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Coronary Artery Disease is Associated With Impaired Atrial Function Regardless of Left Ventricular Filling Pressure

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Abstract

Background—Left atrial (LA) strain is impaired in left ventricular (LV) diastolic dysfunction, associated with increased LV end diastolic pressure (LVEDP). In patients with preserved LV ejection fraction (LVEF), coronary artery disease (CAD) is known to impair LV diastolic function. The relationship of LVEDP with CAD and impact on LA strain is not well studied.

Methods and Results—Patients with LVEF >50% (n=37, age 61±7 years) underwent coronary angiography, high-fidelity LV pressure measurements and cardiac magnetic resonance imaging. LA volumes, LA emptying fraction (LAEF), LA reservoir strain (LARS) and LA long-axis shortening (LALAS) were measured. By coronary angiography, patients were assigned into 3 groups: severe-CAD (n=19, with obstruction of major coronary arteries >70% and/or history of coronary revascularization), mild-to-moderate-CAD (n=10, obstruction of major coronary arteries 30-60%), and no-CAD (n=8, obstruction of major coronary arteries and branches <30%). Overall, LVEF was 65±8% and LVEDP was 14.4±5.6 mmHg. Clinical characteristics, LVEDP and LV function measurements were similar in 3 groups. Severe-CAD group had lower LAEF, LALAS and LARS than those in no-CAD group (P<0.05 all). In regression analysis, LARS and LALAS were associated with CAD severity and treatment with Nitrates, whereas LAEF and $LAEF_{active}$ were associated with CAD severity, treatment with Nitrates and LA minimum volume (P<0.05 all). $LAEF_{passive}$ was associated with LVED volume (P<0.05).

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Conclusions—LA functional impairment may be affected by coexistent CAD severity, medications, in particular, Nitrates, and loading conditions, which should be considered when assessing LA function and LA-LV interaction. Our findings inspire exploration in a larger cohort.

Keywords

coronary artery disease; left ventricular diastolic dysfunction; left atrial function; left atrium strain; left ventricular relaxation; cardiac magnetic resonance imaging

1. Introduction

Assessment of left atrial (LA) function including LA strain is a promising tool for evaluation of left ventricular (LV) diastolic function in patients with preserved LV ejection fraction (LVEF).[1] Echocardiographic studies showed that the magnitude of LA longitudinal strain progressively diminishes with increasing LV filling pressure and severity of LV diastolic dysfunction (LVDD).[2–5] LA strain was markedly reduced in LVDD subjects without heart failure clinical symptoms,[6] and lower LA strain was associated with worse outcomes.[7] In echocardiography, LA strain has recently been studied as a single diagnostic tool for LVDD or as an integral part of the existing diagnostic algorithms.[8–10] Cardiovascular magnetic resonance (CMR) can accurately measure cardiac structure and function.[11, 12] CMR-measured LA strain metrics (e.g., LA reservoir strain (LARS), LA conduit strain and conduit strain rate) and volumetric metrics (e.g., LA minimum and maximum volume indexes, LA emptying fraction (LAEF)) differ in patients with heart failure with preserved LVEF (HFpEF) when compared to controls and revealed a strong prognostic value for incident HF admission and death.[13–16] Moreover, CMR-derived LA metrics have been used for assessment of LV filling pressure for LVDD diagnostics.[17] Yet, the applicability of LA strain in early stages of LVDD or subclinical heart failure with preserved LVEF has not been extensively studied or validated, especially in the presence of coronary artery disease (CAD). It has been shown that CAD can influence the relationship between echocardiographic and hemodynamic indices.[1, 18] LV systolic function measured as LVEF plays an important role in this relationship.[19] Importantly, it has been noted that LA longitudinal strain is impaired in CAD patients compared to those without CAD before changes in other LA and LV measurements, which prompted tests of 2D and 3D LA strain metrics as non-invasive tools for CAD diagnostics or its severity.[20–23] Since LA strain impairment has been found to occur in both CAD patients and non-CAD patients with LVDD, it is unclear whether the altered LA strains reflect elevation in LV filling pressure as CAD progresses. We sought to investigate this in a small but well-characterized patient cohort.

2. Methods

2.1. Study population

This study included 37 participants (age 61±7 years) that underwent coronary angiography for chest pain and/or dyspnea evaluation and were subjects of a prospective research study that included left heart catheterization for clinical indications and CMR.[24] Clinical characteristics are described in Table 1. Major exclusion criteria included

reduced LVEF (<50%), acute myocardial infarction, coronary intervention during cardiac catheterization, abnormal segmental wall motion, atrial fibrillation, hypertrophic cardiomyopathy, myocarditis, and moderate or severe valvular disease. Eleven volunteers without known heart disease were additionally enrolled as a control group for LA function measurements. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the University of Alabama at Birmingham and US Department of Veterans Affairs Institutional Review Boards. Informed consent was obtained from all patients at time of enrollment.

2.2. Invasive assessment of LV hemodynamics

Hemodynamic assessment was performed using a high-fidelity pressure sensor (Millar Instruments, Houston, TX, or St. Jude, Little Canada, MN). LV end diastolic pressure (LVEDP), LV minimum diastolic and LV maximum systolic pressure were quantified from the median measurement obtained from 3-7 recorded tracings with total of ≈20 to 30 beats in a blinded fashion.

2.3. Cardiac magnetic resonance imaging for assessment of LA and LV function

CMR was performed on a 1.5-T scanner (Signa, GE Healthcare, Milwaukee, WI) on the same day or within 3 days (median 2 days) following cardiac catheterization. ECG-gated breath-hold steady-state free precision technique was used to obtain short- and long-axis LV views as previously described.[24] LV geometric parameters were measured from endo- and epicardial contours manually traced on cine images acquired near ventricular end-diastole (ED) and ventricular end-systole (ES) from a series of short-axis LV views, then propagated throughout the cardiac cycle (Supplementary Figure 1A). LV mass was measured at ED, excluding the papillary muscles. LA volume (LAV) was measured using endocardial contours from a series of short-axis LA views (Supplementary Figure 1B).[24] LV and LA volume-time curves were used to calculate the peak filling rates as well as LV ejection and LA emptying rates (Supplementary Figure 1A,B).[11] Total LA emptying fraction during ventricular diastole ($LAEF = 100\%*(LAV_{maximum} - LAV_{minimum})/LAV_{maximum}$; defined as reservoir function), LA passive emptying fraction ($LAEF_{passive} = 100\%*(LAV_{maximum} - LAV_{pre\text{-}A})/LAV_{maximum}$) and LA active emptying fraction ($LAEF_{active} = 100\%*(LAV_{pre\text{-}A} - LAV_{minimum})/LAV_{pre\text{-}A}$) were calculated as described.[11, 25] LA conduit function was assessed as a contribution of LA conduit volume to LV stroke volume calculated as $100\%*(\text{LV stroke volume} - (LAV_{maximum} - LAV_{minimum}))/\text{LV stroke volume}$.[26] Left atrioventricular coupling index was calculated as $100\%*LAV_{minimum}/LVEDV$.[27] LA reservoir strain (LARS) was calculated as follows: $LARS = 100\%*(LAEBL_{ES} - LAEBL_{ED})/LAEBL_{ED}$,[28] where LAEBL is LA endocardial border length (perimeter) manually delineated at ED and ES and measured in 2- and 4-chamber views and then averaged (Supplementary Figure 2) in a similar manner as reported.[29] LA stiffness index were calculated as LVEDP/LARS.[30] LA length was also measured using 2- and 4-chamber views, and LA long-axis shortening ($LALAS = 100\%*(LA_{maximum\_length} - LA_{minimum\_length})/LA_{maximum\_length}$) was calculated using 2- and 4-chamber views and averaged (Supplementary Figure 2) similar as reported.[31] CMR measurements were performed blinded to the results of cardiac angiography, patient history, and LV pressure measurements.

2.4. Group categorization based on CAD severity

Based on prior CAD history and new coronary angiogram findings, patients were divided into 3 groups: 1) without CAD (NO_CAD, diameter obstruction in major epicardial arteries <20% and branches <30%, and no existing stents/ percutaneous coronary intervention (PCI)/ coronary artery bypass grafting (CABG)); 2) mild-to-moderate CAD (MM_CAD, diameter obstruction in major epicardial arteries >20% but <60% and/or in branches >60%, and/or irregularities in multiple vessels (>3); and no existing stents/PCI/CABG); and 3) severe CAD (SVR_CAD, diameter obstruction in major epicardial arteries >70% and/or existing stents/PCI/CABG). As additional tests for microvascular dysfunction were not performed during the study, the presence or absence of ischemia with non-obstructed coronary arteries (INOCA) in the study cohort patients were not considered.

2.5. Statistical analysis

Data are mean ± SD for normally distributed variables, median (interquartile range) for non-normally distributed variables, or numbers (%). For normally distributed variables, groups were compared using one-way ANOVA (three groups with Bonferroni's Multiple Comparison Post-Test). Proportions were compared using Fisher's exact test. Univariate and subsequent multivariate linear regression analysis (for variables with $P<0.05$ in univariate analysis) was used to assess the relationship between the LAEF, LARS, LALAS, and different demographic and clinical factors, medications, as well as LA and LV volumetric and functional parameters. Intra-observer (O.F.S.) and inter-observer (O.F.S. and A.A.G.) reliability tests were performed for LARS measurements in 19 randomly selected study subjects. Intraclass correlation coefficients (ICCs), and coefficients of variation (CoV) defined as the standard deviation of the differences divided by the mean were calculated. A set of LV and LA function measurements in patients, in particular, LA strain estimates was also compared to that obtained from normal control group using one-way ANOVA (four groups with Dunnett's Multiple Comparison Post-Test). Statistical analysis was performed using SPSS, v.23 (IBM, Armonk, NY). A two-tailed P-value < 0.05 was considered significant.

3. Results

3.1. Basic clinical characteristics, LV function and LVEDP in groups

The study cohort included 37 patients (61±7 yrs.) with primary complaints of chest pain and/or dyspnea (symptomatically, NYHA class I (58%) or II (42%)). Most patients had hypertension (86%), and almost half had diabetes mellitus (46%). By coronary angiography results and patient history, patients were assigned into 3 groups: 1) NO_CAD (n=8); 2) MM_CAD (n=10); and 3) SVR_CAD (n=19). Between groups, there was no difference in demographics, clinical characteristics, and medications (Table 1).

3.2. LV pressure and function in groups

Average LVEDP in the entire study population was 14.4 ± 5.6 mmHg. Values of LVEDP and other LV invasive diastolic and systolic hemodynamic measurements were not increased in CAD groups compared to NO_CAD ($p>0.8$ by One-Way ANOVA for LVEDP, Table 1).

LV systolic function was normal in study participants. Average LV mass and volumes were within normal range, and were similar between groups (Table 2). While most LV geometric and functional metrics including LV peak ejection and filling rates, LV sphericity indices, LV longitudinal shortening were similar between the groups, CAD group had somewhat low LV fractional shortening of 25±10% (p=0.059 by One-Way ANOVA, Table 2).

3.3. LA function in groups

LA volumes and lengths were not different between groups (Table 3). There was a trend in slower LA filling and early emptying rates with CAD severity, but it was not statistically significant (Table 3). Also, LA late emptying rates were somewhat higher in the MM_CAD group (Table 3). Notably, the trend of changes of LA early and late emptying rates among the groups resembled the trend of LV early and late filling rates (Table 2 and Table 3), indicative of mutual complementarity of volume changes between the coupled LA and LV chambers.

The differences between groups were significant for LA strain estimates, LARS and LALAS, and for LA functional parameters, including total LAEF and its passive and active components (Table 3). Values of LAEF and LALAS were decreased in SVR_CAD group compared to NO_CAD ($p<0.05$, Table 3) and values of LARS and LALAS decreased compared to MM_CAD ($p<0.05$, Table 3). Patterns of changes in $LAEF_{passive}$ and $LAEF_{active}$ with CAD severity were different for different LA parameters. $LAEF_{passive}$ was decreased in MM_CAD and SVR_CAD groups compared to NO_CAD ($p<0.05$ for both vs. NO_CAD). $LAEF_{active}$ was increased in MM_CAD group compared to NO_CAD ($p<0.05$ vs. NO_CAD), however in SVR_CAD group, it was similar to that of NO_CAD group ($p>0.05$ vs. NO_CAD, $P<0.05$ vs. MM_CAD, Table 3). Indices, expected to increase in patients with LVDD or HFpEF, such as atrioventricular coupling,[27] fraction of LV stroke due to LA conduit volume,[26] and LA stiffness index[30] were somewhat larger in SVR_CAD group, however the increase was not statistically significant (for all, $P>0.05$ vs. NO_CAD) (Table 3). Notably, LA function metrics that were found significantly impaired in SVR_CAD group (n=19), in this analysis, were also proved significant when SVR_CAD group data was compared to the data calculated for combined NO_CAD and MM_CAD group (i.e., all patients without severe CAD (n=18), Supplemental Table S1).

3.4. Association of LA strain estimates with clinical and LV function variables

There was a mutual correlation between LAEF and LA strain indices in the study cohort. LAEF correlated with LARS and LALAS ($r=0.53$, $P<0.001$; $r=0.66$, $P<0001$), and LARS correlated with LALAS ($r=0.67$, $P<0.0001$). Notably, LAEF and left atrioventricular coupling index correlated with NYHA class ($r=-0.36$, $P=0.030$, and $r=0.44$, $P=0.006$, respectively). Univariate and multivariate regression analysis indicated that amongst a variety of factors (demographic, anthropometric, clinical, and CMR measured) only CAD severity and Nitrates prescription were consistently associated with changes in LARS, LALAS, and LAEF (Table 4). LVEDP did not correlate with LARS, LALAS, LAEF, and was not part of the model (Table 4). $LAEF_{passive}$ correlated with LVEDV Index ($r=0.45$, $P<0.01$) and $LAEF_{active}$ correlated with $LAV_{minimum}$ index and Nitrates use ($r=0.36$, $P<0.05$ and 0.63, $P<0.01$, respectively) (Supplemental Table S2). There was an association between

diuretic use and lower LARS (Table 4). In additional analysis, we found an association between diuretics use and lower LV stroke volume index (r= −0.35, P=0.032); the latter was marginally associated with LARS (r=0.32, P=0.051).

As treatment with Nitrates was significantly associated with LA strain and LA functional parameters in our cohort, we also investigated if treatment with Nitrates is associated with changes in LV function (LVEF, LVED volume, stroke volume and cardiac index, left atrioventricular coupling index) and clinical parameters (NYHA, CAD severity, hypertension, diabetes mellites, body mass index) using univariate regression analysis. We found that Nitrates use was indeed significantly associated with a higher-class NYHA (class II) (r=0.37, P=0.026), higher values of left atrioventricular coupling index (r=0.39, P=0.016), and lower cardiac index (r= −0.34, P=0.040).

3.5. Comparisons of LA strain estimates in normal volunteers

Eleven volunteers without known heart disease (age, 56±7 yrs., 4 male/7 female, body surface area, 2.0±0.1 kg/m^2) had values of systolic blood pressure and diastolic blood pressure (128±21 mmHg and 76±11 mmHg), LV mass (52 ± 12 kg/m^2), LV volumes (LV end diastolic volume, 70±21 ml/m^2, LV end systolic volume, 27±12 ml/m^2, LV stroke volume, 43±10 ml/m^2), and LV function (LVEF, 62±8 %, cardiac index, 2.9±0.4 L/min/m^2) similar to that of measured in patient's subgroups (P>0.05 to all, see Table 1 and Table 2). LA volumes (LAV_{max} 30±5 ml/m^2 and LAV_{min} 12±2 ml/m^2) and left atrioventricular coupling index (18.8±5%) in normal volunteers were not different from any of patient's subgroups. LARS was 29.7±3.2 %, similar to reported in controls.[12] LARS and LALAS (26.6±3.9 %) were significantly larger than that in SVR_CAD group (P<0.05 to all, see Table 3) but not to NO_CAD or MM_CAD groups (P>0.05). Similar pattern was observed for values of LAEF (59±4 %), however its difference vs. SVR_CAD was not statistically significant in multiple comparison posttest (p>0.05).

3.6. Reliability of LARS measurements

In randomly selected study subjects, we performed the intra-observer and inter-observer reliability tests for LARS measurements. For intra-observer testing, there was an excellent agreement between two measurements (ICC 0.92 (P<0.001), mean delta/SD 0.2/2.8, CoV 10.7%). Reproducibility was also excellent for inter-observer testing (ICC 0.91 (P<0.001, mean delta/SD 0.8/2.2, CoV 7.6%). There was no measurement bias observed in both tests.

4. Discussion

Our study demonstrated that CAD is associated with LA functional impairment in patients with preserved LVEF, but LA volume and strain metrics may not necessary be related to LVEDP in those with CAD. The latter finding may be in part be related to certain load-dependent properties of LA strain and effects of medications, which should be considered when using LA strain parameters as a surrogate for the loading factors, particular in CAD patients.

Patients with CAD have abnormal LV diastolic hemodynamics, a finding that has been known since the 1970s.[32] Moreover, there is evidence that the relationship between

echocardiographic Doppler assessment of LV diastolic function and association with hemodynamic values is poor in patients with CAD, in particular those with preserved LVEF.[18, 19, 33] In fact, the American Society of Echocardiography (ASE) recommendations acknowledged this phenomenon.[1] Accuracy of the ASE-recommended algorithm for diastolic assessment may be limited in patients with unrecognized CAD.[33] Therefore, there is a continuing interest in the developing new non-invasive metrics for LVDD diagnostics, with LA strain being the focus of extensive research. Previously, an association was shown between echocardiographic measurements of LA strain and LVDD grades.[2, 6, 8] A negative correlation between LA strain metrics and invasively measured estimates of LV filling pressure was reported in several studies,[3, 4, 10] including studies which specifically enrolled angiographically confirmed CAD or with myocardial ischemia[9, 30, 34].

On the other hand, several studies that assessed the accuracy of LA strain or LAEF metrics to predict elevated LVEDP or LVDD/HFpEF have provided only limited information to demonstrate the power of the relationship between these metrics and LVEDP,[5, 14, 17, 30, 35] calling into question the strength of these associations. Some studies reported that LA strain did not correlate with invasive measures of LV diastolic function, such as time constant of LV relaxation (tau) and LV diastolic stiffness constant (β).[14, 35] Other studies such as the work of Freed et al., that studied over 300 HFpEF patients (with high prevalence of CAD (50%) and symptom burden (46% NYHA III), reported a very weak correlation between LARS and pulmonary artery wedge pressure with r= −0.15 (p=0.05)).[7] This might indirectly support our surprising findings of absence of relevant correlation between LA strain estimates and LVEDP for the entire study cohort. In addition, after close inspection of data from several published studies, we found that the reported significant correlations were largely driven by values at extreme ends of LVEDP and strain; when restricting analysis of the prior published data[4, 5, 9, 30] to ranges seen in our present study, the correlations are less impressive or nonexistent. In this respect, the absence of correlation in our study (across a narrower range of LVEDP and LA strains) is at least somewhat consistent with prior reports.[7, 14, 35]

Other factors such as different patient population (less symptomatic patients—only NYHA class I and II), different methodology in LA volume quantification and LVEDP acquisition (e.g., with vs. without inspiratory breath-hold during catheterization to match the CMR measurements)[3, 17] could also be a reason for discrepancy of our data with some reported echocardiographic or CMR studies.

Our data showed that more severe CAD was associated with worse LA diastolic impairment regardless of LVEDP values (Tables 1 and 3). As a result, age-adjusted LA metrics could be more effective in identifying those who may have CAD than use of normal or elevated LVEDP values as a possible indicator of the presence of CAD. In another group of ischemic patients (patients with signs and symptoms of ischemia and no obstructive coronary artery disease, INOCA), studies also reported discrepancies between intuitive expectations between values of LARS and values of invasively-measured LVEDP or severity of echocardiography-assessed LVDD.[30, 36] On the other hand, severity of LARS impairment in INOCA was

significantly associated with severity of LV microvascular dysfunction (distal microvascular resistance).[36]

In the present study, compared to NO_CAD, MM_CAD group had lower $LAEF_{passive}$ and elevated $LAEF_{active}$, which somewhat resembles E/A dynamics in LVDD grade I. Furthermore, such distribution of LA conduit and pump strains has been previously found in LVDD grade I patients[6] and CAD patients with poorly controlled diabetes[37]. Decreased LA passive strain and $LAEF_{passive}$ and preserved LA active strain and $LAEF_{active}$ were previously found in CAD patients with normal LVEF, LV size and LA size, while those with CAD, with low LVEF and elevated LA size, had impairments of both LA passive and active strains.[20] In our SVR_CAD group, with CAD defined more severely than in other studies (>70% occlusion in our study, and not >50% as in abovementioned work[20]), both $LAEF_{passive}$ and $LAEF_{active}$ were impaired as was seen in the LVDD grade II scenario.[6] Progressive impairment of LA strain with CAD severity has been also shown in previous studies.[21–23]

Importantly, despite the significant worsening of LA function in SVR_CAD group, the LV function parameters and indices, including LVEDP, were not significantly different from NO_CAD group (Tables 2 and 3). This could result from more aggressive medication therapy, which may reduce preloading conditions (angiotensin-converting enzyme inhibitors/angiotensin II type-1 receptor blockers, diuretics, vasodilators) and myocardial ischemia (vasodilators, beta-blockers) (Supplemental Tables S3 and S4).[38, 39] However, the changes in hemodynamics do not immediately reverse the intrinsic myocardial properties such as stiffness—leading to persistent characteristic features of LVDD. For instance, the $LAV_{minimum}$ does not quickly revert to normal size post mitral valve repair in patients with mitral valve regurgitation, even when LV size is normalized.[11, 40] It has been also reported that interventions reducing LVEDP may not cause a reduction of echocardiographic E/e'.[41–43] Also, it has been shown that preload reduction does not necessarily improve LA longitudinal strain and E/e'.[44] Alternatively, LVEDP elevation due to hemodynamic change may not necessarily result in E/e' increase,[43] which may be also true for LA strain, as E/e' typically correlates with LA strain.[44, 45] All our measurements were done under resting conditions; testing during exercise may reveal impairments in filling rates and strains, as adverse LA remodeling is associated with lower exercise capacity.[14]

In HFpEF, treatments with Nitrates is associated with less physical activity,[46] and with either no improvements in HF hospitalization and mortality[47] or significantly increased risk of cardiovascular events.[48] In our cohort, treatment with nitrates was associated with higher NYHA class (II) and higher values of left atrioventricular coupling index, which is a strong predictor for the incidence of HFpEF, atrial fibrillation, myocardial infarction, and coronary heart disease death.[27] Whether there is indeed a direct causative relationship between Nitrates intake and decreased LA strain and function in patients with preserved LVEF including those with CAD, as measured in our cohort, requires further investigation. Similarly, whether the observed association between diuretics and LARS was primarily due to dose-dependent effects on LA strain should be further evaluated.

4.1. Limitations

Our cohort is small, which can certainly be seen as a limitation. Alternatively, this study provides a demonstration of how a concept established using large statistics (e.g., LARS vs. LVEDP relation) can be applied to a random group of patients from a single center. Also, our CMR and LV invasive measurements were performed close in time, but not simultaneously as logistically it was not possible with our present equipment. Therefore, our findings are potentially vulnerable to hemodynamic fluctuations; however, the non-simultaneous nature of CMR and invasive measurements is common across studies utilizing these two tools, since only very specialized research centers have equipment in which CMR and invasive catheterization can be performed simultaneously. Our study protocol excludes any cause-effect conclusions. The observed associations between LA function and medications (in particular, nitrates, diuretics) did not consider the timing and intensity of the medical therapy. This study may not reflect the general population, as the participants were referred to catheterization due to chest pain and/or dyspnea to evaluate possible CAD; a high prevalence of CAD/ischemia is typically found in studies evaluating the accuracy of non-invasive imaging parameters,[10, 49] and the high prevalence and impact of CAD on HFpEF has been recognized.[50] CAD-associated HFpEF may represent a distinct phenotype due to its worse prognosis (albeit potential for improvement through revascularization).[50] Recent data indicate that high coronary microvascular resistance may be associated with reduced LARS,[36] however it was not evaluated in our study subjects, in particular those with chest pain and non-significant epicardial CAD. Multiple indices of LA strain and other functional parameters were measured blinded and independently by different investigators with a good correlation amongst the measures. Any errors are expected to be random and free of bias.

5. Conclusions

In conclusion, our study suggests that alterations in LA strain and related functional impairments are sensitive indicators of CAD regardless of measured LVEDP. Thus, LA function parameters may be markers of early impairment in LV diastolic function in CAD patients with preserved LVEF and could provide additional value for CMR evaluation of these patients. On the other hand, our data suggests that it would be unreliable to predict an instantaneous value of LVEDP based on LA strain in each individual CAD patient without accounting for possible confounders, including medications. Due to several limitations, our results should be considered to prompt evaluation in a larger cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- LA strain and function are impaired in CAD regardless of LVEDP
- LA function may be affected by coexistent CAD severity, medications and loading conditions
- LA strain alone may be insufficient to accurately predict LVEDP in patients with CAD

Table 1.

Patient characteristics in groups with various severity of CAD.

Variables	All Patients (n=37)	NO_CAD (n=8)	MM_CAD (n=10)	SVR_CAD (n=19)
Clinical Characteristics				
Age	61 ± 7	60 ± 7	60 ± 8	63 ± 6
Male, %	86	75	100	84
Weight, kg	91 ± 18	91 ± 12	91 ± 14	92 ± 22
Body Mass Index, kg/m^2	29.4 ± 5.2	30.4 ± 3.9	28.4 ± 3.6	29.5 ± 6.3
Body Surface Area, m^2	2.1 ± 0.2	2.0 ± 0.2	2.1 ± 0.2	2.1 ± 0.2
Black/White, %	35/65	50/50	40/60	26/74
Systolic Blood Pressure, mmHg	131 ± 17	122 ± 13	132 ± 16	134 ± 18
Diastolic Blood Pressure, mmHg	74 ± 10	72 ± 12	73 ± 10	76 ± 10
NYHA class I/II, (%)	58/42	75/25	70/30	47/53
Hypertension, %	86	87.5	60	100
Diabetes Mellitus, %	46	25	50	53
Medications				
AI/AT1RB, %	46	12.5	40	63
Beta-blockers, %	62	50	50	74
Diuretics, %	40	62.5	20	42
Nitrates, %	27	25	10	37
Calcium Blockers, %	19	12.5	20	21
Insulin/Oral Hypoglycemics, %	35	25	30	42
Statins, %	65	50	50	79
LV Invasive hemodynamic measurements				
LV End Systolic Pressure, mmHg	128 ± 18	119 ± 15	126 ± 20	132 ± 18
LV minimum diastolic pressure	7.8 ± 4.2	7.4 ± 5.3	6.8 ± 3.7	8.5 ± 4.0
LV End Diastolic Pressure, mmHg	14.4 ± 5.6	13.8± 6.6	14.1 ± 5.7	15 ± 5.2

Values are mean±SD or percentage (if indicated).

NYHA= New York Heart Association; AI/AT1RB= angiotensin-converting enzyme inhibitor/ Angiotensin II type-1 receptor blocker; LV=left ventricular; CAD groups: no CAD (NO_CAD), mild-to-moderate CAD (MM_CAD), severe CAD (SVR_CAD).

Table 2.

CMR-measured LV characteristics in groups with various severity of CAD.

Variables	All Patients (n=37)	NO_CAD (n=8)	MM_CAD (n=10)	SVR_CAD (n=19)
LV Ejection Fraction, %	65 ± 8	65 ± 9	68 ± 8	63 ± 9
LV ED Volume Index, ml/m^2	65 ± 15	68 ± 19	64 ± 15	64 ± 15
LV ES Volume Index, ml/m^2	24 ± 9	25 ± 12	21 ± 8	24 ± 9
LV Stroke Volume Index, ml/m^2	42 ± 9	43 ± 8	43 ± 9	40 ± 9
Heart Rate, bpm	68 ± 11	68 ± 12	66 ± 10	69 ± 12
Cardiac Index, L/min/m^2	2.8 ± 0.6	2.9 ± 0.8	2.8 ± 0.6	2.7 ± 0.5
Peak Early Filling Rate, ml/s	304 ±93	324 ±97	309 ±85	292 ±98
Peak Late Filling Rate, ml/s	209 ± 106	210 ± 97	236 ± 85	202 ± 113
Peak Ejecting Rate, ml/s	418 ± 101	419 ± 119	425 ± 76	415 ± 110
LV Mass Index, g/m^2	53 ± 11	46 ± 8	57 ± 12	54 ± 11
LV Longitudinal Shortening, %	22 ± 5	22 ± 4	23 ± 6	21 ± 5
LV Fractional Shortening, %	29 ± 10	32 ± 9	33 ± 6	25 ± 10
LVEDP/LVEDV, mmHg/ml	0.11 ± 0.05	0.10 ± 0.05	0.11 ± 0.06	0.115 ± 0.04

Values are mean±SD.

CAD=coronary artery disease; LV=left ventricular; ED=end diastolic; ES=end systolic; LVEDV=left ventricular end diastolic volume; CAD groups: no CAD (NO_CAD), mild-to-moderate CAD (MM_CAD), severe CAD (SVR_CAD).

Table 3.

LA characteristics in groups with various significance of CAD.

Variables	All Patients (n=37)	NO_CAD (n=8)	MM_CAD (n=10)	SVR_CAD (n=19)
LAV minimum Index, ml/m^2	12±4	10±4	12±5	12±4
LAV maximum Index, ml/m^2	27±8	28±9	28±9	27±8
LAEF$_{passive}$, %	**34±13**	**44±11**	**29±10** *	**32±13** *
LAEF$_{active}$, %	**35±14**	**34±12**	**44±14** *	**30±14** †
LAEF, %	**58±9**	**64±5**	**59±9**	**54±9** *
Peak LA Filling Rate, ml/s	134±47	151±39	126±34	131±55
Peak LA Early Emptying Rate, ml/s	117±56	137±44	118±50	108±64
Peak LA Late Emptying Rate, ml/s	125±71	95±44	160±62	119±79
LA Long-Axis Shortening, %	**24±6**	**27±5**	**27±5**	**22±6** *,†
LA Reservoir Strain, %	**26±6**	**28±6**	**29.5±5**	**23.5±6** †
Left atrioventricular coupling Index, %	18.5±6	16±7	19±8	19.5±5
LA conduit % LV stroke volume	63±8	59±10	63±8	64±8
LVEDP/LARS, mmHg/%	0.57±0.21	0.52±0.29	0.50±0.22	0.63±0.16

Values are mean ± SD.

LA= left atrial; LAV= left atrial volume; LAEF=left atrial emptying fraction; CAD groups: no CAD (NO_CAD), mild-to-moderate CAD (MM_CAD), severe CAD (SVR_CAD).

* p<0.05 vs. NO_CAD

† p<0.05 vs. MM_CAD (One-Way ANOVA with Bonferroni post hoc test).

Table 4.

Standardized beta coefficient of linear regression of relationship between LA strain/ function estimates and different factors.

Variables		LAEF, %		LARS, %		LALAS, %	
		Univariate model	Multivariate model[a]	Univariate model	Multivariate model[a]	Univariate model	Multivariate model[a]
Demographic factors	Age, years[b]	−.30		**−.37** *		−.30	
	Sex [b]	−.07		−.08		−.05	
	Race[b]	−.16		−.23		**−.33** *	
Comorbidities and Anthropometric factors	CAD severity[b]	**−.50** **	**−.39** **	**−.37** *	**−.41** **	**−.39** *	**−.33** *
	Hypertension[b]	−.24		**−.36** *		**−.33** *	
	Diabetes Mellitus[b]	−.30		.03		−.07	
	Body Mass Index, kg/m^2	.01		.26		.10	
Medications	AI/AT1RB	−.08		−.11		−.22	
	Beta-blockers	−.21		−.11		−.26	
	Diuretics	−.17		**−.38** *	**−.42** **	−.17	
	Nitrates	**−.48** **	**−.37** **	**−.41** *		**−.48** *	**−.43** **
	Calcium Blockers	.16		−.05		.22	
	Insulin/Oral Hypoglycemics	−.23		.00		−.12	
LA and LV volumes	LAV minimum Index, ml/m^2	**−.40** *	**−.28** *	−.05		−.26	
	LAV maximum Index, ml/m^2	.09		.22		−.01	
	LVEDVI, ml/m^2	.28		.20		.10	
	LVSVI, ml/m^2	.31		.32		.20	
LV function	LVEF, %	.05		.15		.19	
	Heart Rate, bpm	−.11		−.14		.08	
	Cardiac Index, ml/min/m^2	.23		.22		.28	
	LVEDP, mmHg	−.04		.12		.10	

CAD=coronary artery disease; LAEF=left atrial emptying fraction; LARS=left atrial reservoir strain; LALAS=left atrial long-axis shortening; AI/AT1RB= angiotensin-converting enzyme inhibitor/ Angiotensin II type-1 receptor blocker; LAV=left atrial volume; LA=left atrial; LV=left ventricular; LVEDVI=left ventricular end diastolic volume index; LVSVI= left ventricular stroke volume index; LVEF= left ventricular ejection fraction; LVEDP=left ventricular end ventricular pressure.

*P<0.05

**P<0.01

***P<0.005.

[a]Backward multivariate linear regression model was built (probability of F for entry: 0.5 and removal: 0.1) by testing variables with P<0.05 in univariate model.

[b]CAD severity, (1 no, 2 mild-to-moderate, 3 severe) Sex, (1 M/2 F) Race, (1 AA/2 W), Medications (1 no, 2 yes), Hypertension (0 no, 1 yes), Diabetes Mellitus (0 no, 1 yes).