Cardiac imaging characteristics of patients with COPD: prognostic implications

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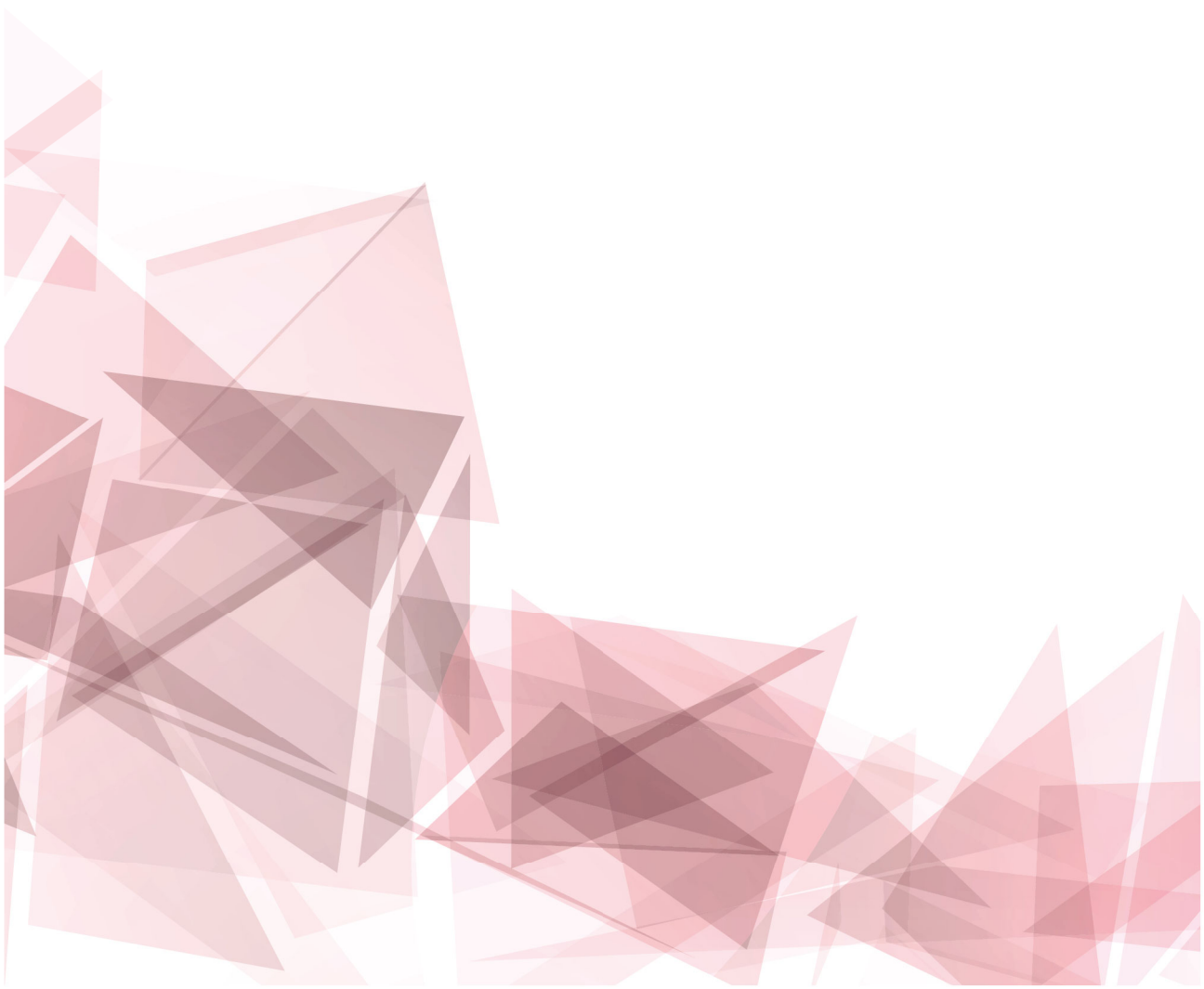

Chapter 4

ST-segment Elevation Myocardial Infarction in Patient With Chronic Obstructive Pulmonary Disease: Prognostic Implications of Right Ventricular Dysfunction as Assessed with Two-Dimensional Speckle-Tracking Echocardiography

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Abstract

Background Right ventricular (RV) systolic function in patients admitted with ST-segment elevation myocardial infarction (STEMI) with chronic obstructive pulmonary disease (COPD) as well as its impact on prognosis have not been characterized. The present study aimed at comparing the prevalence of RV systolic dysfunction in COPD versus non-COPD patients with STEMI and evaluating the prognostic implications.

Methods 117 STEMI patients with COPD with transthoracic echocardiography performed within 48 hr of admission were retrospectively selected. Matched on age, gender and infarct size (determined by cardiac biomarkers and left ventricular ejection fraction (LVEF)), 207 non-COPD patients were selected. RV dysfunction was defined based on tricuspid annular plane systolic excursion <17 mm (TAPSE), tricuspid annular systolic excursion velocity <6 cm/s (S'), RV fractional area change <35% (FAC), and RV free wall strain measured with speckle tracking echocardiography >-20% (FWS). Patients were followed for the occurrence of all-cause mortality.

Results RV assessment was feasible in 112 COPD and 199 non-COPD patients (mean age 69±10, 74% male, mean LVEF 47±8%). Patients with COPD had significantly lower RV FAC (38±11 vs 40±9%, p=0.04), equal TAPSE and S' (17.9±3.7 vs 18.1±3.8 mm, p=0.72 and 8.4±2.2 vs 8.5±2.2 cm/s, p=0.605, respectively) and more impaired RV FWS (-21.1±6.6 vs -23.4±6.5%, p=0.005), compared to patients without COPD. RV dysfunction was more prevalent in patients with COPD, particularly when assessed with RV FWS (46% vs. 32%, p=0.021). During a median follow-up of 30 (IQR 1.5- 44) months, 49 patients died (16%). Multivariate models stratified for COPD status showed that RV FWS >-20% was independently associated with 5 year all-cause mortality (HR 2.05, 95% CI 1.12 – 3.76, p =0.020), after adjusting for age, diabetes, peak troponin level and LVEF. Interestingly, RV FAC <35%, S'<6 cm/s and TAPSE <17 mm were not independently associated with survival.

Conclusion In a STEMI population with relatively preserved LVEF, COPD patients had significantly worse RV FWS compared to patients without COPD. Moreover, RV FWS >-20% was independently associated with worse survival. In contrast, conventional parameters were not associated with survival.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by remodelling of the pulmonary vasculature which can occur at any stage of the disease.[1] In combination with a loss of pulmonary vessels, increased pulmonary vascular resistance and hypoxia, COPD is often accompanied by secondary pulmonary hypertension.[1] Although often mild and slowly progressing, this pulmonary hypertension can cause pressure overload of the right ventricle (RV), leading to RV remodelling and dysfunction.[2] These changes in RV function and anatomy can occur at early stages of COPD when pulmonary hypertension is not yet present.[3]

In patients with ST-segment elevation myocardial infarction (STEMI), RV involvement has been reported in 10-75% of patients, irrespective of infarct location, and has important prognostic implications.[4-6] Assessment of RV systolic function and dimensions can be challenging due to the complex geometry of the ventricle. Several imaging modalities are available, using different functional parameters to quantify RV systolic function.[7] Transthoracic echocardiography (TTE) remains the imaging technique of first choice. Quantification of RV systolic function on TTE can be performed using different parameters of which tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic excursion velocity (S') and fractional area change (FAC) are most frequently used.[8] However, these measurements are limited by their dependency on loading conditions and the geometric assumptions of the RV shape. Furthermore, when regional dysfunction may be present, i.e. in RV infarction, TAPSE or S' might not be sensitive enough to reflect on systolic function of the whole ventricle.[9] RV longitudinal strain determined by speckle tracking echocardiography (STE) overcomes these limitations by measuring the active deformation of the regional segments without relying on geometric assumptions and being angle-independent. Previous studies have shown the incremental prognostic value of RV strain over left ventricular ejection fraction (LVEF) in patients with myocardial infarction.[5,10] Patients with COPD who may have RV subclinical dysfunction due to concomitant pulmonary hypertension may have further impairment of RV systolic dysfunction after STEMI. However, this has not been investigated and the impact of RV longitudinal strain in COPD patients after STEMI remains elusive. Therefore, the hypothesis of the present study is that STEMI patients with COPD may have more frequently RV systolic dysfunction when assessed with conventional and speckle tracking echocardiography as compared to patients without COPD. In addition, the prognostic implications of RV systolic function measured with conventional echocardiographic parameters (TAPSE, S' and FAC) will be compared to those of advanced echocardiography measuring RV longitudinal strain with speckle tracking.

Methods

Patient population and data collection

The study population was selected from an ongoing clinical registry of patients admitted with STEMI in a tertiary care center (Leiden University Medical Center, Leiden, The Netherlands). Patients admitted between February 2004 and May 2013, with a registered history of COPD were identified. The control group consisted of STEMI patients without COPD, admitted during the same time period. Patients with and without COPD were matched on a 1:2 basis by age, gender and infarct size (determined by peak levels of troponin and creatine kinase (CK) and LVEF). Patients were treated as per prevailing guidelines.[11-13] Transthoracic echocardiography was performed within 48 hours of admission. Patients without complete echocardiographic data were excluded.

Demographic and biochemical data (peak levels of troponin and CK, kidney function) were collected. Furthermore, cardiovascular risk factors and medication use at discharge were registered. Hypertension was defined as previous use of antihypertensive medication or a blood pressure of ≥140 mmHg systolic or ≥90 mmHg diastolic.[14] Diabetes mellitus was defined as a registered history of diabetes mellitus and use of oral glucose-lowering therapy, insulin or a diet. Patients were considered to have hypercholesterolemia when registered in medical records and/or statin use. During invasive angiography, the culprit vessel was identified and the presence of multivessel disease was defined by >50% luminal stenosis in more than one vessel.

Clinical and echocardiographic data were prospectively collected in the departmental Cardiology Information System (EPD-vision, Leiden University Medical Center, Leiden, the Netherlands) and echocardiographic database, respectively, and analysed retrospectively. For retrospective analysis of clinically acquired data and anonymously handled, the institutional review board waived the need for patient written informed consent.

Transthoracic echocardiography

Images were obtained with the patient at rest, in left lateral decubitus position using a commercially available ultrasound system (Vivid 7 and E9, GE Healthcare, Horten, Norway). Standard 2-dimensional (2D), M-mode, color, pulsed- and continuous-wave Doppler images were acquired with a 3.5MHz or M5S transducer in the parasternal, apical and subcostal views. Images were acquired during breath-hold and 3 consecutive heartbeats were digitally stored in cine-loop format. Data analysis was performed offline with the use of dedicated software (EchoPac, version BT13, GE medical systems, Horton, Norway).

Left ventricular (LV) function was evaluated by measuring end-systolic and end-diastolic volumes in the apical 2- and 4-chamber views, with subsequent calculation of LVEF using Simpson's biplane method.[8] LV mass was calculated according to Devereux' formula and indexed to body surface area (BSA).[8] The severity of mitral regurgitation (MR) was graded as none/mild, trivial, moderate and severe in accordance with current

guidelines.[15] Diastolic function was assessed by obtaining pulsed-wave Doppler images of the mitral inflow, placing the sample volume between the tips of the mitral leaflets. Peak early (E) diastolic velocity was measured.[16] Subsequently, E/e' ratio was calculated by using the average e', measured at both septal and lateral side of the mitral annulus with tissue Doppler imaging.[16]

Right ventricular (RV) end-diastolic dimensions were acquired from the RV focused apical 4-chamber view at the basal, mid and longitudinal level.[9] In addition, the proximal RV outflow tract diameter was measured at the parasternal long-axis view.[9] Right atrial area was traced in end-systole at the apical 4-chamber view.[9] As a measure of RV systolic function, tricuspid annular plane systolic excursion (TAPSE) was evaluated in the apical 4-chamber view using M-mode. The total displacement of the tricuspid annulus was measured from end-diastole to end-systole.[8, 9] In addition, RV fractional area change (RV FAC) was calculated by tracing the RV end-diastolic area (RV EDA) and end-systolic area (RV ESA) at the apical 4-chamber view and using the formula: (RV EDA – RV ESA)/RV EDA x 100.[8, 9] To evaluate longitudinal tricuspid annular systolic excursion velocity, color-coded tissue Doppler images (TDI) of the apical 4-chamber view were used for offline analysis. For this, the sample was placed at the level of the tricuspid annulus of the RV free wall and the peak systolic velocity (S') was measured after ignoring the initial peak which is observed during isometric ventricular contraction.[9] Tricuspid regurgitation (TR) severity was graded based on ratio of the regurgitant jet and right atrial area.[15] To evaluate systolic pulmonary arterial pressure (SPAP), RV and RA pressures were added. To estimate RV pressure, the maximum velocity of the tricuspid regurgitation jet was calculated using the modified Bernoulli equation.[9] RA pressure was estimated by measuring the diameter and the inspiratory collapse of the inferior vena cava (IVC).[9]

2-Dimensional speckle tracking echocardiography

To obtain reliable analysis, speckle-tracking analysis was performed in images acquired with >40 frames per second. Although speckle-tracking analysis was originally designed and extensively tested to assess left ventricular function, previous research has shown its accuracy and feasibility in evaluating RV function.[5, 17] Peak systolic longitudinal strain of the RV free wall (FWSL) was measured at the apical 4-chamber view by tracing the endocardial border at end-systole. The automatically created region of interest was manually adjusted to the thickness of the myocardium. Subsequently, the software generates peak systolic longitudinal strain curves for the 3 segments of the RV free wall (basal, mid and apical) and RV FWSL was determined by calculating the mean value of these 3 segments. Segments with poor tracking quality were (manually) excluded. Conventionally, longitudinal strain is presented as negative value since it reflects myocardial shortening: more negative values indicate larger shortening and better function.

Follow-up

Patients were treated with optimal, maximum tolerated medical therapy and regularly evaluated at the outpatient clinic. Occurrence of all-cause mortality at 5 years of follow-up was obtained from medical records and civil municipal registries.

Statistical analysis

Continuous data are presented as mean and standard deviation (SD) or median and 25th – 75th percentile. Categorical data are expressed as frequencies and percentages. Baseline characteristics were compared between patients with and without COPD. For continuous data, Student t-test or Mann-Whitney U test were used, as appropriate. For categorical variables, χ^2 test or Fisher's exact were used, as appropriate. In accordance with the most recent guidelines, RV dysfunction was defined as TAPSE <17 mm, S' < 6cm/s, RV FAC <35% and RV FWSL >-20%.[8] Determinants of RV dysfunction were evaluated with binary logistic regression analysis. Clinical and echocardiographic variables with a p-value <0.20 in univariate analysis were included in a multivariate model. For each parameter of RV function, separate uni- and multivariate analyses were performed. Inter-observer and intra-observer variabilities for RV FWSL were evaluated in 20 randomly selected COPD patients with intraclass correlation coefficients. All measurements were performed by experienced observers (L.G. and V.D.) who were blinded for the first analysis. For intra-observer variability, the second measurements were performed at a different time point.

To evaluate which RV function parameter has the strongest association with all-cause mortality at 5 years, Kaplan-Meier analysis and Cox proportional hazard regression analysis were performed. The cumulative event rates between groups were compared using log-rank tests. Age, diabetes mellitus, previous myocardial infarction, peak level of troponin, kidney function, Killip class at admission, LVEF and E/e' ratio had a p-value <0.10 in univariate Cox regression analysis. To avoid overfitting, a conditional forward stepwise method was used to select the variables for the final multivariate model. All multivariate models were stratified for COPD status. The final baseline model included age, diabetes, peak troponin level and LVEF. TAPSE, RV FAC, S' and RV FWSL were introduced as dichotomous variables in separate multivariate models. The change in χ^2 after introducing the RV function parameters to the baseline model was calculated to assess the incremental prognostic value of each parameter. A two-sided p-value of <0.05 was considered statistically significant. All data were analysed using the SPSS (version 24, IBM SPSS statistics for windows, Armonk, New York).

Results

In total, 324 patients were included in the present study (mean age 68±10, 74% male), including 117 patients with COPD and 207 matched controls without COPD. Quantification

of RV function was feasible in 311 patients (112 with COPD and 199 without COPD, mean age 69±10, 74% male) and formed the study population.

Patient characteristics

Table 1 shows the baseline characteristics for patients with and without COPD. Patients with COPD were more frequently current or previous smokers (69% vs. 50%, p<0.001). In addition, patients with COPD had more frequently a history of myocardial infarction. In terms of procedural findings and medication use, no differences were observed between COPD and non-COPD patients.

Table 1. Baseline characteristics for patients with and without COPD.

Variable	COPD (n=112)	No COPD (n=199)	p-value
Age (years, SD)	69±10	68±10	0.465
Male (n %)	83 (74%)	144 (72%)	0.739
Systolic blood pressure (mmHg, SD)	138±28	135±26	0.367
Diastolic blood pressure (mmHg, SD)	83±17	80±16	0.103
Body surface area (m^2)	1.93±0.19	1.92±0.18	0.529
Previous myocardial infarction (n %)	11 (10%)	9 (5%)	0.067
Hypertension (n %)	45 (40%)	79 (40%)	0.962
Diabetes (n %)	14 (13%)	19 (10%)	0.426
Dyslipidaemia (n %)	20 (18%)	28 (14%)	0.331
Smoking (current or previous) (n %)	77 (69%)	99 (50%)	**0.001**
Culprit vessel (n %)			0.494
LAD	38 (34%)	83 (42%)	
RCA	49 (44%)	85 (43%)	
RCx	23 (21%)	29 (15%)	
Multivessel disease (n %)	61 (55%)	120 (61%)	0.292
Killip class ≥ 2 (n %)	7 (6%)	11 (6%)	0.779
eGFR (ml/min/1,73m^2)	83±26	83±26	0.902
Peak CK (U/l)	1315 [627 – 2061]	1116 [602 - 2074]	0.438
Peak cTnT (ug/l)	3.17 [1.49 – 6.42]	3.12 [1.39 – 5.57]	0.621
Medication at discharge (n=317):			
Aspirin (n %)	106 (98)	192 (98)	1.000
Thienopyridines (n %)	107 (99)	192 (99)	1.000
B-blockers (n %)	97 (90)	183 (93)	0.272
ACEi/ARB (n %)	105 (97)	189 (96)	1.000
Statin (n %)	108 (100)	194 (99)	0.540

Bold values represent significant p-values (<0.05). ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CK, creatine kinase; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; LAD, left anterior descending; RCA, right coronary artery; RCx, ramus circumflexus.

Echocardiographic characteristics

Table 2 displays the echocardiographic characteristics of the two groups. LVEF was relatively preserved in the total population (mean 47±8%). As per design of the study, there were no differences in left ventricular volumes and function. Regarding RV dimensions, patients with COPD had a slightly larger diameter of the proximal RVOT (34±5.2 vs. 33±4.4 mm,

for COPD and non-COPD patients respectively, p=0.039). On the contrary, longitudinal diameter was significantly smaller in COPD patients compared to the matched controls (74±10.4 vs. 78±7.7 mm, p<0.001). Patients with COPD had higher SPAP as compared to their counterparts (31±8 vs. 28±8 mmHg, p = 0.028; analysis only feasible in 246 patients due to unavailable IVC images or absence of tricuspid regurgitation).

Table 2. Baseline echocardiographic measurements of patients with and without COPD

Echocardiographic parameters	COPD (n=112)	No COPD (n=199)	p-value
LVEDV (mL)	100±40	100±32	0.985
LVESV (mL)	53±26	54±21	0.680
LVEF (%)	47±8	47±8	0.740
LV mass index (g/m²)	104±30	108±33	0.297
E/e' ratio	13.3 [10.6 – 17.9]	12.6 [9.5 – 16.9]	0.163
Moderate or severe MR (n %)	9 (8)	22 (11)	0.421
RVOT diameter proximal (mm)	34±5.2	33±4.4	**0.039**
RV diameter basal (mm)	43±7.8	42±6.5	0.780
RV diameter mid (mm)	27±6.1	27±6.4	0.971
RV diameter longitudinal (mm)	74±10.4	78±7.7	**<0.001**
RA area (cm²)	14.2±4.4	14.1±3.9	0.816
Moderate or severe TR (n %)	10 (9%)	17 (9%)	0.910
SPAP (mmHg) (n=246)	31±8	28±8	**0.028**
TAPSE (mm)	17.9±3.8	18.1±3.8	0.718
S' (cm/s) (n=228)	8.5±2.2	8.4±2.2	0.605
RV FAC (%)	38±11	40±9	**0.038**
RV FWSL (%) (n=286)	-21.1±6.6	-23.4±6.5	**0.005**

Bold values represent significant p-values (<0.05). FAC, fractional area change; FWSL, longitudinal free wall strain; LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; RA, right atrial; RV, right ventricular; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion.

In terms of RV function parameters, TAPSE was similar in COPD and non-COPD patients (Figure 1). Similarly, no differences in S' were observed, although this could only be measured in 228 patients due to unavailable TDI images. Interestingly, COPD patients had significantly lower RV FAC and more impaired RV FWSL, as compared to patients without COPD (38±11% vs. 40±9%, p=0.038 and -21.1±6.6% vs. -23.4±6.5%, p=0.005 for RV FAC and RV FWSL, respectively [Figure 1]).This difference in RV FWSL between COPD and non-COPD patients was predominantly present in patients with inferior infarction, defined by the right coronary artery (RCA) as culprit vessel (-19.3±6% vs. -22.4±6%; p=0.009 and -22.6±7% vs. -24.2±6%; p=0.130, for inferior and non-inferior infarction, respectively). For RV FAC, similar results were observed (34±14% vs. 39±10%; p=0.007 and 41±8% vs. 41±9%; p=0.951, for inferior and non-inferior infarction in COPD and non-COPD patients, respectively).

RV FWSL analysis in COPD patients showed a good inter- and intra-observer variability with intraclass correlation coefficients of 0.804 and 0.805, respectively.

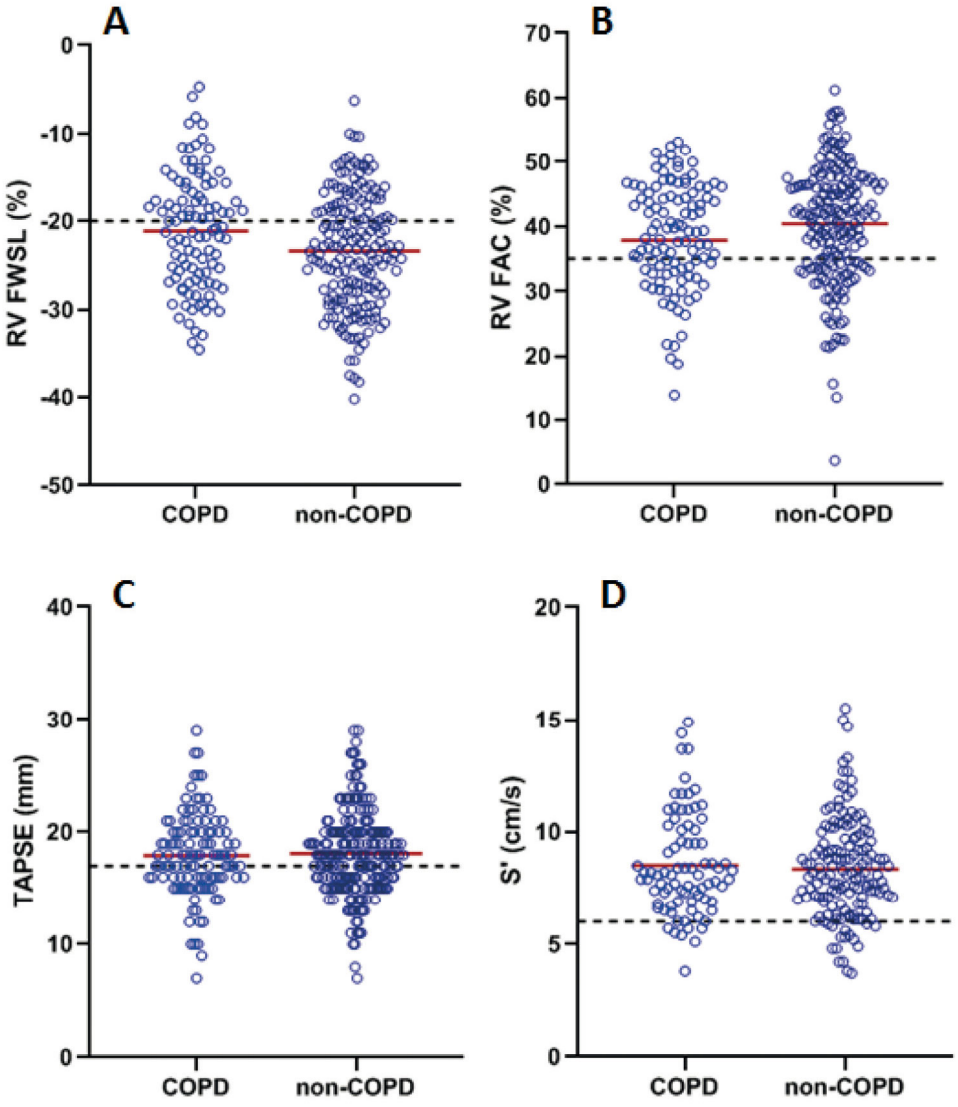

Figure 1. Differences in right ventricular (RV) systolic function after ST-segment elevation myocardial infarction between patients with (light blue) and without (dark blue) chronic obstructive pulmonary disease (COPD), either determined by RV longitudinal free wall strain (FWSL; panel **A**), fractional area change (FAC; panel **B**), tricuspid annular plane systolic excursion (TAPSE; panel **C**) or tricuspid annular systolic excursion velocity (S'; panel **D**). **Dots** represent individual patient data. The solid red line represents the **mean** value and the **cut-off** for RV dysfunction is represented by the dotted line (>-20% [less negative] for RV FWSL, <35% for RV FAC, <17 mm for TAPSE and <6 cm/s for S').

Determinants of right ventricular systolic dysfunction

Using the predefined cut-off values of RV systolic dysfunction for the different parameters, RV systolic dysfunction occurred more frequently in patients with COPD as compared to their counterparts. However, the prevalence of RV systolic dysfunction was significantly higher among COPD patients as compared to non-COPD patients when RV FWSL was considered (46% vs 32%, p=0.021)(Figure 1 and 2). This suggest that RV FWSL is a more sensitive parameter to identify patients with RV systolic dysfunction. Logistic regression analysis was performed for each RV functional parameter separately (Table 3). LVEF and RA area were significant correlates of RV systolic dysfunction when assessed with TAPSE, whereas systolic blood pressure and infarct location (inferior) were significant determinants of RV systolic dysfunction using RV FAC. An impaired S' seemed to be associated mostly with right sided dimensions (RA area, RV basal- and longitudinal diameter) although these parameters were no longer statistically significant in multivariate analysis. Finally, COPD was only significantly associated with RV systolic dysfunction when defined by RV FWSL (odds ratio 1.83, 95% CI 1.01 – 3.31, p=0.047).

Table 3. Determinants of right venticular dysfunction as defined by TAPSE (<17 mm), RV FAC (<35%), S' (<6 cm/s) or RV FWSL (>-20%)

	TAPSE			RV FAC		
Variable*	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Age (years)	0.99	0.97 – 1.03	0.806	-	-	-
COPD, yes/no	1.04	0.58 – 1.84	0.905	1.16	0.63 – 2.12	0.640
Previous myocardial infarction, yes/no	3.13	0.90 – 10.93	0.074	-	-	-
Multivessel disease, yes/no	1.54	0.87 – 2.71	0.135	-	-	-
Body surface area (m^2)	0.59	0.12 – 3.03	0.430	-	-	-
eGFR (ml/min/1,73m^2)	0.99	0.98 – 1.00	0.065	-	-	-
LVEF (%)	**0.96**	**0.93 – 0.99**	**0.013**	-	-	-
MR grade ≥ 2, yes/no	1.83	0.79 – 4.28	0.161	-	-	-
TR grade ≥ 2, yes/no	1.76	0.69 – 4.49	0.240	-	-	-
RA area (cm^2)	**0.92**	**0.85 – 1.00**	**0.039**	1.02	0.95 – 1.10	0.545
RVOT proximal diameter (mm)	-	-	-	1.03	0.96 – 1.10	0.423
Peak cTnT (ug/l)	-	-	-	1.05	0.98 – 1.13	0.164
Gender (female), yes/no	-	-	-	0.47	0.21 – 1.06	0.070
RCA as culprit vessel, yes/no	-	-	-	**2.12**	**1.16 – 3.86**	**0.014**
SBP (mmHg)	-	-	-	**0.98**	**0.96 – 0.99**	**0.010**
DBP (mmHg)	-	-	-	1.02	0.99 - 1.05	0.254
Killip class ≥ 2, yes/no	-	-	-	-	-	-
E/e' ratio	-	-	-	-	-	-
RV longitudinal diameter (mm)	-	-	-	-	-	-
RV basal diameter (mm)	-	-	-	-	-	-

		S'		RV FWSL		
Variable*	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Age (years)	-	-	-	**1.05**	**1.01 - 1.09**	**0.012**
COPD, yes/no	0.72	0.25 – 2.07	0.545	**1.83**	**1.01 – 3.31**	**0.047**
Previous myocardial infarction, yes/no	-	-	-	-	-	-
Multivessel disease, yes/no	-	-	-	-	-	-
Body surface area (m^2)	-	-	-	2.24	0.37 - 13.43	0.379
eGFR (ml/min/1,73m^2)	-	-	-	-	-	-
LVEF (%)	-	-	-	-	-	-
MR grade ≥ 2, yes/no	2.76	0.81 – 9.49	0.106	-	-	-
TR grade ≥ 2, yes/no	2.53	0.68 – 9.40	0.166	-	-	-
RA area (cm^2)	1.01	0.85 – 1.19	0.937	1.00	0.92 – 1.08	0.969
RVOT proximal diameter (mm)	-	-	-	1.06	0.99 – 1.13	0.094
Peak cTnT (ug/l)	-	-	-	1.05	0.97 – 1.13	0.256
Gender (female), yes/no	-	-	-	-	-	-
RCA as culprit vessel, yes/no	-	-	-	-	-	-
SBP (mmHg)	-	-	-	-	-	-
DBP (mmHg)	1.03	0.99 – 1.06	0.091	-	-	-
Killip class ≥ 2, yes/no	-	-	-	1.54	0.48 – 5.00	0.469
E/e' ratio	-	-	-	1.02	0.95 – 1.09	0.633
RV longitudinal diameter (mm)	1.00	0.95 – 1.07	0.922	-	-	-
RV basal diameter (mm)	1.03	0.95 – 1.12	0.502	-	-	-

*Variables with a p-value <0.20 in univariate analysis were introduced into a multivariate model. Bold values represent significant p-values (<0.05). COPD, chronic obstructive pulmonary disease; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RA, right atrium; RCA, right coronary artery; RV, right ventricular; RV FAC, right ventricular fractional area change; RV FWSL, right ventricular longitudinal free wall strain; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

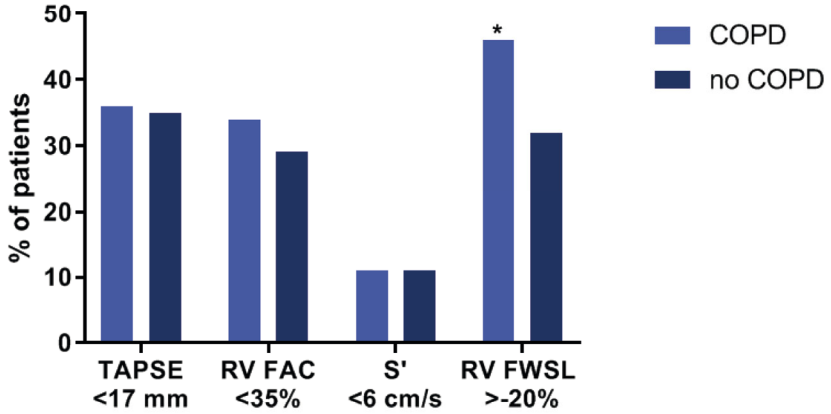

Figure 2. Bar charts illustrating the percentage of STEMI patients with and without COPD with right ventricular (RV) dysfunction defined by different echocardiographic parameters (TAPSE <17 mm, RV FAC <35%, S'< 6 cm/s and RV FWSL >-20%). *Indicates p<0.05 compared to patients without COPD. Abbreviations: COPD, chronic obstructive pulmonary disease; RV FAC, right ventricular fractional area change; RV FWSL, right ventricular longitudinal free wall strain; STEMI, ST-segment elevation myocardial infarction; TAPSE, tricuspid annular plane systolic excursion.

RV systolic dysfunction and clinical outcome

During 5 years of follow-up, 49 patients died (16%) with a median follow-up of 30 months (IQR 1.5 – 44 months). Separate Kaplan-Meier curves for COPD and non-COPD patients with the groups divided by the presence of RV dysfunction (as defined by the before mentioned cut-offs) are shown in Figure 3. For both COPD and non-COPD patients the cumulative survival rates for patients with RV FWSL >-20% were significantly lower, although markedly worse in COPD patients (5-year survival rates 69% and 78% for COPD and non-COPD patients, respectively). In univariate analysis, S'<6 cm/s was associated with increased 5-year all-cause mortality only in COPD patients (Figure 3D).

To determine which RV functional parameter has the best predictive value for mortality, separate multivariate models were created and stratified for COPD status. In univariate analysis, TAPSE and RV FWSL as continuous variable were both significantly associated with all-cause mortality (HR 0.91, 95%CI 0.83 – 0.98, p=0.018 and HR 1.07, 95% CI 1.03 – 1.12, p=0.002, for TAPSE and RV FWSL, respectively), whereas RV FAC and S' were not (HR 0.99, 95% CI 0.97 – 1.02, p=0.542 and HR 1.03, 95% CI 0.88 – 1.20, p=0.719, for RV FAC and S', respectively). Using the predefined cut-off values for RV systolic dysfunction, only RV FWSL was significantly associated with all-cause mortality in univariate analysis (HR 2.75, 95% CI 1.52 – 5.00, p=0.001).

Table 4. Cox regression multivariate analysis for all-cause mortality at 5 years follow-up, stratified for COPD status.

	Model 1			Model 2		
Variable	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age, per 1 year	**1.10**	**1.06 – 1.14**	**<0.001**	**1.10**	**1.06 – 1.14**	**<0.001**
Diabetes, yes/no	1.95	0.94 – 4.05	0.072	1.95	0.91 – 4.19	0.086
LVEF, per 1%	0.98	0.94 – 1.01	0.228	0.98	0.94 – 1.02	0.284
Peak cTnT, per 1 unit	1.04	0.97 – 1.11	0.302	1.03	0.95 – 1.10	0.486
TAPSE <17 mm, yes/no	1.13	0.63 – 2.06	0.682			
RV FAC <35%, yes/no	-	-	-	1.41	0.77 - 2.57	0.268
S' <6 cm/s, yes/no	-	-	-	-	-	-
RV FWSL >-20%, yes/no	-	-	-	-	-	-
Δ chi-square		0.167	0.683*		1.193	0.275*
	Model 3			**Model 4**		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age, per 1 year	**1.09**	**1.04 – 1.14**	**<0.001**	**1.10**	**1.06 -1.15**	**<0.001**
Diabetes, yes/no	1.73	0.71 – 4.21	0.228	1.62	0.73 – 3.59	0.234
LVEF, per 1%	0.95	0.91 – 1.00	0.048	0.99	0.95 - 1.03	0.630
Peak cTnT, per 1 unit	1.06	0.98 – 1.15	0.171	1.04	0.96 – 1.11	0.353
TAPSE <17 mm, yes/no	-	-	-	-	-	-
RV FAC <35%, yes/no	-	-	-	-	-	-
S' <6 cm/s, yes/no	1.63	0.66 – 4 05	0.289	-	-	-
RV FWSL >-20%, yes/no	-	-	-	**2.05**	**1.12 – 3.76**	**0.020**
Δ chi-square		1.020	0.313		5.508	**0.019***

*p-value reflecting the change in chi-square compared to the baseline model (including age, diabetes, LVEF and peak cTnT level). Bold values represent significant p-values (<0.05). COPD, chronic obstructive pulmonary disease; FAC, fractional area change; FWSL, longitudinal free wall strain; LVEF, left ventricular ejection fraction; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

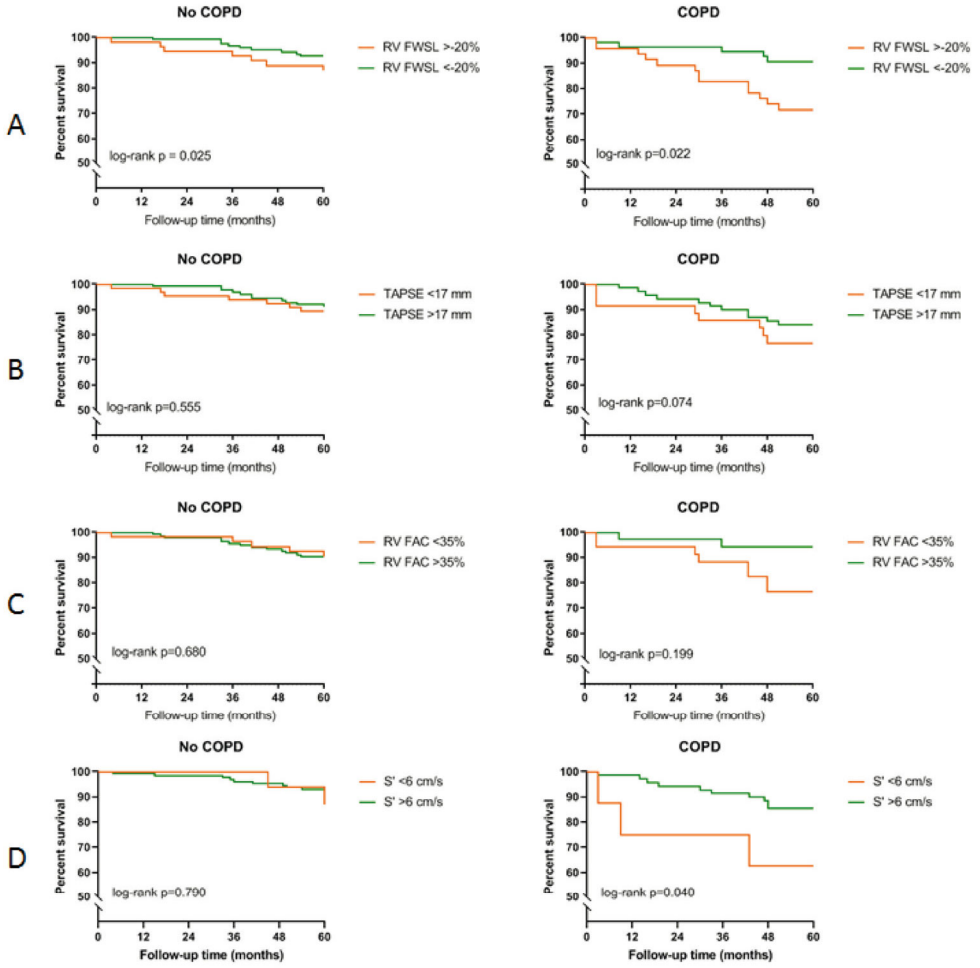

Figure 3. Kaplan-Meier estimates for 5 year all-cause mortality. Separate analysis were performed for patients with (n=112; right panel) and without (n=199; left panel) chronic obstructive pulmonary disease (COPD). Cumulative event rates were compared between patients with (red line) and without (green line) right ventricular (RV) dysfunction as defined by RV longitudinal free wall strain (FWSL) >-20% (A), tricuspid annular plane systolic excursion (TAPSE) <17 mm (B), fractional area change (FAC) <35% (C) or tricuspid annular systolic excursion velocity (S') <6 cm/s (D).

When correcting for age, diabetes, peak troponin level and LVEF, neither TAPSE <17 mm nor RV FAC <35% nor S' <6 cm/s were independently associated with 5-year all-cause mortality in multivariate analysis (Table 4). In contrast, RV FWSL >-20% (less negative) was independently associated with all-cause mortality (HR 2.05, 95% CI 1.12 – 3.76, p=0.020). Finally, when adding RV FWSL>-20% to the baseline model, a significant change in chi-square (p=0.015) was observed suggesting that RV FWSL provides incremental prognostic value to the baseline model (Table 4).

Discussion

This study shows for the first time that STEMI patients with COPD had a significantly worse RV systolic function when assessed with FAC or RV FWSL than when assessed with TAPSE or S'. Furthermore, STEMI patients with COPD had significantly more often RV dysfunction, defined by RV FWSL >-20% (less negative). Additionally, RV FWSL was independently associated with all-cause mortality whereas conventional parameters for RV systolic function were not.

RV systolic dysfunction after STEMI

The importance of RV systolic function assessment after STEMI has been emphasized in previous studies including a majority of patients with inferior infarction.[5, 6, 10] The rate of RV systolic dysfunction after STEMI in previous literature ranges from 5% up to 32%, depending on the echocardiographic parameter used.[10, 18] In our study, >30% of patients had RV systolic dysfunction, either determined by TAPSE, FAC or RV FWSL. The percentage of patients with RV systolic dysfunction was higher in COPD patients for these parameters. The rate of RV dysfunction determined by S' was markedly lower and similar for both patient groups. This could in part be explained by the lower number of patients in which assessment was feasible. Furthermore, the most reliable and robust data on S' is known from pulsed TDI, which was not available in the present study. For offline analysis by color-coded TDI, less data is available with wider confidence intervals for normality.[9] In addition, S' analysis assumes that evaluation of the tricuspid annulus represents the function of the RV as a whole, which might not be the case in myocardial infarction.

Assessment of RV function in patients with COPD using 2D echocardiography has been performed in several studies consisting of small study populations.[3, 19-22] In general, when COPD patients are compared to patients without COPD, RV function is more impaired in COPD patients and this is correlated with the presence of pulmonary hypertension and COPD severity.[3, 21] Nonetheless, RV remodelling and functional impairment has shown to be present even in patients with mild stages of COPD.[3, 22] Few studies considering RV systolic dysfunction in STEMI populations, have either mentioned COPD as comorbidity or excluded COPD patients.[6, 23] Studies focusing on a relationship between COPD and RV systolic dysfunction during or after STEMI are lacking. In the present study, COPD patients exhibit worse RV systolic function compared to non-COPD patients although this was not detected by measuring TAPSE or S'. Although the average RV FWSL for both COPD and non-COPD patients is still within normal range as defined by current literature, there is a notable difference with healthy subjects aged >60 years old as recently described by Park et al.[17] Interestingly, the difference in RV systolic function was mainly present in patients with inferior infarction. A possible explanation for this observation, is that COPD patients are more prone to develop RV dysfunction after inferior infarction, i.e. have less contractile reserve when RV ischemia occurs. The absence of a significant difference in RV systolic

function between COPD and non-COPD patients with non-inferior infarction supports this hypothesis, despite the absence of data on RV remodelling prior to the STEMI in our COPD patients. From a clinical point of view, in patients with COPD and inferior infarction more awareness could be raised towards assessment of RV systolic function shortly after STEMI. The presented data raise the need for further research on this subject, in order to elucidate the impact of COPD on cardiac function after STEMI.

Prognostic implications of RV systolic function

Previous studies have demonstrated the prognostic implications of RV systolic function in patients with acute myocardial infarction.[10, 24, 25] The most recent study by Park et al. assessed RV systolic function in 282 patients with inferior infarction (culprit vessel RCA), using various echocardiographic parameters (RVFAC, TAPSE and RV global longitudinal strain [GLS]).[10] RV GLS was independently associated with major adverse cardiac events at long term follow-up (HR 1.149, 95% CI 1.052-1.225; p=0.002), whereas TAPSE and RVFAC were not.[10] In the present study we confirmed the independent prognostic value of RV FWSL in COPD patients. Additionally, in agreement with the results from Park et al.[10] FAC and TAPSE were not significantly associated with mortality. RV dysfunction in patients with COPD without overt cardiovascular disease has also been associated with increased mortality and decreased functional capacity.[21, 26, 27] The results of the present study indicate that RV FWSL might be the parameter most suitable for risk stratification in STEMI patients with COPD.

Study limitations

This study is limited by the retrospective, single centre design. As a consequence, pulmonary function tests were not available for all patients and COPD diagnosis was based on thorough chart review. Due to the retrospective nature of the study, we were unable to provide information on RV function prior to the infarction, since echocardiograms were not available in our tertiary care center prior to the index event in the majority of the patients included in this study. Also, dedicated image acquisition for RV function analysis was not performed, resulting in the absence of pulsed-wave TDI of the RV. Therefore, S' was assessed offline using color-coded TDI which was available for more than two-thirds of the patients. Furthermore, for RV function analysis we used the reference value for RV FWSL as stated in de current guidelines.[8] Unfortunately, we do not have 3D echocardiography nor CMR data for validation. Since this is a retrospective study, power analysis was not performed in advance. Post-hoc power analysis for the Cox regression analysis demonstrated insufficient power to determine the prognostic value of impaired TAPSE or S'. However, for both RV FAC and RV FWSL sufficient power was established. Finally, data on RV infarction diagnosed by right precordial lead electrocardiography was not available and distinction between inferior and non-inferior infarction was solely based on the angiographic culprit vessel.

Conclusion

In summary, in a STEMI population with relatively preserved left ventricular function, patients with COPD exhibit more impaired RV FWSL when compared to patients without COPD. Additionally, the presence of COPD was independently associated with RV dysfunction (defined by RV FWSL >-20% [less negative]). Finally, this study confirms the prognostic value of RV FWSL in STEMI patients over conventional echocardiographic parameters for RV function, even after correction for the presence of COPD. Therefore, RV FWSL might be the most suitable echocardiographic parameter to quantify RV systolic function after STEMI in patients with COPD.

Conflicts of interest

The Department of Cardiology of the Leiden University Medical Centre received grants from Biotronik, Medtronic, Boston Scientific Corporation, GE Healthcare and Edwards Lifesciences. Victoria Delgado received speaker fees from Abbott Vascular.

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