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FULL RESEARCH PAPER
Diabetes and metabolic disorders

Pulmonary hypertension during exercise underlies unexplained exertional dyspnoea in patients with Type 2 diabetes

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Aims To compare the cardiac function and pulmonary vascular function during exercise between dyspnoeic and non-dyspnoeic patients with Type 2 diabetes mellitus (T2DM).

Methods and results Forty-seven T2DM patients with unexplained dyspnoea and 50 asymptomatic T2DM patients underwent exercise echocardiography combined with ergospirometry. Left ventricular (LV) function [stroke volume, cardiac output (CO), LV ejection fraction, systolic annular velocity (s′)], estimated LV filling pressures (E/e′), mean pulmonary arterial pressures (mPAPs) and mPAP/COslope were assessed at rest, low- and high-intensity exercise with colloid contrast. Groups had similar patient characteristics, glycemic control, stroke volume, CO, LV ejection fraction, and E/e′ ($P > 0.05$). The dyspnoeic group had significantly lower systolic LV reserve at peak exercise (s′) ($P = 0.021$) with a significant interaction effect ($P < 0.001$). The dyspnoeic group also had significantly higher mPAP and mPAP/CO at rest and exercise ($P < 0.001$) with significant interaction for mPAP ($P < 0.009$) and insignificant for mPAP/CO ($P = 0.385$). There was no significant difference in mPAP/COslope between groups ($P = 0.706$). However, about 61% of dyspnoeic vs. 30% of non-dyspnoeic group had mPAP/COslope > 3 ($P = 0.009$). The mPAP/COslope negatively predicted $\dot{V}O_{2peak}$ in dyspneic group ($\beta = -1.86$, 95% CI: −2.75, −0.98; multivariate model R^2:0.54).

Conclusion Pulmonary hypertension and less LV systolic reserve detected by exercise echocardiography with colloid contrast underlie unexplained exertional dyspnoea and reduced exercise capacity in T2DM.

Keywords Diabetes • Heart • Echocardiography • Shortness of breath • Pulmonary arterial pressure

Introduction

Exertional dyspnoea is a typical symptom of heart failure (HF). It is commonly observed in Type 2 diabetes mellitus (T2DM) [OR: 3.92 (95% CI: 3.28–4.68; $P < 0.001$),[1] and it reflects altered hemodynamics and pulmonary abnormalities during exercise.[2] Considering that patients with T2DM have a two-fold higher risk of developing coronary heart disease than healthy adults[3,4] and up to four-fold higher mortality risk than HF patients without T2DM,[3,4] it is important to investigate the underlying causes of dyspnoea in T2DM.

Cardiac dysfunction and pulmonary vascular dysfunction occur across the spectrum of severity in T2DM. Diastolic dysfunction relates to the duration and severity of T2DM, worsens during exercise,[5–8] and is characterized by adverse myocardial remodelling.[9,10]

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In addition, exercise testing improves the sensitivity of detecting diastolic dysfunction.[6,11–13] However, the sensitivity of detecting early cardiac dysfunction via diastolic dysfunction is questionable,[14] considering that diastolic dysfunction becomes evident mostly after prolonged or complicated T2DM.[8,9] On the other hand, systolic dysfunction has been recorded in asymptomatic patients with T2DM via impaired global longitudinal strain.[15] Finally, an impaired pulmonary vascular response to exercise was shown in patients with early T2DM without resting systolic and diastolic dysfunction and perfusion defects.[16] However, the invasiveness of evaluating pulmonary vascular response has confined the use of this method.

In recent years, it was shown that pulmonary vascular function can be evaluated non-invasively by exercise echocardiography with colloid contrast.[17] The invasively measured pulmonary pressures during exercise correlate excellently with pulmonary artery wedge pressure, which helps accurately discriminate HF with preserved ejection fraction from the non-cardiac dyspnoea.[18] When a good tricuspid regurgitation velocity (TRV) signal is obtained with colloid contrast, the slope of the mean pulmonary arterial pressure (MPAP) to cardiac output (CO) (PAP/COslope) estimated by exercise echocardiography correlates well with invasively measured mPAP/COslope.[17] It remains unknown, however, whether the non-invasive evaluation of pulmonary vascular function via exercise echocardiography with colloid contrast uncovers the cause of dyspnoea in T2DM.

Therefore, the purpose of this study is to compare the cardiac function and pulmonary vascular function at rest and exercise between T2DM patients with and without unexplained exertional dyspnoea. We hypothesize that the dyspnoeic group of T2DM has a worse cardiac function and pulmonary vascular function than the non-dyspnoeic group.

Methods

Study design and subjects

We retrospectively evaluated exercise echocardiographic assessments of 47 ambulatory T2DM patients referred to the Jessa Hospital (Hasselt, Belgium) due to unexplained exertional dyspnoea. The control group consisted of 50 patients with T2DM without exertional dyspnoea or symptoms of cardiac dysfunction who participated in our group's previous study (NCT03299790). A diagnosis of T2DM was based on medical history. The exclusion criteria were as follows: T2DM, pulmonary disease, oncological disorders, cardiovascular disorders or health problems such as congenital heart disease, history of coronary revascularization, valve diseases, HF, and arrhythmias. This study was approved by the Ethical Committee of Jessa hospital.

Blood parameters

Medical records were screened for recent (<10 weeks prior and after the echocardiographic assessment) analyses of glycated haemoglobin A1c (HbA1c), lipid profile (total cholesterol, HDL- and LDL-cholesterol and triglycerides), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.

Exercise echocardiography combined with ergospirometry

Echocardiographic assessments were carried out by cardiologists (J.V. and S.J.) with a phased array probe (Vivid E90 and GE M5S 1.5-4.5 MHz, GE Health Medical, Milwaukee, Wisconsin, USA).[19] Cardiac function was evaluated in the apical two-, four- and five-chamber view (AP2C, AP4C, AP5C) and the apical long-axis view. Images of at least three cardiac cycles for each measure were digitally stored in a cine-loop format and analyzed in EchoPAC software v201 (General Electric Vingmed, Horten, Norway). Diastolic function was evaluated as recommended by Lancellotti *et al.*,[13] including mitral inflow pattern with early (E) and late (A) diastolic flow, using pulsed-wave Doppler at the tips of mitral leaflets and pulsed-wave tissue Doppler imaging (TDI) to determine early diastolic velocity (e′) at the septal annulus and consequently E/e′ as an estimation of LV filling pressure. TDI was used to evaluate peak systolic annular velocity (s′) of the LV. The LV ejection fraction (LVEF) was calculated from the end-systolic and end-diastolic volumes using Simpson's biplane method in the AP4C view.[20] The CO was evaluated using the velocity–time integral of the LV outflow tract (LVOT) via pulsed-wave Doppler, heart rate (HR), and the LVOT (outflow tract diameter determined at rest in the supine position as the cross-sectional area of the aortic valve in the parasternal long-axis in mid-systole). Maximal tricuspid regurgitation velocities (TRVs) obtained with agitated colloid contrast[17,21] were used to estimate systolic pulmonary arterial pressures (sPAPs). The mean PAP was calculated by Chemla's formula (mPAP, $mPAP = 0.61 \times sPAP + 2$).[22]

Ergospirometry was used for the evaluation of respiratory exchange ratio (RER) and oxygen uptake ($\dot{V}O_2$) (CS-200 Ergo-Spiro, Schiller AG, Switzerland). An intended duration of an incremental ramp protocol (0 W + 1-30 W/min, 60–65 revolutions/min) on a semi-supine bicycle was 10 min (Ergocouch erg 911 LS, Ergosana, Rotterdam, The Netherlands). The echocardiographic assessment was carried out at rest, low-intensity (HR <80–100 b.p.m., before fusion of E and A[13]) and high-intensity exercise (RER of 1.03–1.05). Blood pressure and heart function were continuously monitored via sphygmomanometer and a 12-lead ECG (Omron®, Omron Healthcare, IL, USA; and CardioSoft v6.7, Acertys, Aartselaar, Belgium).

Statistical analyses

We used SPSS V.24 and 28 (IBM SPSS Statistics for Windows, Chicago, IL, USA). Data were reported as either mean ± standard deviation (SD) or median (interquartile range). Normality was tested with the Shapiro–Wilk test. Descriptive statistics included independent sample *t*-tests, Mann–Whitney *U*-test and analysis of covariance (ANCOVA) with gender and beta-blockers as covariates where needed. Differences in proportions between groups were evaluated using the χ^2 test (or Fisher's exact test). Pearson (r) or Spearman correlations (ρ) were used for detecting associations between cardiac function and exercise capacity. Two-way mixed analyses of variance were used for the detection of mean differences and interaction effects of cardiac and pulmonary vascular function during different exercise stages. Box's test and Mauchly's test of sphericity were carried out and corrections applied when necessary (Huynh–Feldt or Greenhouse–Geisser). Two-way mixed ANCOVA with gender and beta-blockers as covariates were carried out when appropriate. Multiple regression analyses (backward elimination) were performed to investigate the influence of cardiac function on exercise capacity. A two-tailed P-value < 0.05 was statistically significant. Data were analyzed per protocol.

Results

Patient characteristics

Ninety-seven T2DM patients (50 asymptomatic, 47 with dyspnoea) were included (*Figure 1*). The dyspnoeic group of patients consisted of more women (53% vs. 18%, $P < 0.001$) and had a lower body mass

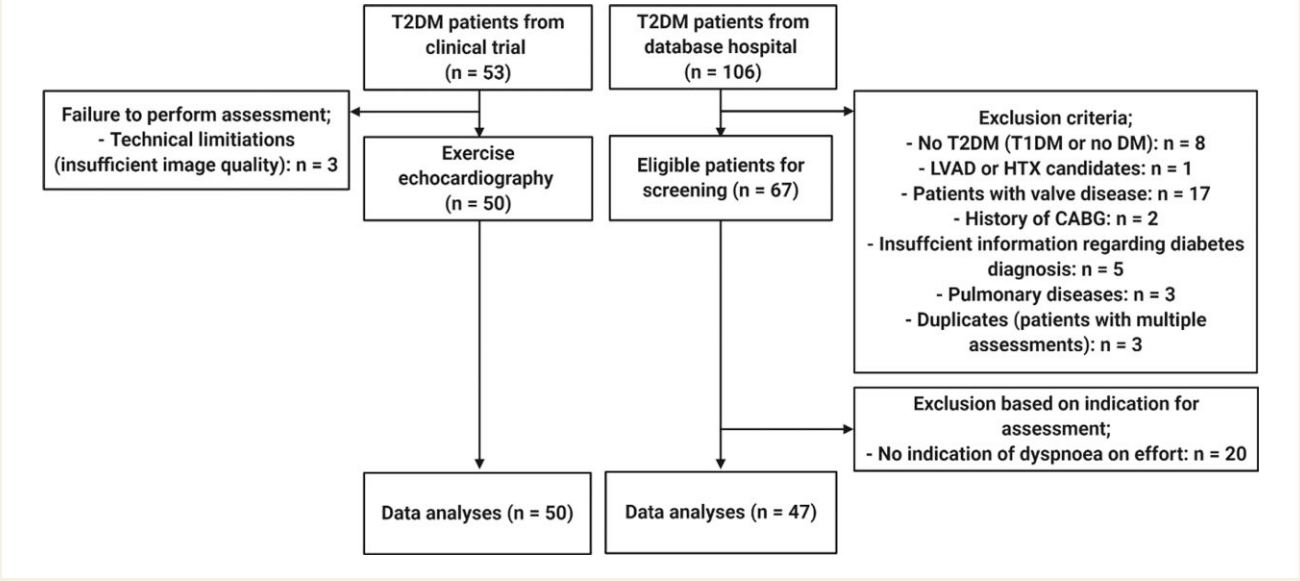


Figure 1 Flowchart. T2DM, Type 2 diabetes mellitus; T1DM, Type 1 diabetes mellitus; DM, diabetes mellitus; LVAD, left ventricular assist device; HTX, heart transplantation; CABG, coronary artery bypass grafting.

than the non-dyspnoeic group (80 kg vs. 85 kg, $P = 0.048$) (*Table 1*). Groups had similar age, disease duration, body mass index, body surface area, glycaemic control, and lipid profile ($P > 0.05$). Plasma levels of NT-proBNP were significantly higher in the dyspnoeic group ($P = 0.004$, *Table 2*).

Cardiac function

Stroke volume (SV), CO, LVEF, early mitral inflow (E), and LV filling pressures (E/e′) were similar between groups at rest and during exercise (*Table 3*, $P > 0.05$). The systolic LV reserve at peak exercise (s′) was significantly lower in the dyspnoeic group ($P = 0.021$) and the interaction effect was significant ($P < 0.001$). The mPAP was higher at all stages in the dyspnoeic group [16 (5) vs. 13 (4) mmHg at rest, 26 (9) vs. 20 (6) mmHg during low-intensity exercise, and 33 (9) vs. 25 (5) mmHg during high-intensity exercise; $P < 0.001$] with a significant interaction effect ($P = 0.009$). The mPAP/CO was higher at all stages of evaluation in the dyspnoeic group [3.3 (1.5) vs. 2.4(1.1) mmHg/L/min at rest, 3.5 (1.4) vs. 2.4 (1.2) mmHg/L/min at low-intensity exercise, and 3.4 (1.2) vs. 2.5 (1) mmHg/L/min at high-intensity exercise; $P < 0.015$]. Finally, the mPAP/COslope did not significantly differ between groups [3.3 (1.8) vs. 2.3 (1.5) mmHg/L/min, $P = 0.706$]. However, 61% of the dyspnoeic vs. 31% of the non-dyspnoeic group had mPAP/COslope > 3 mmHg/L/min ($P = 0.049$).

Exercise capacity

Peak oxygen uptake was significantly lower in the dyspnoeic group ($\dot{V}O_{2peak}$, 14 (5.4) mL/kg/min vs. 17.7 (6.9) mL/kg/min, $P = 0.042$, *Table 4*), as well as peak work rate (W_{peak}, 75 ± 29 W vs. 113 ± 32 W, $P < 0.001$). The RER and VE/VCO_2 slope were significantly higher in dyspnoeic group [RER: 1.10 (0.1) vs. 1.06 (0.07), $P < 0.001$; and VE/VCO_2 slope: 30.5 (6.4) vs. 26.8 (4.5), $P < 0.001$].

Correlations and regression

The following cardiac parameters correlated significantly with exercise capacity ($\dot{V}O_{2peak}$, mL/kg/min) in the dyspneic group: E/e′ at rest and high-intensity exercise ($\rho = -0.408$ and $\rho = -0.483$, $P = 0.004$ and $P = 0.001$), E at rest ($\rho = -0.346$, $P = 0.017$), e′ and s'_s at high-intensity ($r = 0.493$ and $\rho = 0.426$, $P = 0.001$ and $P = 0.003$), CO at high-intensity exercise ($r = 0.511$, $P < 0.001$), mPAP/COslope ($\rho = -0.465$, $P < 0.001$), and maximal HR ($r = 0.516$, $P < 0.001$). Multiple regression analysis was carried out for the dyspnoeic group (including E at rest, E/e′ at rest and high-intensity, CO, mPAP and s′ at high-intensity exercise, and mPAP/COslope). The analysis showed that 50.4% of the variance in $\dot{V}O_{2peak}$ (mL/kg/min) could be attributed to E/e′ and mPAP at high-intensity exercise and mPAP/COslope [$F(3,40) = 15.56$, $P < 0.001$, *Table 5*]. The e′ values were eliminated due to collinearity. Linear regression revealed that the variance was mainly explained by E/e′ and mPAP/COslope ($R^2 = 24.6\%$ and $R^2 = 23.8\%$, $P < 0.001$).

Discussion

The main findings of this study were lower $\dot{V}O_{2peak}$, higher mPAP/CO and a lower s′ during peak exercise in dyspneic than in the non-dyspnoeic group of T2DM. This indicates a higher prevalence of cardiac and pulmonary vascular dysfunction during exercise and lower aerobic fitness in the dyspneic group of T2DM. Finally, this highlights the use of combined exercise echocardiography with colloid contrast and ergospirometry for detecting cardiac and pulmonary vascular dysfunction and exercise intolerance in T2DM patients with unexplained exertional dyspnoea.

The 2021 ESC guidelines suggest basing a diagnosis of HFpEF on signs or symptoms, LVEF > 50% and cardiac structural and functional abnormalities consistent with LV diastolic dysfunction or raised LV

Table 1 Baseline characteristics

	n	Non-dyspnoeic patients (n = 50)	n	Dyspnoeic patients (n = 47)	P-value
Demographics					
Age (years)	50	70 (18)	47	72 (17)	0.485
Male [n (%)]	50	41 (82)	47	22 (47)	**<0.001***
Body length (cm)	50	175 ± 8	47	167 ± 8	0.070
Body mass (kg)	50	85 (22)	47	80 (18)	**0.048***
BMI (kg/m^2)	50	28.6 ± 4.3	47	29.2 ± 5.1	0.514
BSA (m^2)	50	1.9 (0.3)	47	1.9 (0.3)	0.517
Disease duration (years)	47	8 (7)	28	9 (19)	0.374
Smoking [n (%)]	44	5 (11.4]	41	7 (17.1)	0.450
H2FPEF score (points)	47	4 ± 2.4	50	4.3 ± 2.3	0.456
Medication use					
Statins [n (%)]	50	28 (56)	45	27 (60)	0.693
Bèta blocker [n (%)]	50	13 (26)	45	29 (64)	**<0.001***
ACE inhibitor [n (%)]	50	8 (16)	45	14 (31)	0.081
Diuretics [n (%)]	50	8 (16)	45	25 (56)	**<0.001***
Sartans [n (%)]	50	8 (16)	45	6 (13)	0.714
Calcium antagonists [n (%)]	50	9 (18)	45	11 (24)	0.442
Fibrates [n (%)]	50	3 (6)	45	0	0.244
Anticoagulation/antithrombotics [n (%)]	50	12 (24)	45	29 (64)	**<0.001***
Metformin [n (%)]	50	43 (86)	45	33 (73)	0.123
Insulin secretion stimulation drugs [n (%)]	50	13 (26)	45	12 (27)	0.941
Incretin mimetics and DPP4-inhibitors [n (%)]	50	16 (32)	45	3 (7)	**0.002***
SGLT2 inhibitors [n (%)]	50	8 (16)	45	5 (11)	0.489
Insulin therapy [n (%)]	50	11 (22)	45	15 (33)	0.216

Data are expressed as mean ± SD, as median (interquartile range) or number (percentages) as appropriate.
BMI, body mass index; BSA, body surface area; H2FPEF, Score for Heart Failure with Preserved Ejection Fraction; ACE, angiotensin-converting enzyme; SGLT2, sodium–glucose co-transporter 2.
Significant differences between groups at *$P < 0.05$.

Table 2 Blood sample analyses

	n	Non-dyspnoeic patients (n = 50)	n	Dyspnoeic patients (n = 47)	P-value
HbA1c (%)	50	6.9 ± 0.8	17	7.3 ± 0.8	0.092
Triglycerides (mg/dL)	48	124 (60)	12	189 (122)	0.074
HDL cholesterol (mg/dL)	48	49 (18)	13	43 (12)	0.164
LDL-cholesterol (mg/dL)	48	83 ± 32	13	92 ± 29	0.385
Total cholesterol (mg/dL)	48	157 ± 37	13	169 ± 33	0.277
NT-proBNP (ng/μL)	49	50 (18)	12	160 (430)	0.198

Data are expressed as mean ± SD or as median (interquartile range) as appropriate.
HbA1c, blood glycated haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Significant differences between both groups at *$P < 0.05$.

filling pressures. The thresholds for detecting cardiac and pulmonary vascular dysfunction at peak exercise are E/e′ ≥ 15, TR velocity > 3.4,[23] mPAP/COslope > 3[24] and s′ < 9.5.[25] In our study, s′ combined with mPAP/COslope seems to discriminate dyspnoeic from non-dyspnoeic patients better than E/e′ combined with either mPAP/COslope or TR velocity (*Figure 2*). About 50% of the dyspnoeic group had s′ < 9.5 and mPAP/COslope > 3 compared with only 12% of the non-dyspnoeic group ($P = 0.003$). In addition, s′ alone was significantly lower in the dyspnoeic group at peak exercise indicating worse LV filling in the dyspnoeic group. Our finding of reduced s′ in dyspnoeic patients is consistent with the previous study on dyspnoeic patients at risk of HFpEF.[25] This emphasizes the importance of evaluating LV filling pressures at peak exercise in T2DM, considering that cardiac dysfunction at rest often remains unnoticed.[26,27]

The mPAP/COslope and E/e′ were negative predictors of exercise capacity suggesting that dyspnoea might be linked to a lower left

Table 3 **Cardiac function**

	Rest					Low intensity					High intensity					*P* time	*P* interaction
	n	Non-dyspneic patients (*n* = 50)	*n*	Dyspneic patients (*n* = 47)	*P*-value	*n*	Non-dyspneic patients (*n* = 50)	*n*	Dyspneic patients (*n* = 47)	*P* value	*n*	Non-dyspneic patients (*n* = 50)	*n*	Dyspneic patients (*n* = 47)	*P* value		
SV (mL)	50	69 ± 15	47	66 ± 16	0.673	50	82 ± 17	47	79 ± 16	0.418	50	83 ± 16	47	83 ± 15	0.737	—	—
CO (L/min)	49	4.8 ± 1.3	47	4.9 ± 1.4	0.289	50	7.7 ± 1.9	47	7.6 ± 1.6	0.797	50	9.6 ± 2.9	47	9.7 ± 2.4	0.434	—	—
LVEF (%)	49	63 (16)	46	58 (18)	0.411	48	63 ± 13	45	64 ± 11	0.197	49	65 ± 13	44	66 ± 13	0.354	—	—
E (cm/s)	49	54 (21)	47	62 (30)	0.241	48	85 ± 14	47	96 ± 25	0.365	45	108 ± 19	47	117 ± 24	0.100	<0.001*	0.925
e′ (cm/s)	49	6 (2)	47	6 (3)	0.903	48	8.5 ± 2	47	8.5 ± 2.9	0.853	45	12 ± 3.2	47	10.8 ± 4	0.423	—	—
E/e′	49	12.5 (7)	47	12 (6)	0.279	48	12 (7)	47	11 (8)	0.359	44	12 (7)	47	11 (5)	0.110	0.387	0.926
s′ (cm/s)	44	5 (2)	45	5 (3)	0.999	44	8.3 ± 2.2	45	7 ± 2.4	0.2684	43	11 (5)	45	8 (4)	0.021*	<0.001*	<0.001*
mPAP (mmHg)	46	13 (4)	47	16 (5)	<0.001*	41	20 (6)	47	26 (9)	<0.001*	42	25 (5)	47	33 (9)	<0.001*	<0.001*	0.009*
mPAP/CO (mmHg/L/min)	35	2.4 (1.1)	46	3.3 (1.5)	<0.001*	31	2.4 (1.2)	46	3.5 (1.4)	0.006*	31	2.5 (1)	46	3.4 (1.2)	0.015*	0.828	0.385
mPAP/COslope (mmHg/L/min)											30	2.3 (1.5)	46	3.3 (1.8)	0.706	—	—

Data are expressed as mean ± SD, median (interquartile range) or number (percentages).

SV, stroke volume; CO, cardiac output; LVEF, left ventricular ejection fraction; E, peak velocity of early diastolic filling phase; e′, early diastolic velocity at the septal annulus; E/e′, left ventricular filling pressure; s′, peak systolic velocity at the septal annulus; mPAP, mean pulmonary artery pressure.

Significant differences between groups at *$P < 0.05$. Gender used as a covariate when necessary.

Table 4 Exercise capacity

	n	Non-dyspnoeic patients (n = 50)	n	Dyspnoeic patients (n = 47)	P-value
Rest					
HR_{rest} (b.p.m.)	49	71 ± 9	47	75 ± 17	0.039*
BPsys (mmHg)	49	146 (25)	41	143 (27)	0.722
BPdia (mmHg)	49	84 ± 10	41	78 ± 14	0.069
VT1					
HR (b.p.m.)	46	95 ± 10	45	106 ± 20	0.001*
$\dot{V}O_2$ (mL/min)	46	796 (280)	45	860 (400)	0.003*
VT2					
HR (b.p.m.)	39	126 ± 19	34	120 ± 28	0.912
$\dot{V}O_2$ (mL/min)	39	1477 ± 418	34	1049 ± 428	0.011*
High-intensity exercise					
HR_{peak} (b.p.m.)	46	126 ± 17	47	119 ± 25	0.382
BPsys (mmHg)	25	197 ± 21	28	171 ± 31	0.041*
BPdia (mmHg)	25	85 ± 13	28	78 ± 16	0.180
RER	49	1.06 (0.07)	46	1.10 (0.10)	<0.001*
W_{peak} (watt)	48	113 ± 33	47	75 ± 29	<0.001*
$\dot{V}O_{2peak}$ (mL/kg/min)	50	17.7 (6.9)	47	14 (5.4)	0.042*
$\dot{V}O_{2peak}$ (%predicted)	50	77 ± 18	42	76 ± 21	0.857
VE/VCO_2 slope	50	26.8 (4.5)	45	30.5 (6.4)	<0.001*
O_2 pulse (mL/beat)	50	10.2 (3.6)	47	8.8 (4.9)	0.305
Recovery					
HR at 1 min recovery (b.p.m.)	50	112 ± 14	39	106 ± 21	0.151

Data are expressed as mean ± SD, median (interquartile range) or number (percentages).
HR, heart rate; BP, blood pressure; VT1, first ventilatory threshold; VO_2, oxygen uptake; VT2, second ventilatory threshold; W, workload; VE, ventilation; VCO_2, carbon dioxide.
Significant differences between groups with correction for gender when needed at *$P < 0.05$.

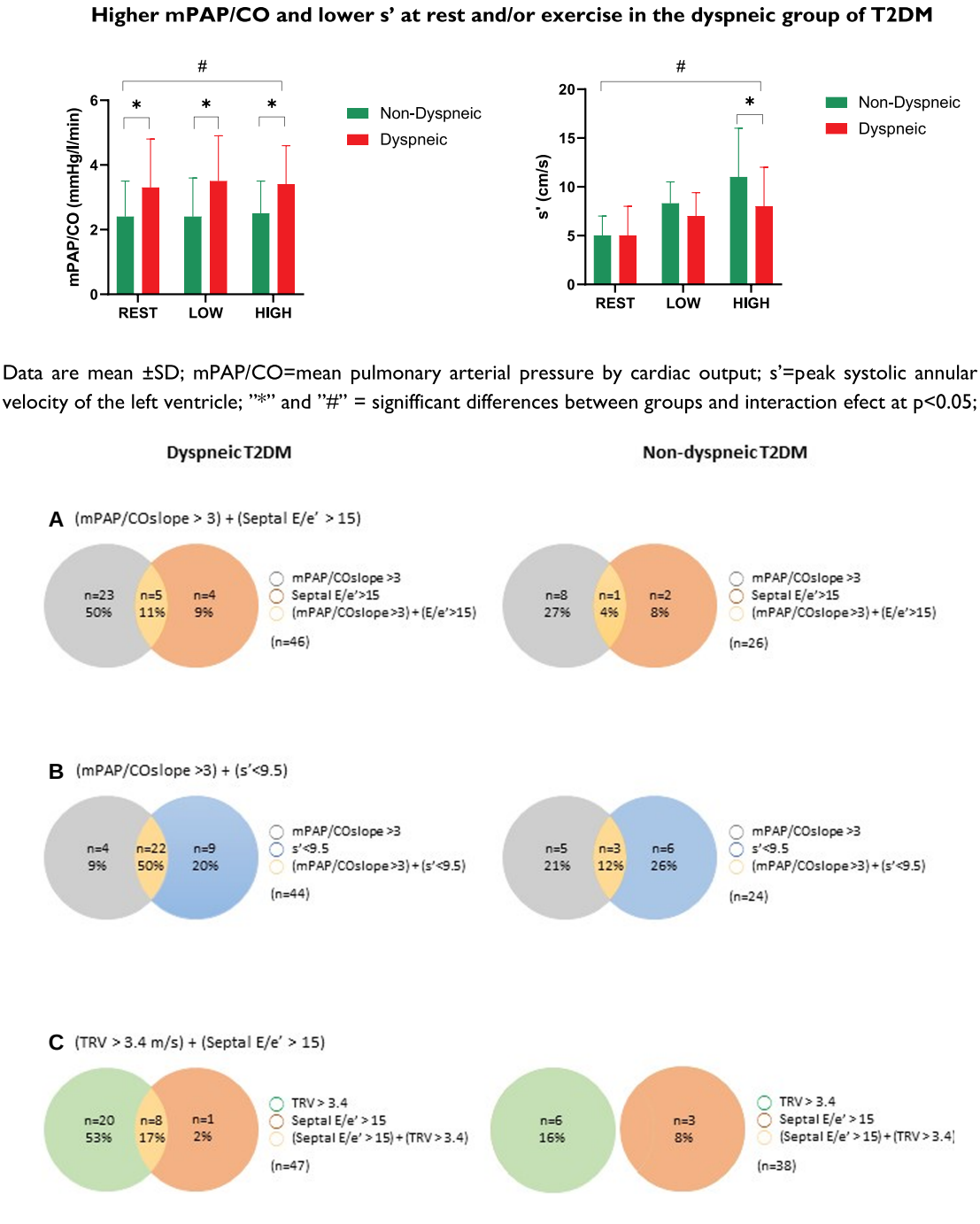
Table 5 Multiple regression analysis in dyspnoeic group of patients with T2DM

$VO_{2\ peak}$ (mL/kg/min)	B	95% CI for B		SE B	β	R^2	ΔR^2
		LL	UL				
Model							
Constant	16.34*	10.516	22.163	2.881		0.539	0.504
E/e's at high-intensity exercise	−0.551*	−0.79	−0.312	0.118	−0.559		
mPAP at high-intensity exercise	0.338**	0.112	0.564	0.112	0.427		
mPAP/COslope	−1.865*	−2.753	−0.976	0.44	−0.574		

Multiple regression model.
Model: 'Backward' method in SPSS Statistics; *B*, unstandardized regression coefficient; CI, confidence interval; LL, lower limit; UL = upper limit; SE *B*, standard error of the coefficient; β, standardized coefficient; R^2, coefficient of determination; ΔR^2, adjusted R^2.
*$P < 0.001$.
**$P < 0.05$.

ventricular (LV) and atrial compliance. Unexpectedly, there was no significant difference between groups in mPAP/COslope, despite a significant difference in mPAP/CO at rest and all stages of exercise. The lack of difference in mPAP/COslope could be explained by high between-subjects variability in both groups. This is clinically relevant as even mildly increased PAP/COslope during exercise predicts frequent hospitalizations and lower survival rates from cardiovascular events in dyspnoeic patients.[26] Evaluating mPAP/COslope, especially in dyspnoeic patients with T2DM, could have therapeutic implications. For example, SGLT2 inhibitors can acutely decrease mPAP and reduce cardiovascular mortality and hospitalizations in patients with HF.[28]

In line with previous studies,[27,29,30] aerobic fitness measured by a submaximal exercise test was reduced in both groups ($\dot{V}O_{2peak} \approx$ 77%predicted), but the dyspnoeic group had significantly worse fitness than the non-dyspnoeic group ($P = 0.042$). Moreover, a higher VE/VCO_2 slope in the dyspnoeic group suggests more ventilatory inefficiency typically seen in HF.[31] Slightly reduced aerobic fitness and



Proportions of patients in each group with combined pulmonary hypertension and/or impaired systolic and diastolic function.
mPAP/CO=mean pulmonary arterial pressure by cardiac output; s'= peak systolic annular velocity of the left ventricle; E/e' = mitral inflow pattern with the early diastolic flow by the early diastolic velocity at the septal annulus; TRV = tricuspid regurgitation velocity ($TRV = \sqrt{sPAP/4}$); Venn's diagrams=data are from high-intensity exercise;"*" and "#"=signifficant differences between groups and interaction efect at p<0.05;

Figure 2 Central illustration. Higher mPAP/CO and lower s′ at rest and/or exercise in the dyspnoeic group of T2DM. Data are mean ± SD; mPAP/CO = MPAP by CO; s′ = peak systolic annular velocity of the left ventricle; '*' and '#' = signifficant differences between groups and interaction efect at $P < 0.05$. Proportions of patients in each group with combined pulmonary hypertension and/or impaired systolic and diastolic function. mPAP/CO = MPAP by CO; s′ = peak systolic annular velocity of the left ventricle; E/e′ = mitral inflow pattern with the early diastolic flow by the early diastolic velocity at the septal annulus; TRV = tricuspid regurgitation velocity ($TRV = \sqrt{sPAP/4}$); Venn's diagrams = data are from high-intensity exercise; '*' and '#' = signifficant differences between groups and interaction efect at $P < 0.05$.

worse ventilatory efficiency pinpoint the subtlety of more pronounced cardiac dysfunction in the dyspnoeic group. The importance of significantly higher RER in the dyspnoeic group is questionable considering that no differences in the cardiac-related events exist across different peak RER subgroups in HF.[27] Although there were no differences in the HR at high-intensity exercise, a higher HR at baseline and VT1 in the dyspnoeic group might point to more cardiac autonomic neuropathy in the dyspnoeic group, which is known to occur in early T2DM.[29]

This study has two potential limitations. First, the groups were not matched for gender and beta-blockers, but this was statistically accounted for. And second, the left atrium was not evaluated thus limiting the interpretation.

The main advantage of this study was successfully obtained PAP during exercise in >90% of the patients with agitated colloid contrast.[17] Previous echocardiographic studies in T2DM mainly focused on E/e′ and e′[5–8,30] probably due to the uncertain feasibility and accuracy of measuring PAP without contrast.[6,11] Moreover, these studies evaluated cardiac function and exercise capacity in different postures, which impeded control of exercise capacity and stroke volume.[5–8] Our evaluations were done at similar relative exercise intensity by using RER.

To conclude, dyspnoeic patients with T2DM have more cardiac dysfunction, pulmonary vascular dysfunction and lower aerobic fitness than non-dyspnoeic patients with T2DM. Pulmonary hypertension and LV filling pressures evaluated non-invasively by exercise echocardiography with the colloid contrast could be valuable diagnostic markers in T2DM patients with unexplained exertional dyspnoea.

Author contributions

All the authors made a substantial contribution to the work design, data acquisition, and interpretation. T.G. and L.V.R. analyzed the data and drafted the article. Co-authors revised it and approved the submission.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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