.001 by Chi-Square test.

(Table 2, Grouping 1 and Table 3, Grouping 1). We also found no effects of age, gender, history of smoking, systolic blood pressure, and obesity in this cohort (*Supplementary Table S4*).

3.4. Effect of 'adequate' treatment of CAD & CVD RFs on LV concentricity and diastolic hemodynamic and mechanical properties

Using a simple model, we considered CAD & CVD RFs as 'adequately' treated with medications if HTN was treated with at least one of 4 primary anti-hypertensive medication classes (Table 1), DL was treated with statins, CAD was treated with nitrates, and DM was treated with oral hypoglycemics or insulin. This simple approach unveiled a strong association between the presence of CAD & CVD RFs without 'adequate' medications in participants and the level of impairment of LV hemodynamic and mechanical properties, regardless of concomitant CAD & CVD RFs (Table 2, Grouping 2 and Table 3, Grouping 2). Significant changes were observed in all measured LV diastolic parameters, which included LV EDP, τ, wall stress, EDP/EDV ratio, and chamber stiffness constant β ($P < 0.01$, $P < 0.05$, $P < 0.001$, $P = 0.05$, $P = 0.08$ by One-Way ANOVA, Table 3, Grouping 2). The prevalence of advanced hemodynamic abnormalities was significantly higher in participants with CAD & CVD RFs without 'adequate' medications ($P < 0.001$, Chi-square test, Table 3, Grouping 2). Importantly, there was a specific effect on LV concentricity, which could not be explained by the change in prevalence of HTN and DM ($P > 0.1$, Table 2, Grouping 2) but rather by a decrease in LVEDV ($P < 0.05$ by post-test for linear trend following One-Way ANOVA ($P < 0.05$), Table 3, Grouping 2). These findings were also observed when the patients without 'adequate' medication therapy were combined. Thus, those without (n = 20) and with (n = 18) 'adequate' medication therapy for underlying CAD/CVDRFs had different values of LV end

Table 3
Relation of prevalent CAD, cardiovascular disease risk factors and medication classes with left ventricular properties.

Variables	All subjects	Grouping 1: Number of CAD & CVD RFs				Grouping 2: Number of CAD & CVDRFs without 'adequate' medications			
Group value (n = subjects in group)	(n = 38)	0–2 (n = 13)	3 (n = 13)	4 (n = 12)	*P-value*	2–4 (n = 7)	1 (n = 13)	0 (n = 18)	*P-value*
LV characteristics									
Mass/volume ratio, g/ml	0.86 ± 0.26	0.78 ± 0.20	0.90 ± 0.34	0.90 ± 0.22	*>0.1*	0.62 ± 0.09	0.86 ± 0.20	0.92 ± 0.24	*
Mass index, g/m^2	53 ± 11	52 ± 12	50 ± 12	56 ± 11	*>0.1*	46 ± 4	56 ± 12	52 ± 12	*>0.1*
End diastolic volume index, ml/m^2	65 ± 15	70 ± 14	61 ± 18	64 ± 12	*>0.1*	77 ± 14	66 ± 15	59 ± 14	*
End systolic volume index, ml/m^2	24 ± 9	25 ± 9	22 ± 10	23 ± 8	*>0.1*	30 ± 9	22 ± 10	22 ± 8	*0.1*
Stroke volume index, ml/m^2	41 ± 9	44 ± 8	39 ± 12	41 ± 6	*>0.1*	46 ± 6	44 ± 7	37 ± 10	*
Ejection fraction, %	64 ± 9	64 ± 8	65 ± 10	65 ± 7	*>0.1*	61 ± 7	68 ± 9	63 ± 9	*>0.1*
LV diastolic hemodynamic and mechanical properties									
End diastolic pressure, mm Hg	14.3 ± 5.6	14.9 ± 6.2	12.8 ± 5.9	15.2 ± 4.5	*>0.1*	16.9 ± 4.5	17.5 ± 3.9	11.1 ± 5.3	**
Relaxation time constant (τ), ms	58 ± 10	61 ± 9	55 ± 10	57 ± 9	*>0.1*	66 ± 10	57 ± 9	55 ± 9	*
End diastolic wall stress, 1000 N/m^2	3.1 ± 1.6	3.5 ± 2.0	2.9 ± 1.7	2.9 ± 1.2	*>0.1*	4.8 ± 1.6	3.4 ± 1.4	2.2 ± 1.2	***
End diastolic pressure/volume ratio, mm Hg/ml	0.11 (0.07–0.13)	0.11 (0.07–0.12)	0.10 (0.07–0.15)	0.11 (0.08–0.14)	*>0.1*	0.11 (0.07–0.17)	0.11 (0.10–0.17)	0.08 (0.06–0.12)	*0.05*
Chamber stiffness (β_{ch})	5.88 ± 0.22	5.91 ± 0.25	5.84 ± 0.24	5.90 ± 0.13	*>0.1*	6.02 ± 0.21	5.90 ± 0.20	5.81 ± 0.21	*0.08*
Advanced diastolic hemodynamic abnormalities, (%)	50	62	31	58	*>0.1*	86	69	22	†

Data are mean ± SD or median (interquartile range). CAD: coronary artery disease; CVD RFs: cardiovascular disease risk factors.
* P < 0.05.
** P < 0.01.
*** P < 0.001 by One-Way ANOVA.
† P < 0.005 by Chi-Square test.

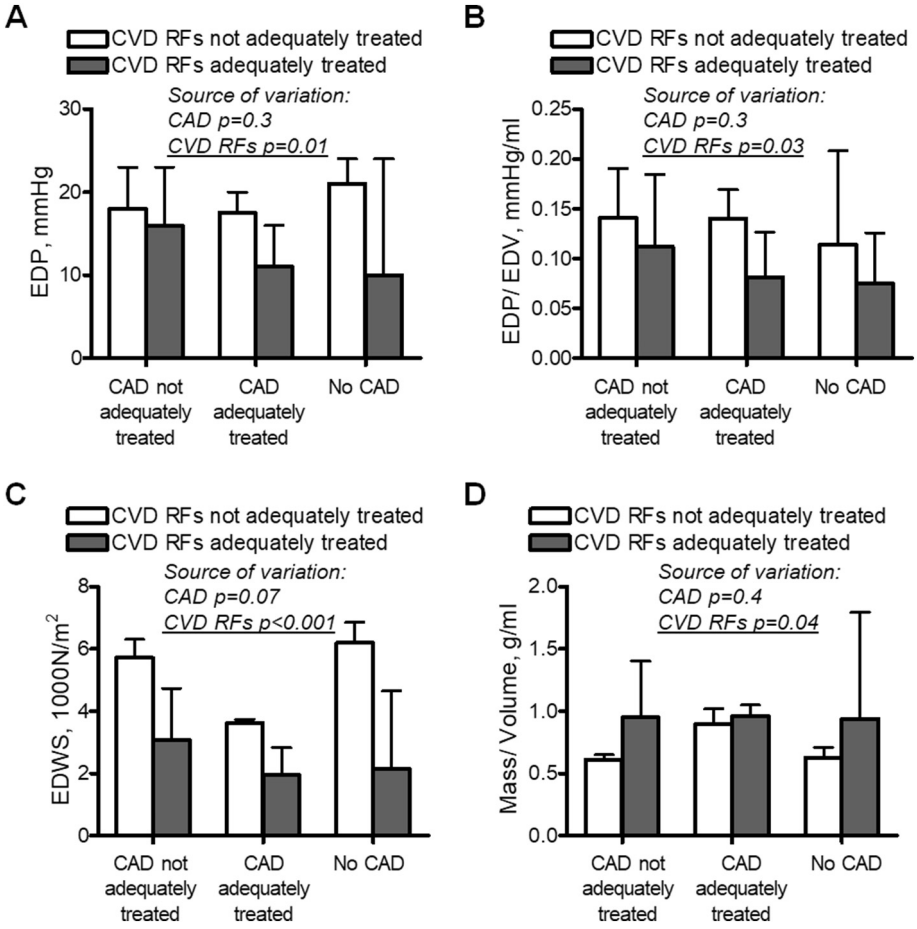

Fig. 1. Independent effects of cardiovascular disease (coronary artery disease, CAD) and cardiovascular disease risk factors (CVD RFs, including hypertension, dyslipidemia, and diabetes) without 'adequate' medication therapy on left ventricular (LV) diastolic hemodynamic properties (A: LV end diastolic pressure (EDP); B: LV end diastolic pressure/volume ratio (EDP/EDV); C: LV end diastolic wall stress (EDWS)) and LV geometry (D: LV mass/volume ratio). Black columns represent data for participants with CVD RFs adequately treated, and white columns represent data for participants with one or more CVD RFs not adequately treated. Effects of CAD and CVD RFs without 'adequate' medication therapy as source of variations were evaluated by 2-Way ANOVA. There was no interaction between CAD and CVDRFs (P > 0.1 for all parameters), but CVDRFs was a source of variation (P < 0.05 for all parameters).

diastolic pressure (17 ± 4 vs. 11 ± 5 mm Hg, P < 0.001), wall stress (3.9 ± 1.6 vs. 2.2 ± 1.2 x1000 N/m^2, P < 0.001), pressure/volume ratio (0.13 ± 0.04 vs. 0.08 ± 0.03 mm Hg/ml, P < 0.01), mass/volume ratio (0.77 ± 0.20 vs. 0.92 ± 0.24 g/ml, P < 0.05), and the prevalence of advanced abnormal diastolic hemodynamics (75% vs. 22%, P < 0.005) but not different systolic blood pressure (134 ± 17 vs. 127 ± 16 mm Hg, P > 0.2) or LV mass index (53 ± 11 vs. 52 ± 12 g/m^2, P > 0.9).

Further, we assessed the impact of 'adequate' medication treatment of CAD vs. CVD RFs, separately, on the associations reported above for LV concentricity and diastolic hemodynamic properties. Fig. 1 demonstrates that the effects of CVD RFs without 'adequate' treatment and CAD without 'adequate' medication on the differences in LV diastolic hemodynamic parameters and LV concentricity were independent.

In alternative analysis, we considered calcium channel blockers as an 'adequate' medication therapy for both HTN and CAD. Adding calcium channel blockers as possible alternative to nitrates as a 'adequate' medication therapy for CAD (i.e., nitrates and/or calcium channel blockers, based on common mechanism of action on coronary blood flow) does not substantially change all major statistical results described above for grouping 2 analysis as shown in *Dataset S1* (*Supplementary Table S5*, *Table S6*, *Table S7*, *Fig. S1*).

4. Discussion

Our study found a clear association between LV diastolic hemodynamic and mechanical derangements with 'adequate' treatment of CAD & CVD RFs in subjects at risk or in early stages of heart failure with preserved LVEF. Our analysis that in patients with adequate medical therapy for underlying CAD and CVD RFs, the underlying CAD and CVD RFs per se may not be the major factors for the severity of LV diastolic hemodynamic and mechanical derangements therefore provides important insights for testing therapeutic approaches. Our results indicate that subjects with CAD or CVD RFs that are unaddressed with 'adequate' medication therapy are more susceptible to LV diastolic hemodynamic and mechanical derangements. These derangements are more severe in those with increasing of number of CVD RFs without 'adequate' medications.

We found that a more concentric LV, in the absence of hypertrophy, was associated with better LV diastolic hemodynamic and mechanical properties. The typical paradigm of LV remodeling in heart failure with preserved LVEF is described based on elevated systolic blood pressure leading to concentric LV remodeling/hypertrophy to normalize systolic wall stress, which may eventually become dysregulated with subsequent dilatation of the LV in the latter stages of heart failure [3]. In our study, we did not a priori select patients with concentric LV hypertrophy but included participants at risk for heart failure with preserved LVEF. In our study cohort, a relatively more concentric LV, in the absence of hypertrophy, was associated with a decreased LV diastolic wall stress, which may be an adaptive mechanism to preserve a satisfactory LV diastolic function in a relatively normal size heart before the heart becomes hypertrophic with compromised and stiff myocardium. This speculative reasoning might in part explain the LV mass increase observed in subjects with DM without HTN or ischemic heart disease [22]. This would be consistent with somewhat decreased LV diastolic wall stress and τ in a subgroup of DM and HTN participants who exhibited increased LV mass and LV mass to volume ratio (*Supplementary Table S2*). Of note, the LV mass values in the current study were intermediate between healthy controls and those with uncontrolled HTN as reported by us previously [21]. Medicines including nitrates [23], statins [24], angiotensin converting enzyme inhibitors [25,26], angiotensin II type-1 receptor blockers [26,27], calcium channel blockers [26], diuretics [28], and beta blockers [29], may also contribute to LV remodeling and prevent the dilation of LV in heart failure with preserved LVEF. We also found that participants with evident diastolic dysfunction not on 'adequate' therapy exhibited a relatively more eccentric LV. Despite being simple, our model pointed out a set of coherent significant associations in changes of LV diastolic hemodynamic and mechanical properties, LV concentricity, LV preload, and the number of CAD & CVD RFs without 'adequate' medications (Table 3, Fig. 1), suggesting that if these abnormalities are treated, the effects on LV diastolic function could be mitigated.

A substantial portion of subjects with impaired LV diastolic hemodynamic and mechanical properties were associated with symptomatic CAD not treated with nitrates (Fig. 1), which produce a direct vasodilatation activity on cardiac vessels increasing coronary blood flow [30]. Our data suggest that this might be important in preserving LV mechanical properties among subjects with symptomatic CAD (*Supplementary Table S8*). Interestingly, calcium channel blockers, which share with nitrates a common vasodilator effect on coronary flow, also reveal overall beneficial effects in CAD cohort (*Supplementary Table S8 and Dataset S1*).

Echocardiographic studies have demonstrated that eccentric hypertrophy is common in many hypertensive populations [8,31,32], however it was not known whether such patients had antecedent concentric hypertrophy. In a large study (The Dallas heart study, n = 1282), the investigators suggested that the transition of concentric LV hypertrophy to dilated cardiomyopathy may be less common [33]. Additionally, a recent work analyzing echocardiographic data from the original Framingham Heart Study participants also reveal a high prevalence of eccentric hypertrophy in a middle aged population (around 50 years old) [34]. Surprisingly, 4-year follow-up data showed a natural history of variable changes of LV geometry in this cohort [34]. The key primary factors associated with abnormal LV geometry in that study were older age, male sex, increased systolic blood pressure, and obesity. In our study, which represents only one time-point snapshot of medically-treated symptomatic outpatient cohort, only the completeness of medication therapy was the primary factor affecting the LV geometry. Previous studies focused on the effects of the medications on LV mass reduction primarily in hypertensive heart disease with LV hypertrophy, or diabetic patients to reduce LV concentricity [35–40], which in this context associated with adverse cardiovascular prognosis [41–43]. However, the relation of LV filling hemodynamic abnormalities and LV concentricity in patients with normal LV mass and size is not well known. Our findings suggest that LV diastolic dysfunction in those with more eccentric hearts may develop in a significant subset of subjects who may not demonstrate antecedent concentric hypertrophy (as LV mass was not elevated) and who may potentially progress directly to heart failure with LV dilatation or hypertrophy. This needs further exploration.

4.1. Study limitations

We are aware of several limitations of this study. We do not have follow-up observations of the subjects' LV concentricity, LV diastolic hemodynamic and mechanical properties and medication history for causative analysis. Analysis of the effects of each specific medication class could not accurately performed due to possible interactions with other medications, and the ensuing confounding effects are hard to evaluate due to a relatively small cohort. The clinical duration of CAD/CVDRFs and the logic or justification for medication treatment strategy for each study participant was not available to the authors. Therefore, the potential cause of 'inadequate medication use' (e.g., possible contraindications to certain drug classes) is beyond the scope of this work. Additionally, the duration and timing of certain drug classes in respect to timing of the left heart catheterization and CMR study was not managed or evaluated by the authors. The possible effect of the latter is also beyond the scope of this work. Due to several reasons mentioned above, we have chosen to consider 'adequate treatment' the existence of specific treatment per se rather than the achievement of specific therapeutic goals. The results of the present exploratory work need to be validated in a prospective study or by analysis of a larger cohort. Because the present work has a limited number of actual outcomes of our primary interest (i.e., LV hemodynamic parameters and LV mass/volume ratio), we have not adjusted P-values for multiple comparisons. We consider this approach the best in order to promote hypothesis generation for future studies.

5. Conclusions

In conclusion, our results suggest a distinct association between LV concentricity, LV diastolic hemodynamic and mechanical derangements and adequacy of therapy of all concomitant CAD & CVD RFs with risk factors for/at early stages of heart failure with preserved LVEF. If confirmed, this concept may lead to important considerations in choosing optimal individualized therapy and planning clinical trials, and thus, requires validation in a prospective study.

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Conflict of interest

Authors have no competing relationship with industry. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100365.

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