Cardiac imaging characteristics of patients with COPD: prognostic implications

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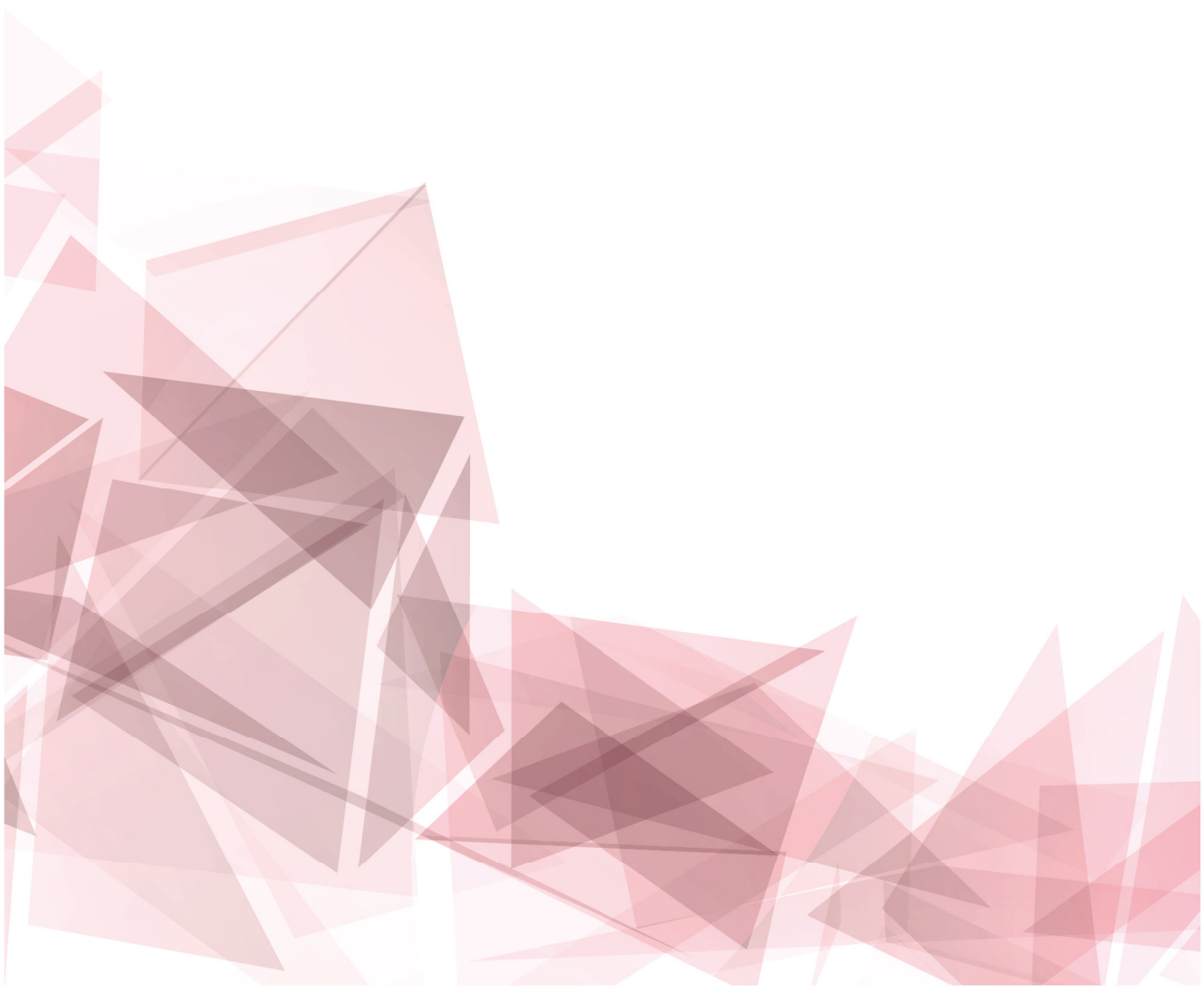
PART I

Impact of COPD on left- and right ventricular function after acute myocardial infarction



Chapter 2

Comparison of Left Ventricular Function and Myocardial Infarct Size Determined by 2-Dimenstional Speckle Tracking Echocardiography in Patients With and Without Chronic Obstructive Pulmonary Disease After ST-Segment Elevation Myocardial Infarction

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Abstract

Patients with chronic obstructive pulmonary disease (COPD) have a high risk of mortality after acute ST-segment elevation myocardial infarction (STEMI). We compared STEMI patients with versus without COPD in terms of infarct size and left ventricular (LV) systolic function using advanced 2-dimensional (2D) speckle tracking echocardiography (STE). Of 1750 STEMI patients (mean age 61±12 years, 76% male), 133 (7.6%) had COPD. With transthoracic echocardiography, LV ejection fraction (LVEF) and wall motion score index (WMSI) were measured. Infarct size was assessed using biomarkers (creatine kinase [CK] and troponin T). LV global longitudinal strain (GLS), reflecting active LV myocardial deformation, was measured with 2D STE to estimate LV systolic function and infarct size. STEMI patients with COPD were significantly older, more likely to be former smokers and had worse renal function as compared to patients without COPD. There were no differences in infarct size based on peak levels of CK (1315 [613–2181] vs. 1477 [682–3047] U/L, p=0.106) and troponin T (3.3 [1.4–7.3] vs. 3.9 [1.5–7.8] µg/L, p=0.489). LVEF (46% vs. 47%, p=0.591) and WMSI (1.38 [1.25–1.66] vs. 1.38 [1.19–1.69], p=0.690) were comparable. In contrast, LV GLS was significantly more impaired in COPD patients as compared to patients without COPD (-13.9±3.0% vs. -14.7±3.9%, p=0.034). In conclusion, despite comparable myocardial infarct size and LV systolic function as assessed with biomarkers and conventional echocardiography, COPD patients exhibit more impaired LV GLS on advanced echocardiography than patients without COPD suggesting a greater functional impairment at an early stage post-STEMI.

Keywords: ST-segment myocardial infarction; chronic obstructive pulmonary disease; global longitudinal strain

Introduction

Patients with chronic obstructive pulmonary disease (COPD) who present with ST-segment elevation myocardial infarction (STEMI) have higher in-hospital and 6-month mortality rates compared with patients without COPD.[1-3] Possible mechanisms underlying this worse prognosis among COPD patients include poor recognition and management of myocardial infarction, under-utilization of secondary prevention therapies as well as pathophysiological factors related to COPD (i.e. chronic inflammation).[3, 4] These factors may result in larger infarct size and worse left ventricular (LV) systolic function. However, it remains unknown whether STEMI patients with COPD differ from patients without COPD in terms of infarct size and LV systolic function acutely after STEMI. LV ejection fraction (EF) and wall motion score index (WMSI) are commonly used in clinical practice to estimate LV systolic function and for risk stratification of STEMI patients.[5, 6] However, these conventional echocardiographic parameters may not be sensitive enough to characterize the extent of myocardial damage after STEMI.[7, 8] Two-dimensional (2D) speckle tracking echocardiography global longitudinal strain (GLS), reflecting active deformation of the LV myocardium, has emerged as a valuable index of LV systolic function and infarct size.[9] The present study aimed at evaluating the differences in infarct size and systolic function in STEMI patients with versus without COPD by measuring biomarkers (creatine kinase [CK] and troponin T) as well as conventional and advanced 2D speckle tracking echocardiography.

Methods

Of an ongoing registry of patients admitted with acute STEMI and treated with primary percutaneous coronary intervention (PCI) at the Leiden University Medical Centre (Leiden, the Netherlands), patients with complete echocardiographic data at baseline (within 48 hours of admission) were included (Figure 1).[10] Patients were managed according to the most recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines.[6, 11] This includes systematic measurements of CK and troponin T and transthoracic echocardiography within 48 hours of admission. Clinical and echocardiographic data were prospectively collected at the departmental Cardiology Information System (EPD-vision, Leiden University Medical Centre), and echocardiography database, respectively, and analyzed retrospectively. For this retrospective analysis of clinically acquired data, the Institutional Review Board waived the need for patient written informed consent.

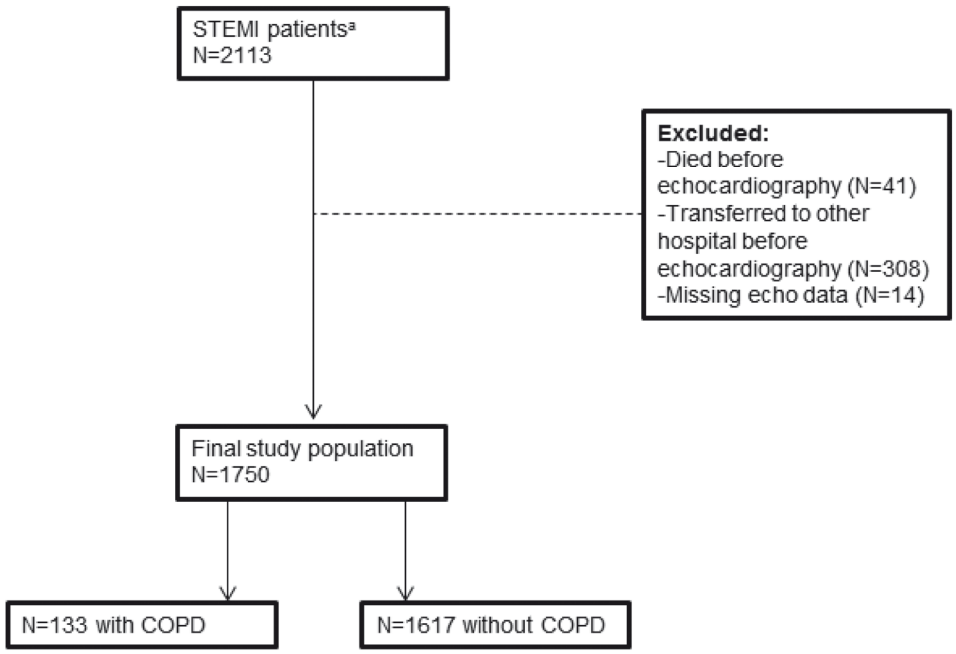

Figure 1. Flowchart of patient selection and enrollment for analysis. [a] STEMI patients wereadmitted between February 2004 and May 2013. Abbreviations: COPD, chronic obstructive pulmonary disease; STEMI, ST-elevation myocardial infarction.

Patient demographic and clinical characteristics were recorded. Hypertension was defined as a systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or previous use of antihypertensive drugs. Hypercholesterolemia was defined as having a recorded history of hypercholesterolemia and/or use of statins. Diabetes mellitus was defined as having a history of diabetes and subsequent treatment with a diet, oral glucose-lowering agents or insulin. Killip class was registered at admission.[12] During invasive coronary angiography, the culprit vessel was identified and multi-vessel disease was defined as more than one vessel with >50% luminal stenosis.

Chronic obstructive pulmonary disease was defined as having a documented history of COPD at admission, after reviewing the entire medical record. When available, pulmonary function tests were considered and COPD was diagnosed if the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio was <0.7.[13] The use of this definition of COPD, when systematic pulmonary function tests are not available, is in line with previous studies.[1, 2, 14-16] Patients with a recorded history of asthma were listed as non-COPD, given the different pathophysiology.[13]

Images were obtained with the patient at rest, in left lateral decubitus position using a commercially available system (Vivid 7 and E9, GE Healthcare, Horten, Norway). Standard 2D images were obtained from the parasternal (long- and short-axis) and apical (long-

axis, 2-and 4-chamber) views, using 3.5-MHz or M5S transducers, and digitally stored in cine-loop format. Furthermore, color, pulsed and continuous wave Doppler images were acquired. Offline analysis of the obtained images was performed using EchoPAC (version BT13, GE Medical Systems, Horten, Norway).

Left ventricular diameters and wall thickness were measured in the parasternal long-axis view. Subsequently, LV mass was calculated using the Devereux's formula and indexed for body surface area.[5] Left ventricular end-systolic and end-diastolic volumes were measured in apical 4- and 2-chamber views and LVEF was calculated using the biplane Simpson's method.[5] For calculation of the wall motion score index, the LV was divided into 16 segments. Each segment was assessed and scored based on its motion and systolic thickening (1= normokinesia, 2=hypokinesia, 3=akinesia, 4=dyskinesia). The wall motion score index was calculated as the sum of the individual segment scores, divided by the number of segments.[5]

Left ventricular diastolic function was assessed based on peak velocity of the early diastolic filling (E-wave) and late filling by atrial contraction (A-wave), together with E-wave deceleration time obtained on the pulsed-wave Doppler recordings of the transmitral flow, the left atrial volume and pulmonary systolic pressures estimated from the tricuspid regurgitation peak velocity on continuous wave Doppler recordings.[17]

For evaluation of LV GLS, 2D speckle tracking analysis was performed as previously described.[18] In brief, the LV endocardial border was traced at an end-systolic frame in the apical long-axis, 2-and 4- chamber views. The automatically created region of interest was manually adjusted to the thickness of the myocardium. Thereafter, the myocardium was automatically tracked throughout the cardiac cycle. LV GLS was calculated by the software as the average of the peak systolic strain of the three apical views, and presented in a 17-segment "bulls-eye" plot. The inter- and intraobserver variability of LV GLS measurements has been previously reported as mean absolute difference of 1.2 ± 0.5 % and 0.9 ± 1.0%, respectively.[19]

Statistical analyses were performed using SPSS software (version 23, IBM SPSS statistics for Windows, Armonk, New York). Continuous variables are presented as mean ± standard deviation when normally distributed and median and interquartile range (IQR) otherwise. Categorical variables are presented as frequencies and percentages. Differences in continuous variables between COPD and non-COPD patients were analyzed using the unpaired Student's t- test or Mann-Whitney U -test, as appropriate. Categorical variables were compared using the chi-square test or Fisherman's exact, as appropriate. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Of 1750 STEMI patients, 133 (7.6%) had a history of COPD. The clinical characteristics of the patients with and without COPD are presented in Table 1. Compared to patients without COPD, patients with COPD were significantly older, more likely to be former smokers and had a higher prevalence of previous MI. In addition, patients with COPD had a significantly worse kidney function and presented more frequently with heart failure. Guideline-based medical therapy at discharge was similar between groups, except for β-blockers, which were less frequently prescribed in patients with COPD as compared with non-COPD patients (89% and 95%, p=0.011).

There were no statistically significant differences between COPD and non-COPD patients in terms of infarct size based on peak levels of CK (1315 [613 – 2181] vs. 1477 [682 – 3047] U/L, p=0.106; respectively) and troponin T (3.3 [1.4 – 7.3] vs. 3.9 [1.5 – 7.8] µg/L, p=0.489, respectively)

Table 1. Clinical characteristics

	COPD		
Variable	**Yes (N=133)**	**No (N=1617)**	**p-value**
Age (years)	69±11	60±12	<0.001
Men	97 (73%)	1229 (76%)	0.427
Systolic blood pressure (mmHg)	140 [120 – 160]	135 [120 – 150]	0.096
Diastolic blood pressure (mmHg)	84±18	81±16	0.071
Heart rate (beats/min)	73±16	74±18	0.709
Body mass index (kg/m^2)	25.7 [24 – 29]	26.0 [24 – 28]	0.502
Killip class			0.045
<2	121 (92%)	1539 (96%)	
≥2	11 (8%)	72 (4%)	
Diabetes mellitus	19 (14%)	168 (10%)	0.163
Hypertension	54 (41%)	569 (35%)	0.226
Hypercholesterolaemia	27 (21%)	325 (20%)	0.879
Family history of cardiovascular disease	47 (37%)	705 (44%)	0.133
Current smoker	68 (51%)	764 (47%)	0.396
Ex-smoker	23 (17%)	173 (11%)	0.021
Previous myocardial infarction	12 (9%)	47 (3%)	<0.001

Table 1. Continued

Culprit coronary artery			0.389
Left anterior descending	49 (37%)	721 (45%)	
Right	55 (42%)	618 (38%)	
Ramus circumflexus	26 (20%)	258 (16%)	
Left main	1 (1%)	10 (1%)	
Number of diseased vessels			0.225
1	61 (46%)	751 (47%)	
2	31 (24%)	555 (35%)	
3	39 (30%)	304 (19%)	
Peak creatinine kinase (U/L)	1316 [613 – 2183]	1477 [682 – 3047]	0.106

Peak troponine T (µg/L)	3.3 [1.4 – 7.3]	3.9 [1.5 – 7.8]	0.489
Glucose (mmol/L)	7.5 [6.3 – 9.8]	8.0 [6.6 – 9.7]	0.223
Creatinine clearance (ml/min/1.73 m^2)	84±33	99±37	<0.001
Medication at discharge			
β-blocker	114 (89%)	1507 (95%)	0.011
ACE inhibitor or angiotensin-II receptor blocker	124 (98%)	1555 (98%)	1.000
Aspirin	124 (97%)	1530 (96%)	0.814
Thienopyridines*	127 (99%)	1587 (100%)	0.462
Statin	128 (100%)	1581 (99%)	0.616

COPD, chronic obstructive pulmonary disease. Continuous variables are presented as mean ± SD or median [25th -75th percentile]. * clopidogrel or prasugrel

Echocardiographic characteristics of the patients with and without COPD are presented in Table 2. Compared to non-COPD patients, patients with COPD had significantly smaller LV dimensions. LVEF was similar in both COPD and non-COPD patients (46±10% and 47±9%, respectively, p=0.591). In addition, the wall motion score index was 1.38 [1.25 – 1.66] for COPD patients and 1.38 [1.19 – 1.69] for non-COPD patients, p=0.690. However, LV GLS was significantly more impaired in patients with COPD compared to patients without COPD (-13.9±3.0% and -14.7±3.9%, p=0.034) indicating more reduced systolic LV function and larger area of infarction in the patients with COPD despite similar infarct size according to enzyme release (biomarkers). Figure 2 presents a more impaired LV GLS in a STEMI patient with COPD compared to a patient without COPD, with comparable LVEF, WMSI and infarct size based on peak levels of CK and troponin T.

Table 2. Echocardiographic characteristics.

		COPD	
Variable	**Yes (n=133)**	**No (n=1617)**	**p-value**
LV end-diastolic diameter (mm)	46±7	48±6	0.001
LV end-systolic diameter (mm)	30 [26 – 37]	32 [27 – 37]	0.101
Posterior wall thickness (mm)	12±2.2	11±2.1	0.031
Interventricular septum thickness (mm)	11 [10 – 13]	11 [10 – 13]	0.181
LV mass (g)	203±75	212±66	0.134
Indexed LV mass (g/m^2)	104±34	108±30	0.171
LV end-systolic volume (mL)	48 [39 – 61]	53 [42 – 68]	0.012
LV end-diastolic volume (mL)	92 [74 – 116]	101 [82 -123]	0.009
Wall motion score index	1.38 [1.25 – 1.66]	1.38 [1.19 – 1.69]	0.690
LV ejection fraction (%)	46±10	47±9	0.591
LV global longitudinal strain (%)	-13.9±3.9	-14.7±3.9	0.034
E-wave peak velocity (cm/s)	66±18	66±19	0.885
A-wave peak velocity (cm/s)	76±21	71±24	0.051
E/A ratio	0.84 [0.69 – 1.06]	0.91 [0.72 – 1.14]	0.039
E-wave deceleration time (ms)	215±85	210±72	0.638

COPD, chronic obstructive pulmonary disease; LV, left ventricle. Continuous variables are presented as mean±SD or median [25th -75th percentile].

Discussion

The present study demonstrates that STEMI patients with concomitant COPD have more impaired LV systolic function and larger infarct area based on LV GLS, as compared to patients without COPD, despite having similar infarct size as assessed with cardiac biomarkers. These findings suggest that STEMI patients with COPD have greater impairment of LV systolic function at an early stage post-STEMI. LVEF and WMSI may not be sensitive enough to detect this impairment of LV systolic function.

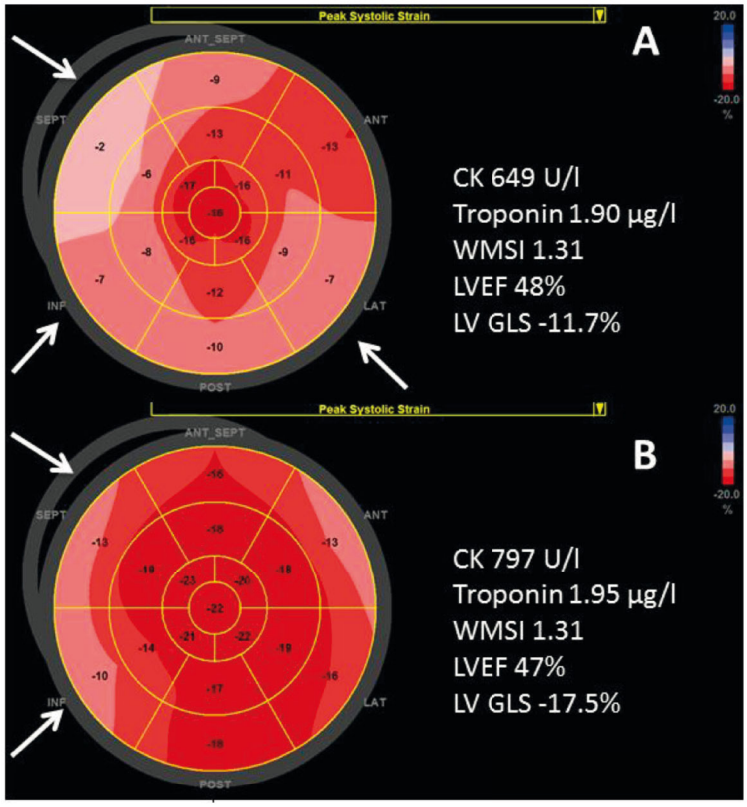

Figure 2. Bull's-eye plot of left ventricular (LV) global longitudinal strain (GLS) assessed by speckle tracking echocardiography. Panel A, STEMI patient with COPD (culprit vessel RCA), with LVEF 48% (comparable to patient B without COPD). LV GLS was more impaired (less negative) than in patient B without COPD, -11.7% vs. -17.5% respectively. **Panel B**, STEMI patient without COPD (culprit vessel RCA) with LVEF 47%. Biomarkers for infarct size (CK and troponin) were similar in both patients. Arrows indicate the infarct location. ANT, anterior; ANT_SEPT, anteroseptal; CK, creatine phosphokinase; INF, inferior; LAT, lateral; LVEF, left ventricular ejection fraction; POST, posterior; RCA, ramus descendens anterior; SEPT, septal; WMSI, wall motion score index.

Infarct size is an important prognostic marker after STEMI.[20] Creatine kinase and troponin levels and imaging modalities including echocardiography, nuclear imaging techniques and late gadolinium contrast-enhanced cardiac magnetic resonance (CMR) are well established methods to estimate the infarct size.[21] Whether the presence of COPD has influence on infarct size, has not been extensively evaluated.[22, 23] In 818 patients with STEMI (8.6% with COPD), Lazzeri et al showed no significant differences in peak troponin I between COPD and non-COPD patients (54.1 [28.7-212] vs. 92.2 [44.1-186.0] ng/ml, p=0.084; respectively).[22] Similar results were demonstrated by Wakabayashi and colleagues in 365 STEMI patients with COPD compared with 2884 patients without COPD (peak CK-MB 59.0±93.2 ng/ml vs. 63.5±97.2 ng/ml, p=0.4; respectively).[23] The present study provides additional information by providing echocardiographic estimates of infarct size. LVEF and WMSI measured on echocardiography have been shown to correlate with infarct size.[20, 24] Particularly, WMSI may reflect infarct size better than LVEF.[25] In this large cohort of patients, LVEF and WMSI were not significantly different between STEMI patients with COPD versus patients without COPD, suggesting that both groups of patients have comparable myocardial damage based on these conventional echocardiographic parameters.

Although LVEF and WMSI are routine echocardiographic parameters measured in STEMI patients to estimate LV systolic function and for risk stratification, the advent of speckle tracking echocardiography (which measures LV strain, deformation of the LV myocardium) has permitted to obtain more sensitive parameters of LV systolic function and better reflectors of myocardial damage.[24, 26] Both global and regional longitudinal strain have shown to be accurate in evaluating global LV function and the presence of segments with transmural necrosis, using CMR as a reference.[27] In addition, using single photon emission computed tomography (SPECT) myocardial perfusion imaging as reference, LV GLS has demonstrated to be superior to LVEF in predicting the infarct size at 30-fay follow-up.[26]

In the present study, STEMI patients with COPD showed more impaired LV GLS compared to non-COPD patients, despite having similar levels of biomarkers and comparable values of conventional echocardiographic parameters of LV systolic function. These results suggest that STEMI patients with COPD have larger myocardial damage than patients without COPD. Therefore, measuring LV GLS in the acute phase of STEMI may be a better marker of true myocardial damage in COPD patients than conventional echocardiographic parameters and may be a more sensitive parameter for risk stratification of these patients. The underlying mechanisms explaining worse LV GLS as a reflect of larger infarct size in COPD patients may relate to the chronic inflammatory status of COPD patients. The severity of the airflow obstruction has been shown to influence the inflammatory status and patients with severe COPD has shown higher levels of C-reactive protein and higher cardiac infarction injury score as compared with patients without airflow obstruction.[28] In addition, systemic inflammation has been linked to reperfusion

injury, causing larger myocardial infarct size.[29] Future research is needed to elaborate this pathophysiologic theory.

Several study limitations should be acknowledged. First, this is a single centre, retrospective study which cannot provide causal relationships. Second, the presence or absence of COPD in the study population was solely based on patients' medical records, since pulmonary function test were not systematically available. However, we did find a similar prevalence of COPD in our population compared to the existing studies in the literature which used the same definition for COPD.[1, 14] In addition, without pulmonary function tests we were not able to classify the severity of COPD.

In conclusion, STEMI patients with and without COPD have comparable myocardial infarct size and LV systolic function as assessed with biomarkers and conventional echocardiography, respectively. However, COPD patients exhibit more impaired LV GLS than their counterparts suggesting more myocardial damage and worse LV systolic function in the early phase post-STEMI in patients with COPD.

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