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Associating the Severity of Emphysema with Coronary Flow Reserve and Left Atrial Conduit Function for the Emphysema Patients with Known or Suspected Coronary Artery Disease

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Purpose: Pulmonary emphysema may associate with ischemic heart disease through systemic microvascular abnormality as a common pathway. Stress cardiovascular MR (CMR) allows for the assessment of global coronary flow reserve (CFR). The purpose of this study was to evaluate the association between the emphysema severity and the multiple MRI parameters in the emphysema patients with known or suspected coronary artery disease (CAD).

Methods: A total of 210 patients with known or suspected CAD who underwent both 3.0T CMR including cine CMR, stress and rest perfusion CMR, stress and rest phase-contrast (PC) cine CMR of coronary sinus, and late gadolinium enhancement (LGE) CMR, and lung CT within 6 months were studied. Global CFR, volumes and functions of both ventricles and atria, and presence or absence of myocardial ischemia and infarction were evaluated. Emphysema severity was visually determined on lung CT by Goddard method.

Result: Seventy nine (71.0 ± 7.9 years, 75 male) of 210 patients with known or suspected CAD had emphysema on lung CT. Goddard score was significantly correlated with CFR (r = –0.246, $P = 0.029$), left ventricular end-diastolic volume index (LV EDVI) (r = –0.230, $P = 0.041$), right ventricular systolic volume index (RV SVI) (r = –0.280, $P = 0.012$), left atrial (LA) total emptying volume index (r = –0.269, $P = 0.017$), LA passive emptying volume index (r = –0.309, $P = 0.006$), LA systolic strain (Es) (r = –0.244, $P = 0.030$), and LA conduit strain (Ee) (r = –0.285, $P = 0.011$) in the patients with emphysema. Multiple linear regression analysis revealed LA conduit function was independently associated with emphysema severity as determined by Goddard method (beta = –0.361, $P = 0.006$).

Conclusion: LA conduit function independently associates with emphysema severity in the emphysema patients with known or suspected CAD after adjusting age, sex, smoking, and the CMR indexes including CFR. These findings suggest that impairment of LA function predominantly occurs prior to the reduction of the CFR in the emphysema patients with known or suspected CAD.

Keywords: *cardiovascular magnetic resonance, global coronary flow reserve, Goddard method, left atrial function, pulmonary emphysema*

Introduction

Pulmonary emphysema is characterized as the destruction of alveolar walls and the permanent enlargement of air spaces distal to the terminal bronchioles.[1] The loss of lung tissue by emphysema impairs pulmonary function. However, pulmonary function tests are limited in diagnosis of emphysema. It is estimated that 30% of the lung is destroyed by emphysema before symptoms or pulmonary function abnormalities become evident.[2] Lung CT is the most accurate diagnostic modality for the diagnosis of emphysema, even in the mild or

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asymptomatic patients. Moreover, lung CT is accurate and reliable technique for evaluating emphysema severity using visual scores based on Goddard classification.[3]

The high spatial and temporal resolution, absence of ionizing radiation, and integrated assessment of atrial and ventricular function, including strain analysis, myocardial ischemia, and infarction are unequivocal advantages of the cardiovascular MR (CMR) in the management of patients with known or suspected coronary artery disease (CAD). Furthermore, phase-contrast (PC) cine CMR quantifies the blood flow in the coronary sinus (CS), which represents approximately 96% of the total blood flow in the myocardium.[4] The measurement of CS blood flow by PC cine CMR during stress and at rest provides a global coronary flow reserve (CFR), which is the ratio of hyperemic total coronary flow to baseline total coronary flow. Global CFR is widely accepted as a surrogate of coronary microvascular dysfunction.[5]

Early pathology studies noted significant pulmonary vascular alteration in emphysema.[6] From those studies, Liebow et al. postulated that changes in the lung microvascular alteration caused alveolar destruction in emphysema.[7] Recent study employing quantitative lung perfusion MRI revealed significant reductions in pulmonary microvascular blood flow and pulmonary microvascular volume in participants with emphysema as compared with those without.[8] Furthermore, recent several studies suggest that pulmonary emphysema is associated with systemic microvascular abnormality, as evidenced in the retinal and renal circulations, and microvascular abnormality could be the common pathway linking emphysema and altered condition in other organs, including heart.[9–12] Recently, Nakamori et al. demonstrated that global CFR was impaired in the patients with chronic obstructive pulmonary disease (COPD), which overlaps partially with emphysema, compared with healthy volunteers, suggesting the coronary microvascular dysfunction in COPD.[13] However, it is uncertain if severity of emphysema is associated with global CFR or not.

Cor pulmonale, which can occur in very severe COPD, is characterized by elevated pulmonary vascular resistance and right heart failure, with associated reductions in left ventricular (LV) filling, LV stroke volume, and cardiac output, although a LV ejection fraction is generally preserved.[14] While whether similar changes occur in milder chronic lung disease had long been unknown, the recent large population-based study demonstrated that the extent of emphysema as detected on CT is inversely related to LV end-diastolic volume, stroke volume, and cardiac output with preserved LV ejection fraction (EF) even among persons without very severe lung disease.[15] A likely mechanism of impaired LV filling in mild-moderate emphysema is the subclinical loss of lung parenchyma and the pulmonary capillary bed, that is, microvascular dysfunction in the lung. Therefore, LV atrial and ventricular volume and function might be influenced by the pulmonary microvascular dysfunction in the lung emphysema.

Thus, CFR and LV atrial and ventricular volume and function might be influenced by the cardiac and pulmonary microvascular dysfunction in the emphysema patient, respectively. However, there has not been any study assessing simultaneously the relation between emphysema, and multiple CMR indices, including global CFR, volumes and functions of both ventricles and atria. Consequently, the purpose of this study was to evaluate the relationship between the emphysema severity and the CMR indices, such as global CFR, volumes and functions of both ventricles and atria, and presence or absence of myocardial ischemia and infarction, in the emphysema patients with known or suspected CAD.

Materials and Methods

Patient population

This retrospective study was approved by the institutional review board and individual consent was waived (H2021-236). A total of 1603 patients with known or suspected CAD underwent stress CMR examination including cine CMR, stress and rest perfusion CMR, stress and rest PC cine CMR of coronary sinus and late gadolinium enhancement (LGE) CMR at 3.0T MR scanner between February 2012 and January 2019. No patient had severe renal failure (glomerular filtration rate $< 30\ mL/m^2$). From this cohort, the patients who had concomitantly cardiomyopathy (n = 234), myocarditis (n = 7), valvular heart disease (n = 109), arrhythmia at a time of CMR or a history of arrhythmia (n = 129), congenital heart disease (n = 34), cardiac tumor (n = 3), a history of heart failure (n = 0), and persistent left superior vena cava (n = 0) were preliminarily excluded. Among the remaining 1087 patients, 277 patients who underwent thin-slice lung CT within 6 months of CMR examination (mean interval, 56.3 ± 54.1 days) were included in this study. Exclusion criteria consisted of 1) history of lobectomy or pneumonectomy (n = 8), 2) history of chemotherapy (n = 23), 3) interstitial pneumonia (n = 24), and 4) suboptimal image quality of CMR (n = 12). Consequently, 210 patients were eligible to this study. Those patients were divided into two groups based on the presence or absence of lung emphysema on CT images (Fig. 1). All subjects refrained from drinking caffeinated beverages for at least 24 hours, and eating for more than 6 hours before CMR.

CMR imaging

CMR studies were performed using a 3.0T MR scanner (Ingenia 3.0T; Philips Medical Systems, Best, the Netherlands) equipped with dS coils. The CMR protocol included cine CMR, PC-cine CMR of the coronary sinus in the resting state and during adenosine triphosphate (ATP) stress, myocardial perfusion CMR during ATP stress and in the resting state, and LGE CMR.

Cine CMR images were acquired with retrospective electrocardiographic gating and a segmented balanced steady-state free precession sequence during brief periods

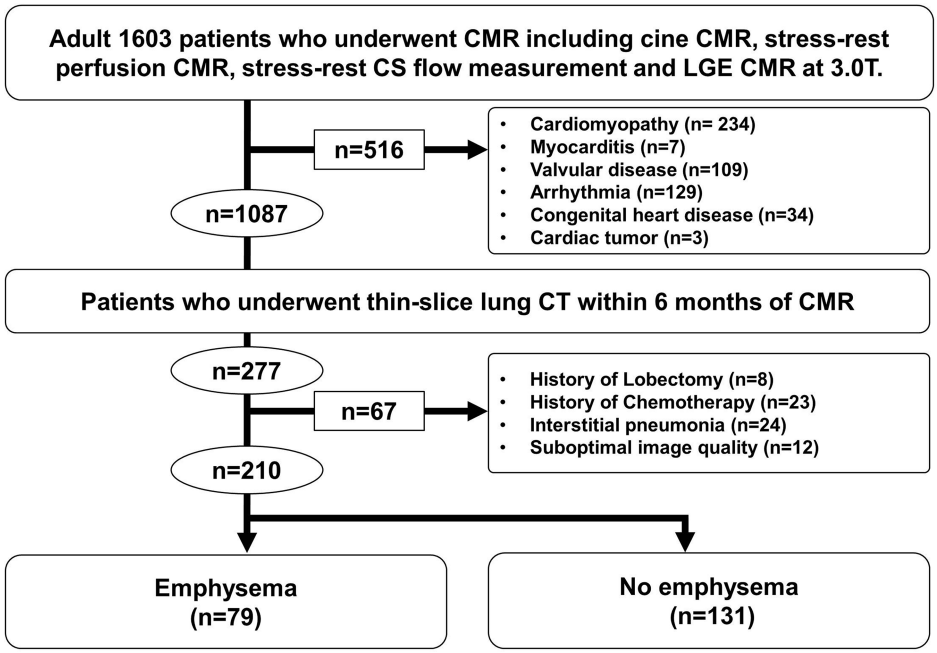


Fig. 1 Overview of study design including patient selection protocol in this study. CMR, cardiovascular MR; CS, coronary sinus; LGE, late gadolinium enhancement.

of breath-holding at a shallow expiration in the following planes: trans axial planes, 2-chamber and 4-chamber views, and short-axis planes covering the entire LV and right ventricle (RV) (TR = 3.4 ms, TE = 1.7 ms, flip angle [FA] = 55°, FOV = 35 × 35 cm, acquisition matrix = 176 × 306; reconstruction matrix = 352 × 352, slice thickness = 10 mm, sensitivity encoding [SENSE] factor = 3, and number of phases per cardiac cycle).

Breath-hold PC-cine CMR images of the coronary sinus were acquired using a vector-electrocardiogram-triggered gradient echo sequence (TR = 4.8 ms, TE = 3.1 ms, FA = 10°, FOV = 25 × 21 cm, acquisition matrix = 176 × 97, 25 phases per cardiac cycle, and velocity-encoding = ± 80 cm/s). For the accurate configuration of imaging slices for coronary sinus blood flow, trans axial cine CMR images through the atrioventricular groove were employed to detect the location of the coronary sinus. The imaging plane for coronary sinus blood flow measurement by PC cine images was positioned perpendicular to the coronary sinus at 2 cm from the ostium of the coronary sinus on trans-axial cine CMR images.

Pharmacological stress was achieved by continuous injection of ATP (160 mg/kg/min) in the left antecubital vein. Symptoms, blood pressure (BP), heart rate (HR), and electrocardiogram (ECG) were monitored while the patients were in the magnet. At least 3 mins after starting ATP administration, the acquisition of stress myocardial perfusion MR images was initiated. Myocardial perfusion CMR images were acquired with a saturation-recovery gradient echo sequence for 1 min with 1 RR interval (3 short-axis slices, TR = 3.0 ms, TE = 1.5 ms, FA = 20°, FOV = 34 × 31 cm, acquisition matrix = 224 × 132, slice thickness = 10 mm, and SENSE factor = 2.8). Immediately after starting perfusion CMR image acquisition, gadolinium contrast medium (Gadoterate meglumine [Gd-DOTA], Magnescope; Guerbet Japan, Tokyo, Japan) was injected into the right antecubital vein at a dose of 0.03 mmoL/kg and a flow rate of 4 mL/s, followed by a 20 mL saline flush. After completion of stress perfusion MRI, PC-cine CMR of the coronary sinus was performed during continuous ATP infusion. With at least 10-mins interval, myocardial perfusion CMR in the resting state was performed.

After the acquisition of rest perfusion CMR, an additional gadolinium was injected to reach a cumulative dose of 0.15 mmol/kg. Then, 10 min later, LGE CMR images were acquired in the same planes as cine CMR images by using an inversion recovery 3D gradient echo sequence (TR = 4.9 ms, TE = 2.4 ms, FA = 15°, FOV = 38 × 34 cm, acquisition matrix = 240 × 192, acquisition thickness = 10 mm, reconstructed matrix = 384 × 384, reconstructed thickness = 5 mm, and SENSE factor = 4). Inversion time was adjusted in each patient to null signal from the normal myocardium by using a look-locker sequence.

CMR image analysis

CMR image analyses were carried out using CMR analysis software (cvi42, version 5.11.2; Circle Cardiovascular Imaging, Calgary, Canada) by an experienced radiologist (MI, 20 years of CMR experience) blinded to the subjects' clinical and lung CT information. Measurements were indexed to body surface area where appropriate.

LV and RV volume and function were analyzed based on the short-axis cine stack. The endocardial and epicardial borders of the LV wall and the endocardial borders of the RV wall were manually traced on cine CMR images in the end-diastolic and end-systolic phases. LV mass was calculated as the volume of the LV myocardium multiplied by the specific gravity of the myocardium (1.05 g/mL).

Left atrial (LA) volume and function were measured based on the biplane area-length method.[16] The LA area in both the 4- and 2-chamber views was manually traced excluding the pulmonary veins and left atrial appendage. LA length was also measured from the midpoint of the mitral annulus plane to the posterior aspect of the left atrium. Right atrial (RA) volume was measured based on the single plane area-length method in the 4-chamber view, similar to the LA. LA and RA measurements were performed for entire cardiac cycle. Parameters for atrial phasic function were calculated following the definition in Table 1 and Fig. 2.[17]

Ventricular and atrial strain analysis was performed by a feature-tracking algorithm.[18] The endocardial and epicardial borders of myocardium were manually traced in the end-diastolic phase of 2- and 4-chamber view cine CMR images for LV global longitudinal strain (GLS). The software then automatically propagated the endocardial and epicardial contours and tracked the motion of the in-plane tissue voxels through the entire cardiac cycle. Global circumferential strain (GCS) and global radial strain (GRS) were determined using short-axis cine stack. Peak GLS, GCS, and GRS were recorded. Similarly, RV circumferential and longitudinal strain (CS, LS, respectively) were measured in a mid RV slice of short-axis plane and in a 4-chamber view, respectively, by a feature-tracking algorithm. LA and RA strains were quantified in 2- and 4-chamber views and 4-chamber view only, respectively, with subsequent computation of the strain curve to assess reservoir function peak systolic strain (Es), conduit strain (Ee), and booster pump function active strain (Ea).[19,20] Variables indicating ventricular and atrial volume were indexed to body surface area (BSA).

On PC-cine CMR images, the contour of the CS was manually traced on the magnitude images at each cine frame.[21] The traced ROI was applied on the corresponding phase image, and the cross-sectional area and mean velocity were recorded in each frame. Volumetric blood flow in the CS (mL/min) was calculated by integrating the product of cross-sectional area and mean velocity in the CS from the 25 images acquired across the cardiac cycle. Global CFR was calculated as stress CS blood flow divided by rest CS blood flow (Fig. 3). Global myocardial blood flow (MBF) (mL/min/g) was calculated as CS blood flow divided by LV mass for stress and rest measurements.

The presence or absence of myocardial infarction and ischemia was determined with the LGE and stress-rest perfusion CMR, respectively. Myocardial infarction was considered present if the sub-endocardial or transmural enhancement was observed on LGE CMR images. Myocardial ischemia was considered present if there was a hypoperfusion during stress that was not observed at rest in an area that did not exhibit abnormal enhancement on LGE CMR images.

Table 1 Definition of atrial phasic function.

Atrial phasic function	Formula
Reservoir function	
Total emptying volume (mL)	$V_{max}–V_{min}$
Total emptying fraction (%)	$100 \times (V_{max}–V_{min})/V_{max}$
Conduit function	
Passive emptying volume (mL)	$V_{max}–V_{PreA}$
Passive emptying fraction (%)	$100 \times (V_{max}–V_{PreA})/V_{max}$
Booster function	
Active emptying volume (mL)	$V_{PreA}–V_{min}$
Active emptying fraction (%)	$100 \times (V_{PreA}–V_{min})/V_{PreA}$

V_{max}, maximum atrial volume (atrial volume at end systole before mitral valve opening); V_{min}, minimum atrial volume (atrial volume at end diastole right after mitral valve closure); V_{PreA}, pre-atrial contraction atrial volume (atrial volume before atrial contraction).

CT scans and image interpretation

Three CT scanners (SOMATOM Definition Flash or SOMATOM Force; Siemens Healthineers, Forchheim, Germany and Discovery CT750 HD; GE Healthcare, Waukresha, WI, USA) were used. The following parameters were used for the lung CT studies: tube voltage, 120 kVp; reconstruction thickness, 1.00 or 1.25 mm; reconstruction interval, 1.00 or 1.25 mm, respectively; and reconstruction kernel, standard soft-tissue reconstruction algorithm. Tube current was determined using an automatic exposure control system with a quality reference of 200 and 160 mA for SOMATOM Definition Flash and SOMATOM Force and with noise index of 11 for Discovery CT750 HD, respectively. Rotation time was 0.5s and 0.4s for Siemens and GE scanners, respectively.

The CT images were viewed on a picture archiving and communication systems (PACS) workstation (EV Insight, version 3.9.3.405; PSP, Tokyo, Japan). Lung CT images were displayed at a 1000-Hounsfield unit (HU) window width and a −800-HU window level. Image filter of "sharpness, weak" was applied. Two experienced pulmonary radiologists (M.K. and S.M., with 10 and 34 years of experience in lung CT, respectively) reviewed the lung CT images and scored using the method of Goddard by consensus blinded to the subjects' clinical and CMR information[3] (Fig. 4). According to the extent of low attenuation areas in the peripheral lung fields, the CT findings were classified into the following five grades; Goddard score: Score 0, normal; Score 1, 1%–25% affected; Score 2, 26%–50% affected; Score 3, 51%–75% affected; and Score 4, 76%–100% affected. Six images were analyzed in 3 slices, which were obtained from the aortic arch level, carina

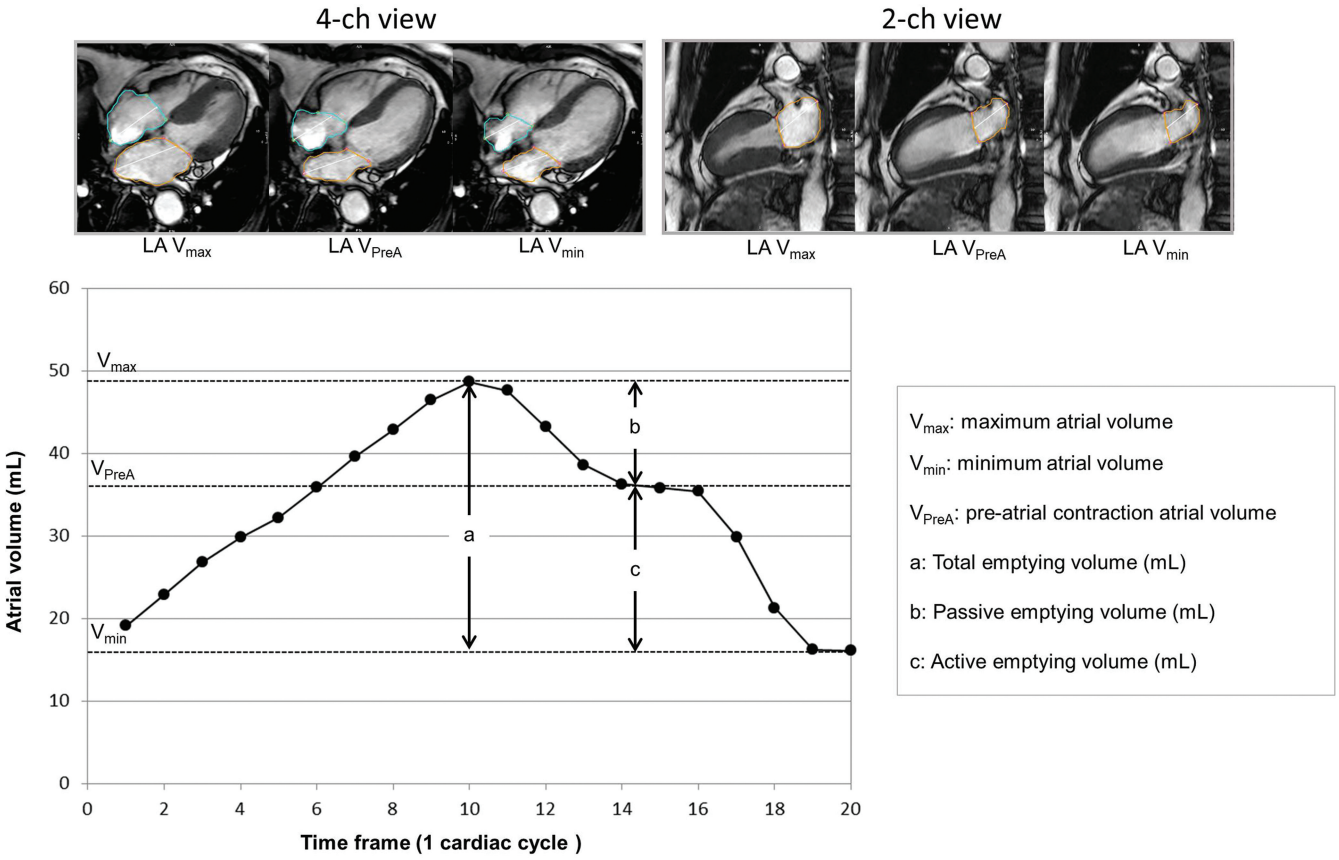
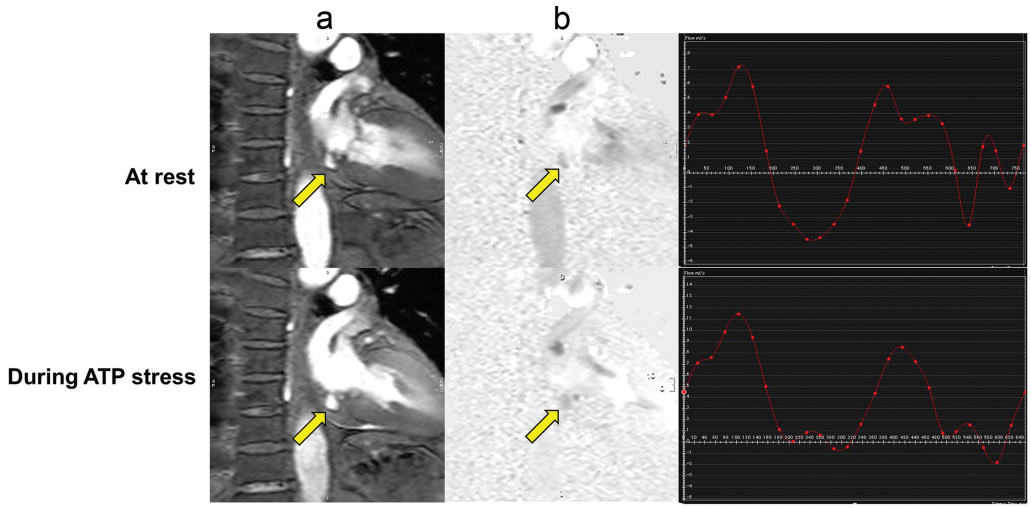


Fig. 2 Representative example of measure of LA volume derived from the biplane area-length method. Left atrial volume time curve with parameters of atrial function including reservoir, conduit, and booster function (see also Table 1) was demonstrated. RA measurement was done similarly but using the single plane area-length method. LA, left atrial; RA, right atrial.



$$\text{Global CFR} = \frac{\text{Stress CMR coronary sinus flow (mL/min)}}{\text{Rest CMR coronary sinus flow (mL/min)}}$$

Fig. 3 Measurement of blood flow in the coronary sinus. Phase-contrast cine MRI: magnitude image (**a**), phase difference (**b**) and blood flow curve in the coronary sinus (arrows) during 1 cardiac cycle. Global CFR is defined as stress CMR coronary sinus flow divided by rest CMR coronary sinus flow. CFR, coronary flow reserve; CMR, cardiovascular MR.

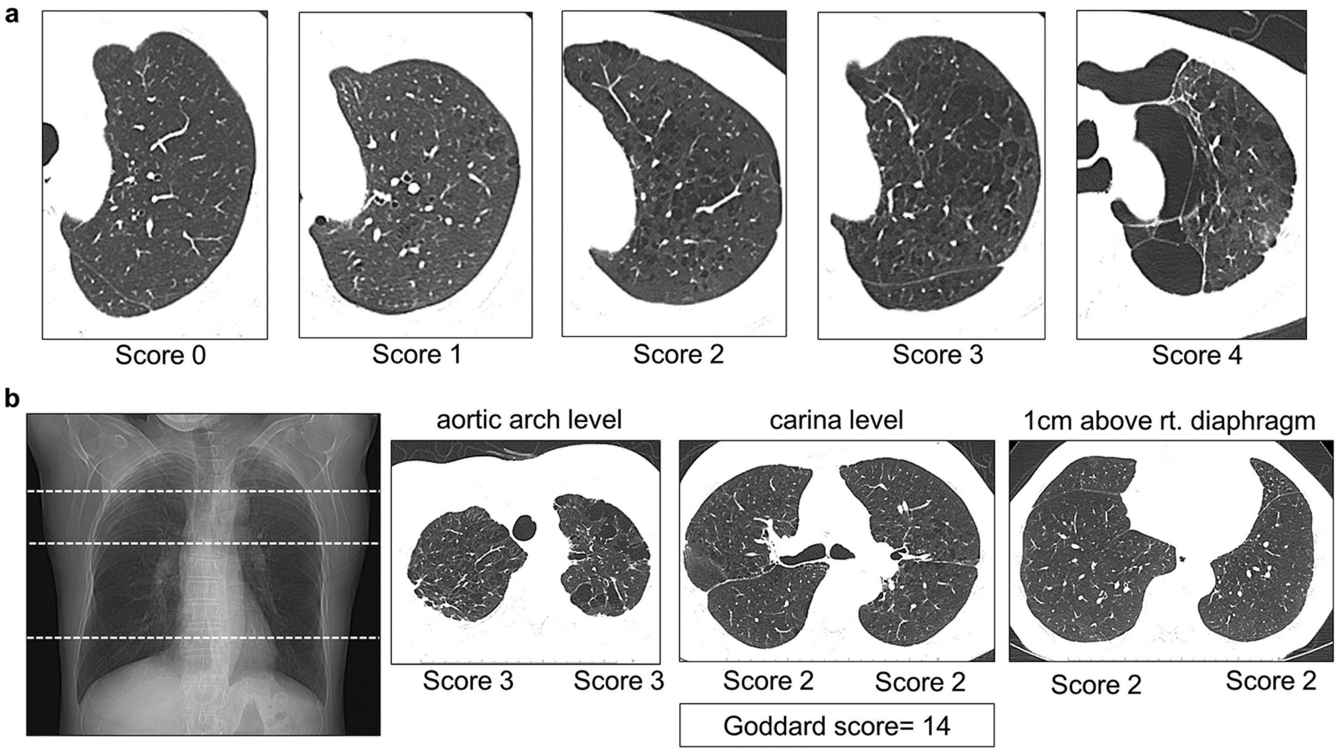


Fig. 4 Goddard scoring system to assess the severity of emphysema. Extent of low attenuation areas is classified using 5-point scale (Score 0, normal; Score 1, 1%–25% affected; Score 2, 26%–50% affected; Score 3, 51%–75% affected; and Score 4, 76%–100% affected) (**a**). Three slices (right and left), at the aortic arch level, carina level, and 1 cm above the right diaphragm are analyzed, and a total score of 6 images is calculated for each person (**b**).

level, and 1 cm above the right diaphragm, and a total score of 6 images was calculated for each person. There was a possible maximum score of 24 for each patient. Mild, moderate, and severe emphysema was classified as Goddard score of < 8, 8–15, 16 ≤, respectively.[3]

In addition, coronary artery calcium (CAC) visual score (0, very low risk; 1, mildly increased risk; 2, moderately increased risk; and 3, moderately to severely increased risk) and number of vessels (0, 1, 2, 3, and 4) were recorded to estimate the risk of the atherosclerotic cardiovascular disease according to coronary artery calcium data and reporting system.[22] Visual grading of aortic calcification (AC) was performed according to the following –point scale (absent [score 0], minor [score 1, less than 9 visible foci or less than 3 foci extending over 3 segments], or major [score 2, more than 9 visible foci or more than 3 foci extending over 3 segments]).[23] Aortic valve calcification (AVC) was visually scored using established visual AVC scoring criteria (none [grade 0], mild [grade 1], moderate [grade 2], and severe [grade 3]).[24]

Statistical analysis

All statistical analyses were done using the SPSS (version 26; IBM, Armonk, New York, USA). Values of $P < 0.05$ were considered indicative of statistical significance. Normality of continuous variables was assessed using the Shapiro–Wilk test. As all continuous variables were normally distributed, data for continuous variables are presented as the mean ± standard deviation (SD). Categorical variables are presented as frequencies and percentages. Comparisons between groups were made using unpaired Student's t test for continuous variables and chi-square tests for categorical variables. Univariate and stepwise multivariate linear regression analyses were performed to identify predictors of Goddard score in the patients with emphysema. Any variable with a P value < 0.1 in a univariate analysis was included in a subsequent multivariable model. Pearson's correlation coefficient was used to measure linear correlations between two variables.

Results

Patient characteristics

Heart rate was 77.8 ± 11.7/min during ATP stress and in the resting state (67.6 ± 10.7/min, $P < 0.001$). Systolic blood pressure was 118.9 ± 20.0 mmHg during ATP stress and 130.2 ± 23.0 mmHg in the resting state ($P < 0.001$). Among the total of 210 participants, lung emphysema was observed in 79 patients. In the 79 patients with emphysema, mean Goddard score was 5.92 ± 4.01. Mild,

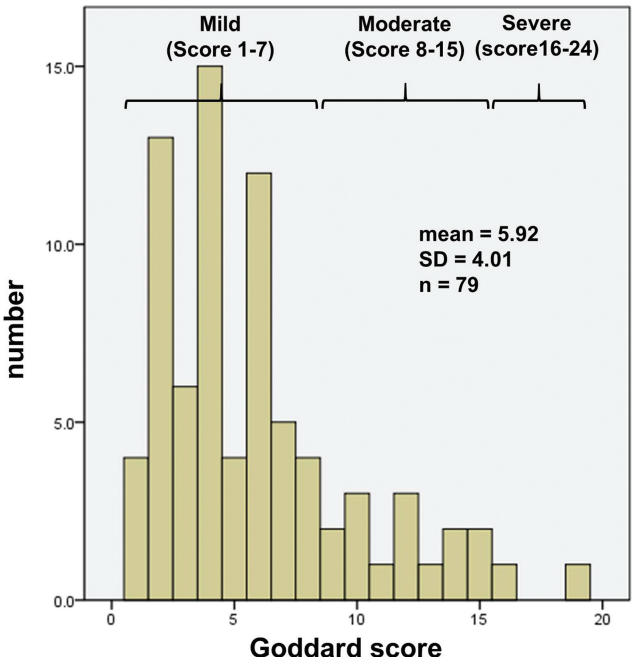


Fig. 5 The bar graph shows the distribution of Goddard score. Mild, moderate, and severe emphysema was observed in 74.7% (59/79), 22.8% (18/79), and 2.5% (2/79), respectively. SD, standard deviation.

moderate, and severe emphysema were observed in 74.7% (59/79), 22.8% (18/79), and 2.5% (2/79), respectively (Fig. 5).

There were no significant differences in the coronary risk factors between the patients with and without emphysema, except for smoking (91.1% and 48.9%, with and without emphysema, respectively, $P < 0.001$). The patients with emphysema were significantly older than those without (71.0 ± 7.9 years vs. 67.9 ± 11.8 years, $P = 0.027$). Body mass index (BMI) was significantly smaller in the patients with emphysema (22.6 ± 3.3 kg/m^2) compared with those without (24.0 ± 4.4 kg/m^2, $P = 0.015$) (Table 2). The patients with emphysema had significantly impaired LV GLS (-12.9 ± 3.4 % vs. -11.9 ± 2.9 %, $P = 0.019$), LA Es (15.9 ± 3.5 % vs. 14.7 ± 3.6 %, *P = 0.019*), LA Ea (8.7 ± 3.0 % vs. 7.8 ± 2.2 %, $P = 0.020$), RA total emptying fraction (47.1 ± 9.2 % vs. 43.0 ± 12.2 %, $P = 0.010$), RA Es (16.2 ± 4.1 % vs. 14.8 ± 4.1 %, *P = 0.008*), and RA Ee (7.6 ± 2.9 % vs. 6.7 ± 2.4 %, $P = 0.023$) as compared with the patients without emphysema. RAV_{min} index of patient with emphysema (21.8 ± 8.1 mL/m^2) was significantly larger than those of patients without emphysema (19.6 ± 6.8 mL/m^2, $P = 0.030$) (Supplementary Table 1).

Correlation between CMR parameters and Goddard score in the patients with emphysema

Univariate linear regression analyses showed that, among CMR parameters, Goddard score was significantly correlated with CFR ($r = -0.246$, $P = 0.029$), LV end-diastolic volume index (EDVI) ($r = -0.230$, $P = 0.041$), right ventricular systolic volume index (RV SVI) ($r = -0.280$, $P = 0.012$), LA total emptying volume index ($r = -0.269$, $P = 0.017$), LA passive emptying volume index ($r = -0.309$, $P = 0.006$), LA Es ($r = -0.244$, $P = 0.030$), and LA Ee ($r = -0.285$, $P = 0.011$) in the patients with emphysema (Table 3 and Fig. 6).

On stepwise multivariate linear regression analyses that included age, sex, smoking, CFR, LV EDVI, LV SVI, RV SVI, LA total emptying volume index, LA passive emptying volume index, LA passive emptying fraction, and LA Es and LA Ee as variables, CFR and LA passive emptying volume index was the independent predictor of Goddard score (beta = –0.254, $P = 0.018$; −0.316, $P = 0.004$) in the patients with emphysema (Table 3). Representative cases are shown in Fig. 7.

Discussion

The main finding of this study is that extent of emphysema as assessed CT is independently associated with LA passive emptying volume index among the emphysema patients with known or suspected CAD after adjusting for age, sex, smoking, and the CMR indexes including CFR. The present finding suggests that emphysema severity is independently associated with LA conduit functions in the emphysema patients with known or suspected CAD. To our knowledge, this is the first study assessing the relationship between emphysema and multiple CMR indices, including global CFR, volumes and functions of both ventricles and atria, and presence or absence of myocardial ischemia and infarction in human subjects. Animal studies suggest that pulmonary endothelial dysfunction might contribute to COPD and emphysema.[25,26] Impaired flow mediated dilation (FMD) in large systemic arteries was associated with emphysema.[27] These findings may suggest early pulmonary endothelial and microvascular damage in patients with COPD. Furthermore, previous animal study demonstrated that prolonged hypoxia due to emphysema induces a reduction in capillary density in the heart, suggestive of the microvascular dysfunction in the heart.[28] Recent large, population-based cohort study by Harris et al. demonstrated in human subjects free of clinical cardiovascular disease that spirometrically defined low lung function was associated with microvascular changes in the retina, kidneys, and heart, and emphysema was associated with impaired stress myocardial blood flow determined by quantitative analysis of adenosine stress perfusion CMR.[29] These findings suggest that lung dysfunction may contribute to systemic microvascular disease, or that there may be a shared predisposition. The findings obtained in the emphysema patients with known or suspected CAD in our study are in line with those previous findings in animal and human subjects without cardiac disease. However, in the multi-variate analysis, only LA

Table 2 Patient characteristics.

Patient characteristics	Total (n = 210)	No emphysema (n = 131)	Emphysema (n = 79)	*P* value
Male, n (%)	152	77 (58.8)	75 (97.9)	*<0.001**
Age (yrs), mean ± SD	69.1 ± 10.6	67.9 ± 11.8	71.0 ± 7.9	0.027*
BMI (kg/m^2), mean ± SD	23.5 ± 4.08	24.0 ± 4.4	22.6 ± 3.3	*0.015**
Risk factor				
Hypertension	159 (75.7)	100 (76.3)	59 (74.7)	*0.787*
Diabetes mellitus	80 (38.1)	50 (38.2)	30 (38.0)	*0.978*
Hyperlipidemia	148 (70.5)	96 (73.3)	52 (65.8)	*0.251*
Smoking	136 (64.8)	64 (48.9)	72 (91.1)	*<0.001**
Family history of CAD	48 (22.9)	35 (26.7)	13 (16.5)	*0.086*
Spirometry, n (%)	94 (44.8)	53 (40.5)	41 (51.9)	*n/a*
Clinical diagnosis of COPD	22 (10.5)	5 (3.8)	17 (21.5)	*n/a*
HOT	1 (0.5)	0 (0)	1 (1.3)	*n/a*

Except where otherwise noted, data are presented as the numbers of participants, with percentages in parentheses. Student t test was used to assess differences in continuous variables. Chi-square test/Fisher exact test was used to assess the differences in proportion between categorical variables. BMI, Body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HOT, home oxygen therapy; n/a, not applicable; SD, standard deviation. *$P < 0.05$.

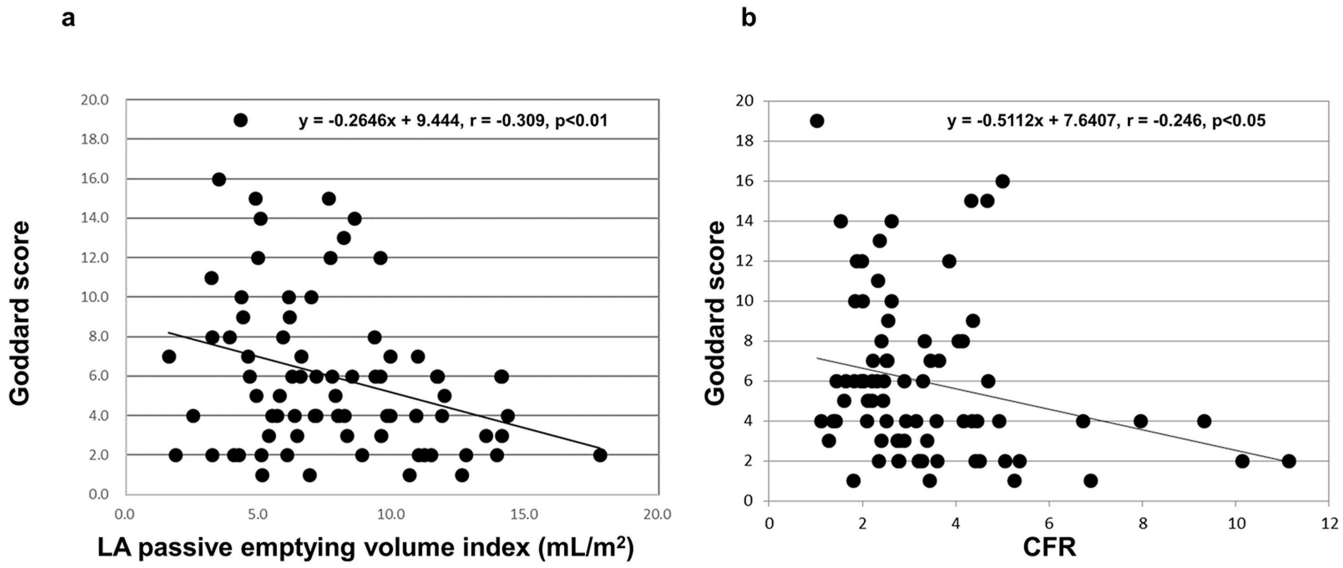


Fig. 6 Correlation of LA passive emptying volume index (**a**) and CFR (**b**) with Goddard score. A significant inverse correlation was observed between LA passive emptying volume index and Goddard score (r = –0.309, $P < 0.01$) and between CFR and Goddard score (r = –0.246, $P < 0.01$). CFR, coronary flow reserve; LA, left atrial.

conduit function parameter was retained as an independent predictor of Goddard score while CFR was not. This may be because age was a confounding factor influencing this analysis.

The principal role of the LA is to modulate LV filling by functioning as a reservoir for pulmonary venous return during ventricular systole, a conduit for pulmonary venous return during early ventricular diastole, and a booster pump that augments ventricular filling during late ventricular diastole.[30] Atrial volume analysis can evaluate both volume and function for atrial reservoir, conduit and contractile function. Generally, the CMR strain analysis of the atrium using feature tracking technique is beneficial because of its non-time-consuming nature as compared to atrial volume analysis. However, the atrial strain analysis provides only functional assessment not volumetric information. In this regard, the volume analysis

Table 3 Correlation of CMR parameters with Goddard score.

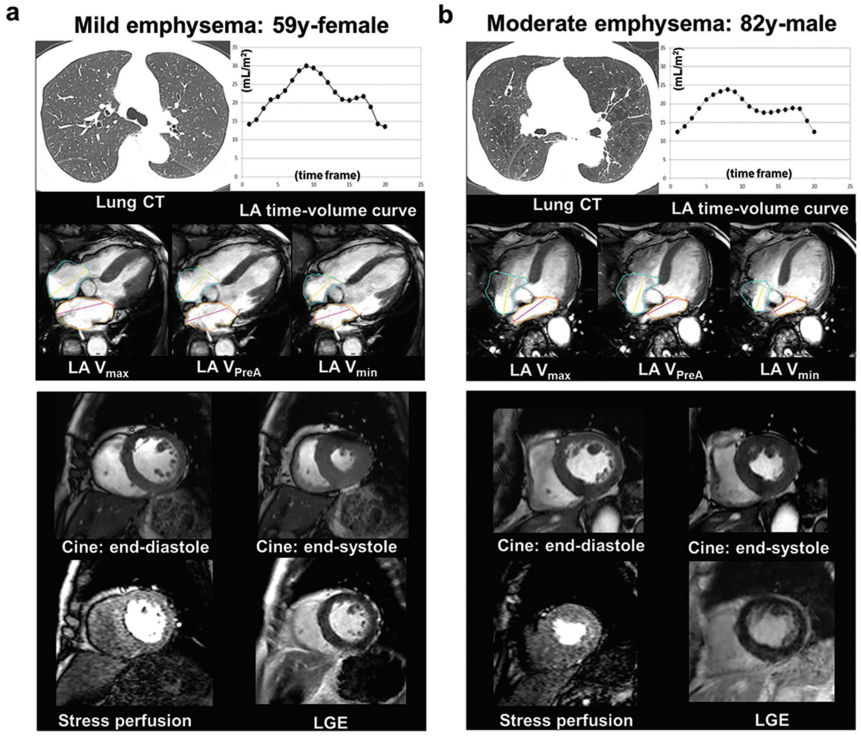
	Univariate analysis		Multivariate analysis	
	r	*P* value	β	*P* value
CFR	−0.246	0.029*		
Global stress MBF	−0.074	0.516		
Global rest MBF	−0.021	0.852		
Age	0.216	0.056†		
Sex	−0.091	0.423		
Smoking	−0.084	0.464		
LV EDVI	−0.230	0.041*		
LV ESVI	−0.152	0.181		
LV SVI	−0.221	0.050†		
LV EF	0.104	0.360		
LV CI	−0.077	0.501		
LV mass index	−0.069	0.546		
LV GLS	0.038	0.743		
LV GCS	−0.072	0.527		
LV GRS	0.108	0.344		
RV EDVI	−0.143	0.208		
RV ESVI	−0.014	0.903		
RV SVI	−0.280	0.012*		
RV EF	−0.106	0.351		
RV CI	−0.109	0.337		
RV CS	−0.140	0.220		
RV LS	0.139	0.222		
LA V_{max} index	−0.178	0.117		
LA V_{min} index	−0.064	0.577		
LA V_{PreA} index	−0.103	0.365		
LA total emptying volume index	−0.269	0.017*		
LA total emptying fraction	−0.117	0.303		
LA passive emptying volume index	−0.309	0.006**	−0.361	0.006*
LA passive emptying fraction	−0.218	0.054†		
LA active emptying volume index	−0.129	0.257		
LA active emptying fraction	−0.022	0.851		
LA Es	−0.244	0.030*		
LA Ee	−0.285	0.011*		
LA Ea	−0.038	0.736		
RA V_{max} index	−0.091	0.425		
RA V_{min} index	−0.069	0.544		
RA V_{PreA} index	−0.083	0.468		
RA total emptying volume index	−0.083	0.469		

(*Continued*)

Table 3 (Continued).

	Univariate analysis		Multivariate analysis	
	r	*P* value	β	*P* value
RA total emptying fraction	−0.008	0.945		
RA passive emptying volume index	−0.058	0.609		
RA passive emptying fraction	0.001	0.994		
RA active emptying volume index	−0.072	0.530		
RA active emptying fraction	−0.007	0.951		
RA Es	0.040	0.727		
RA Ee	−0.041	0.720		
RA Ea	0.089	0.437		
Myocardial infarction	−0.038	0.738		
Myocardial ischemia	0.139	0.223		
CAC visual score	0.058	0.610		
CAC number of vessels	0.084	0.460		
AC	0.099	0.387		
AVC	0.160	0.158		

Univariate and stepwise multivariate linear regression analyses were performed to identify predictors of Goddard score. Any variable with a *P* value < 0.1 in a univariate analysis was included in a subsequent multivariable model. $^{\dagger}P < 0.1$, $^{*}P < 0.05$, $^{**}P < 0.01$. AC, aortic calcification; AVC, aortic valve calcification; CAC, coronary artery calcium; CFR, coronary flow reserve; CI, cardiac index; CS, circumferential strain; Ea, booster pump function active strain; EDVI, end-diastolic volume index; Ee, conduit strain; EF, ejection fraction; Es, reservoir function strain; ESVI, end-systolic volume index; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LA, left atrial; LS, longitudinal strain; LV, left ventricular; MBF, myocardial blood flow; RA, right atrial; RV, right ventricular; SVI, systolic volume index; V_{max}, maximum volume; V_{min}, minimum volume; V_{PreA}, Pre-atrial contraction volume.



c

	59y-female	82y-male
Goddard score	2	14
CFR	5.36	1.54
LA V_{max} index (mL/m^2)	36.8	28.4
LA V_{PreA} index (mL/m^2)	25.3	19.8
LA V_{min} index (mL/m^2)	16.6	11.9
LA total emptying volume index (mL/m^2)	20.2	16.5
LA total emptying fraction (%)	54.8	58.0
LA passive emptying volume index (mL/m^2)	11.5	8.6
LA passive emptying fraction (%)	31.2	30.2
LA active emptying volume index (mL/m^2)	8.7	7.9
LA active emptying fraction (%)	34.4	39.9
LV EDVI (ml/m^2)	92.0	98.3
LV ESVI (ml/m^2)	28.2	53.2
LV SVI (ml/m^2)	63.9	45.1
LV EF (%)	69.4	45.8
LV CI (l/m^2)	4.34	2.84
LV mass index (g/m^2)	58.3	50.6

Fig. 7 Representative imaging findings in patients with mild emphysema (**a**) and with severe emphysema (**b**). Godard score, CFR, LA and LV volume and function are summarized in (**c**). CFR, coronary flow reserve; LA, left atrial; LV, left ventricular.

still has the benefit in the evaluation of atrium. In the univariate analysis in our study, a greater extent of emphysema was associated with smaller LV and RV volume index, lower LA conduit and reservoir function, lower reservoir and conduit strain and lower CFR. In the multi-variate analysis, only LA conduit function retained as the independent predictor of emphysema severity after adjusting for age, sex, smoking, and the CMR indexes including CFR. These observations in our study might indicate that impaired LA conduit function predominantly affect the impaired left ventricular filling in mild to moderate emphysema in our cohort. Recently, Barr et al. demonstrated that extent of emphysema as detected on CT is inversely related to LV end-diastolic volume, stroke volume, and cardiac output with preserved LV EF even among persons without very severe lung disease in a large population-based study.[15] They suggested a likely mechanism of impaired left ventricular filling in mild-moderate emphysema as the subclinical loss of lung parenchyma and the pulmonary capillary bed. The endothelial hypothesis of emphysema suggests that endothelial and microvascular damage increase pulmonary vascular resistance with concomitant increases in emphysema and resultant airflow obstruction.[7] Recent studies in basic science support the fact that endothelial damage may contribute to emphysema.[31] Moreover, recent observations of impaired left ventricular filling in preclinical emphysema indirectly suggest pulmonary vascular damage in the development of emphysema.[14] Our study which simultaneously evaluated ventricular and atrial function reveled that LA function such as conduit function may be an earlier marker for the detection of the reduction of pulmonary venous return in mild to moderate emphysema. This might support the endothelial hypothesis of emphysema. Moreover, the main finding of our study demonstrating the association between emphysema and LA conduit function after adjusting for age, sex, smoking, and the CMR indexes including CFR suggests that the impairment of LA function predominantly occurs prior to the reduction of the CFR in the patients with emphysema.

Severe emphysema resulting in cor plumonale may be involved with loss of pulmonary vascular capacity due to parenchymal destruction, hypoxic pulmonary arterial vasoconstriction, and pulmonary hyperinflation with elevated intrathoracic pressure.[14] However, cor pulmonale is generally absent in mild, moderate emphysema.[31] In the current study, which evaluated with mainly mild-moderate emphysema, where RV and RA volume and function parameters were included in addition to LV and LA parameters in the analysis, there was no significant relation between those RV and RA parameters with emphysema severity. This may suggest that the RA and RV impairment delayed after that of LA in mild-moderate emphysema. In this study, CFR was not significantly different between non-emphysema and emphysema patients, while CFR was significantly correlated with the severity of emphysema in emphysema patients. It is well recognized that the CFR fluctuate widely in the normal subject in the range above CFR of 2.5; however, it is reduced to less than 2.5 in the patients having CAD, those with high risk factor for CAD, or both. As the patient population in this study was those with known or suspected CAD, substantial number of patients had coronary risk factors and myocardial ischemia in both group with similar percentages except for smoking. Further, mild emphysema was dominant in the emphysema patient group. Those factors might be attributable for no significant difference of CFR between non-emphysema and emphysema. On the other hand, as mentioned above, the age of the patient influenced the relation between CFR and Goddard scores.

Several limitations should be acknowledged in our study. First, a relatively long interval between the CMR and lung CT studies had to be allowed to keep the sufficient number of eligible patients due to retrospective nature of this study. However, as the development of emphysema requires relatively long period, less than 6 months of interval between the two studies should be justified. Cases with therapeutic intervention such as lobectomy or pneumonectomy or chemotherapy and with interstitial pneumonia were excluded in our study regardless when it happened. Second, only Goddard visual CT scoring system was used for scaling the emphysema severity. As lung CT scan condition was not uniform in this retrospective study, quantitative low attenuation area (LAA) analysis, which depends on the same scan setting, was avoided. Third, in this study, a relationship between right atrial pressure and central venous pressure and CFR were not evaluated because no patient underwent the evaluation of right atrial pressure and central venous pressure in this study. This is the limitation of the retrospective study. Investigation of the relationship between right atrial pressure and central venous pressure and CFR in patients with emphysema should be warranted in the future prospective study. Lastly, exclusion criteria might have had to include sleep apnea syndrome in addition to the current exclusion criteria in this study. However, due to the retrospective nature of this study, the presence or absence of sleep apnea syndrome was not being able to be determined in most of the patients even though medical record was referenced. Future prospective studies with more strict exclusion criteria should be warranted.

In conclusion, LA conduit function independently associated with emphysema as assessed by Goddard method in the emphysema patients with known or suspected CAD after adjusting for age, sex, smoking, and the CMR indexes including CFR. These findings suggest that impairment of LA function predominantly occurs prior to the reduction of the CFR in the patients with emphysema.

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Conflicts of Interest

All authors have no conflicts of interest to declare.

Supplementary Materials

The supplementary file below is available online.

Supplementary Table 1
Cardiovascular magnetic resonance data.

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