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

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Title: Pulmonary hypertension during exercise underlies unexplained exertional dyspnea in patients with type 2 diabetes

Running title: Cardiac dysfunction in dyspneic type 2 diabetes

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Abstract (≤250 words)

Aim: To compare the cardiac function and pulmonary vascular function during exercise between dyspneic and non-dyspneic patients with type 2 diabetes mellitus (T2DM).

Methods: 47 T2DM patients with unexplained dyspnea and 50 asymptomatic T2DM patients underwent exercise echocardiography combined with ergospirometry. Left ventricular (LV) function (stroke volume, cardiac output, LV ejection fraction, systolic annular velocity (s')), estimated LV filling pressures (E/e'), mean pulmonary arterial pressures (mPAP) and mPAP/COslope were assessed at rest, low- and high-intensity exercise with colloid contrast.

Results: Groups had similar patient characteristics, glycemic control, stroke volume, cardiac output, LV ejection fraction and E/e' ($p>0.05$). The dyspneic group had significantly lower systolic LV reserve at peak exercise (s') ($p=0.021$) with a significant interaction effect ($p<0.001$). The dyspneic 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 dyspneic vs. 30% of non-dyspneic group had mPAP/COslope>3 ($p=0.009$). The mPAP/COslope negatively predicted $\dot{V}O_{2peak}$ in dyspneic group (β= -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 dyspnea and reduced exercise capacity in T2DM.

Keywords: diabetes, heart, echocardiography, shortness of breath, pulmonary arterial pressure

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Introduction

Exertional dyspnea is a typical symptom of heart failure(HF). It is commonly observed in 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 dyspnea 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 remodeling[9][10]. Also, exercise testing improves the sensitivity of detecting diastolic dysfunction. [6,11] [12] [19]. However, the sensitivity of detecting early cardiac dysfunction via diastolic dysfunction is questionable, [13] 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. [14] Finally, an impaired pulmonary vascular response to exercise was shown in patients with early T2DM without resting systolic and diastolic dysfunction and perfusion defects. [15] 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. [16] 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 dyspnea.[17] When a good TRV signal is obtained with colloid contrast, the slope of the mean pulmonary arterial pressure to cardiac output (PAP/COslope) estimated by exercise echocardiography correlates well with invasively measured mPAP/COslope.[16] It remains unknown, however, whether the non-invasive evaluation of pulmonary vascular function via exercise-echocardiography with colloid contrast uncovers the cause of dyspnea 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 dyspnea. We hypothesize that the dyspneic group of T2DM has a worse cardiac function and pulmonary vascular function than the non-dyspneic 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 dyspnea. The control group consisted of 50 patients with T2DM without exertional dyspnea 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: type 1 diabetes mellitus, 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 hemoglobin 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 (CPETecho)

Echocardiographic assessments were done by cardiologists (JV and SJ) with a phased array probe (Vivid E90 and GE M5S 1.5-4.5 MHz, GE Health Medical, Milwaukee, Wisconsin, USA).[18] Cardiac function

was evaluated in the apical two-, four- and five-chamber view (AP2C, AP4C, AP5C) and the apical long-axis view (APLAX). 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.* [19], 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 cardiac output (CO) was evaluated using the velocity-time integral of the LV outflow tract via pulsed wave Doppler, heart rate (HR) and the LV outflow tract (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 (TRV) obtained with agitated colloid contrast[16,21] were used to estimate systolic pulmonary arterial pressures (sPAP). The mean PAP was calculated by Chemla's formula (mPAP, mPAP = 0.61 * sPAP +2).[22]

Ergospirometry was used for the evaluation of respiratory exchange ratio (RER) and oxygen uptake (VO_2) (CS-200 Ergo-Spiro, Schiller AG, Switzerland). An intended duration of an incremental ramp protocol (0W + 1-30 W/min, 60-65 revolutions/min) on a semi-supine bicycle was 10 minutes. (Ergocouch erg 911 LS, Ergosana, Rotterdam, The Netherlands) The echocardiographic assessment was done at rest, low-intensity (heart rate <80-100 bpm, before fusion of E an A.[19]) 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 ANCOVA with gender and beta-blockers as covariates where needed. Differences in proportions between groups were evaluated using the Chi-Square 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 (ANOVA) 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 done and corrections applied when necessary (Huynh-Feldt or Greenhouse-Geisser). Two-way mixed analyses of covariance (ANCOVA) with gender and beta-blockers as covariates were done 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 dyspnea) were included (Figure 1). The dyspneic group of patients consisted of more women (53% vs 18%, p<0.001) and had a lower body mass than the non-dyspneic group (80kg vs 85kg, p=0.048) (Table 1). Groups had similar age, disease duration, body mass index, body surface area, glycemic control and lipid profile (p>0.05). Plasma levels of NT-proBNP were significantly higher in the dyspneic group (p=0.004, Table 2).

Cardiac function

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 dyspneic group (p=0.021) and the interaction effect was significant (p<0.001). The mPAP was higher at all stages in the dyspneic 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 significant interaction effect (p=0.009). The mPAP/CO was higher at all stages of evaluation in the dyspneic 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 dyspneic vs 31% of the non-dyspneic group had mPAP/COslope >3mmHg/L/min (p=0.049).

Exercise capacity

Peak oxygen uptake was significantly lower in the dyspneic group (VO_{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 dyspneic 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 (VO_{2peak}, mL/kg/min) in the dyspneic group: E/e' at rest and high-intensity exercise (ρ=-0.408 and ρ=-0.483, p=0.004 and p=0.001), E at rest (ρ=-0.346, p=0.017), e' and s'_s at high-intensity (r=0.493 and ρ=0.426, p=0.001 and p=0.003), CO at high-intensity exercise (r=0.511, p<0.001), mPAP/COslope (ρ=-0.465, p<0.001), and maximal HR (r=0.516, p<0.001). Multiple regression analysis was done for the dyspneic 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 VO_{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 VO_{2peak}, higher mPAP/CO and a lower s' during peak exercise in dyspneic than in the non-dyspneic 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 dyspnea.

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 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 dyspneic from non-dyspneic patients better than E/e' combined with either mPAP/COslope or TR velocity. (Figure 2) About 50% of the dyspneic group had s'<9.5 and mPAP/COslope>3 compared to only 12% of the non-dyspneic group (p=0.003). Also, s' alone was significantly lower in the dyspneic group at peak exercise indicating worse LV filling in the dyspneic group. Our finding of reduced s' in dyspneic patients is consistent with the previous study on dyspneic 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. [26,29]

The mPAP/COslope and E/e' were negative predictors of exercise capacity suggesting that dyspnea might be linked to a lower left ventricular 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 dyspneic patients.[26] Evaluating mPAP/COslope, especially in dyspneic 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.[27]

In line with previous studies, [29–31] aerobic fitness measured by a submaximal exercise test was reduced in both groups (VO_{2peak} ≈77%predicted), but the dyspneic group had significantly worse fitness than the non-dyspneic group (p=0.042). Moreover, a higher VE/VCO_2 slope in the dyspneic group suggests more ventilatory inefficiency typically seen in HF.[28] Slightly reduced aerobic fitness and worse ventilatory efficiency pinpoint the subtlety of more pronounced cardiac dysfunction in the dyspneic group. The importance of significantly higher RER in the dyspneic group is questionable considering that no differences in the cardiac-related events exist across different peak RER subgroups in HF. [29] Although there were no differences in the heart rate at high-intensity exercise, a higher heart rate at baseline and VT1 in the dyspneic group might point to more cardiac autonomic neuropathy in the dyspneic group, which is known to occur in early T2DM.[30]

This study has two potential limitations. First, the groups were not matched for gender and beta-blockers, but this was statistically accounted for. And secondly, 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.[16] Previous echocardiographic studies in T2DM mainly focused on E/e' and e' [5–8,31] 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, dyspneic patients with T2DM have more cardiac dysfunction, pulmonary vascular dysfunction and lower aerobic fitness than non-dyspneic 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 dyspnea.

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Conflict of interest:

There are no conflicts of interest, financial or otherwise associated with this publication.

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TG, LVR, SJ, IF, EB, TP, SS, PD, VB, LH, DH and JV made a substantial contribution to the work design, data acquisition and interpretation. TG and LVR analyzed the data and drafted the article. Co-authors revised it and approved the submission.

Data availability statement:

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

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Tables, Figures and Central illustration

Table 1: Baseline characteristics

	n	Non-dyspneic patients (n=50)	n	Dyspneic 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/m²)	50	28.6 ± 4.3	47	29.2 ± 5.1	0.514
BSA (m²)	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-dyspneic patients (n=50)	n	Dyspneic 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 hemoglobin A1c, HDL; high-density lipoprotein, LDL; low-density lipoprotein, NT-proBNP; N-terminal pro-B-type natriuretic peptide. Significant differences between both groups at * $P < 0.05$

Table 3: Cardiac function

	Rest					Low intensity					High intensity						
		Non-dyspneic		Dyspneic			Non-dyspneic		Dyspneic			Non-dyspneic		Dyspneic			
	n	patients (n=50)	n	patients (n=47)	P value	n	patients (n=50)	n	patients (n=47)	P value	n	patients (n=50)	n	patients (n=47)	P value	P time	P interaction
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-dyspneic patients (n=50)	n	Dyspneic patients (n=47)	P value
Rest					
HR_{rest} (bpm)	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 (bpm)	46	95 ± 10	45	106 ± 20	0.001*
VO_2 (mL/min)	46	796 (280)	45	860 (400)	0.003*
VT2					
HR (bpm)	39	126 ± 19	34	120 ± 28	0.912
VO_2 (mL/min)	39	1477 ± 418	34	1049 ± 428	0.011*
High-intensity exercise					
HR_{peak} (bpm)	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*
VO_{2peak} (mL/kg/min)	50	17.7 (6.9)	47	14 (5.4)	0.042*
VO_{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 1min recovery (bpm)	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 dyspneic group of patients with T2DM

$VO_{2\ peak}$ (mL/kg/min)	*B*	95% CI for *B*	SE *B*	β	R^2	ΔR^2

		95% CI					
		LL	UL				
Model						0.539	0.504
Constant	16.34 **	10.516	22.163	2.881			
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		

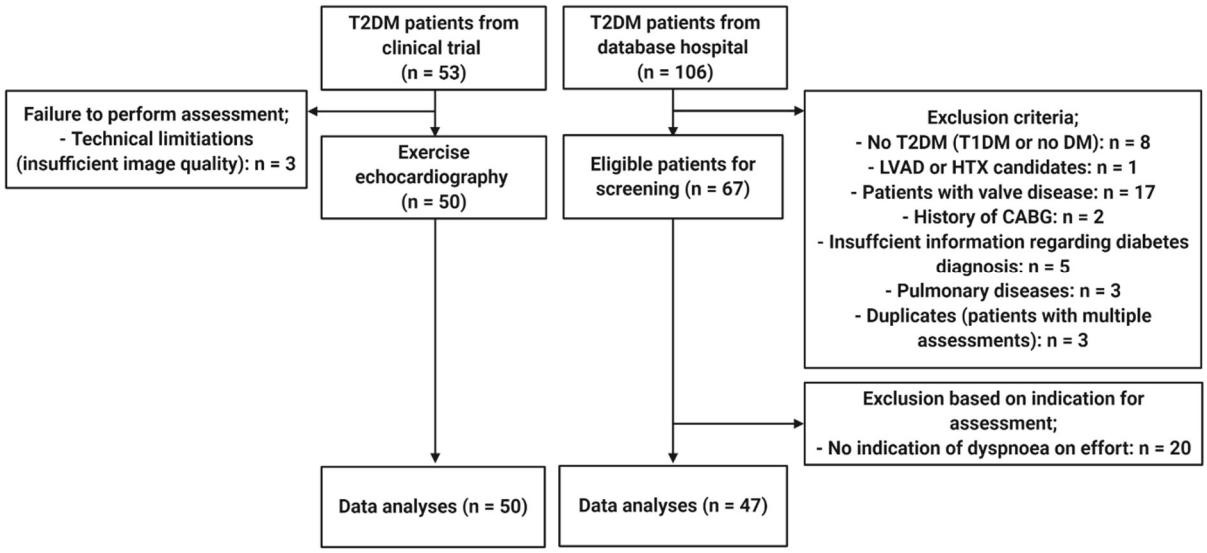
Multiple regression model. Model = "Backward" method in SPSS Statistics; *B* = unstandardized regression coefficient; CI = confidence interval; LL = lower limit; UL = upper limit; SE *B* = standard error of the coefficient; β = standardized coefficient, R^2 = coefficient of determination, ΔR^2 = adjusted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

Supplementary table 1: Cardiac function in males vs females

	Rest				*Low intensity*				*High intensity*			
	Non-dyspneic patients (n = 50)		**Dyspneic patients (n = 47)**		**Non-dyspneic patients (n = 50)**		**Dyspneic patients (n = 47)**		**Non-dyspneic patients (n = 50)**		**Dyspneic patients (n = 47)**	
	Males (n = 41)	Females (n = 9)	Males (n = 22)	Females (n = 25)	Males (n = 41)	Females (n = 9)	Males (n = 22)	Females (n = 25)	Males (n = 41)	Females (n = 9)	Males (n = 22)	Females (n = 25)
SV (mL)	71 ± 15	58 ± 11 †	69 ± 15	64 ± 17	84 ± 18	75 ± 10	83 ± 15	76 ± 16	85 ± 17	77 ± 10	88 ± 13	78 ± 15 †
CO (L/min)	5 ± 1.3	4.1 ± 0.9	5.3 ± 1.3	4.6 ± 1.4	7.8 ± 2	7 ± 1.2	8.1 ± 1.5	7.3 ± 1.6	9.8 ± 3	8.5 ± 2.1	10.6 ± 2.5	8.9 ± 2.1 †
LVEF (%)	61.5 (14)	68 (17.5)	63 ± 11.8	55.4 ± 10.2 †	62 ± 13.5	68.4 ± 11.1	68.3 ± 11	61.4 ± 10.5 †	64.6 ± 14.4	67.7 ± 6.4	69.8 ± 12.3	63.9 ± 13.6
E (cm/s)	55 ± 14	63 ± 19	52 (22)	67 (26) †	84 ± 14	92 ± 13	90 ± 29	101 ± 21	107 ± 20	109 ± 17	113 ± 25	122 ± 24
e' (cm/s)	6 (1)	5.5 (3)	6 (1.3)	5 (3)	8.6 ± 2	8.3 ± 2.4	8.9 ± 3	8.1 ± 2.9 †	12.2 ± 3.4	11.1 ± 2.9	11.4 ± 3.3	10.2 ± 4.5
E/e'	10 ± 2	12 ± 4 †	11 (5)	13 (6)	9 (3)	11 (10)	11 (5)	14 (8)	10 ± 4	10 ± 3	11 (4)	12 (6) †
s' (cm/s)	5.8 ± 1.8	4.5 ± 1.1	5.5 ± 2	4.3 ± 1.8 †	8.8 ± 2.1	6.3 ± 1.3 †	8.1 ± 2.6	6 ± 1.9 †	12 (4)	8 (3) †	9 ± 2.5 *	7.1 ± 2.3 †
mPAP (mmHg)	13 (4)	11 (5)	17 (5) *	16 (5) *	20 (6)	22 (10)	24 (9) *	27 (11) *	26 (7)	23 (6)	33 (10) *	31 (6) *
mPAP/CO (mmHg/L/min)	2.3 ± 0.8	2.8 ± 0.6	3.1 (1.2) *	3.8 (1.7) *	2.4 ± 0.7	2.9 ± 1.1	3.1 (1.1) *	3.9 (1.7)	2.4 ± 0.8	3.1 ± 0.7	3.1 (1.5) *	3.8 (1.5)
mPAP/CO slope (mmHg/L/min)									2.3 (0.8)	3.6 (2)	3.2 ± 1.4	3.9 ± 1.3

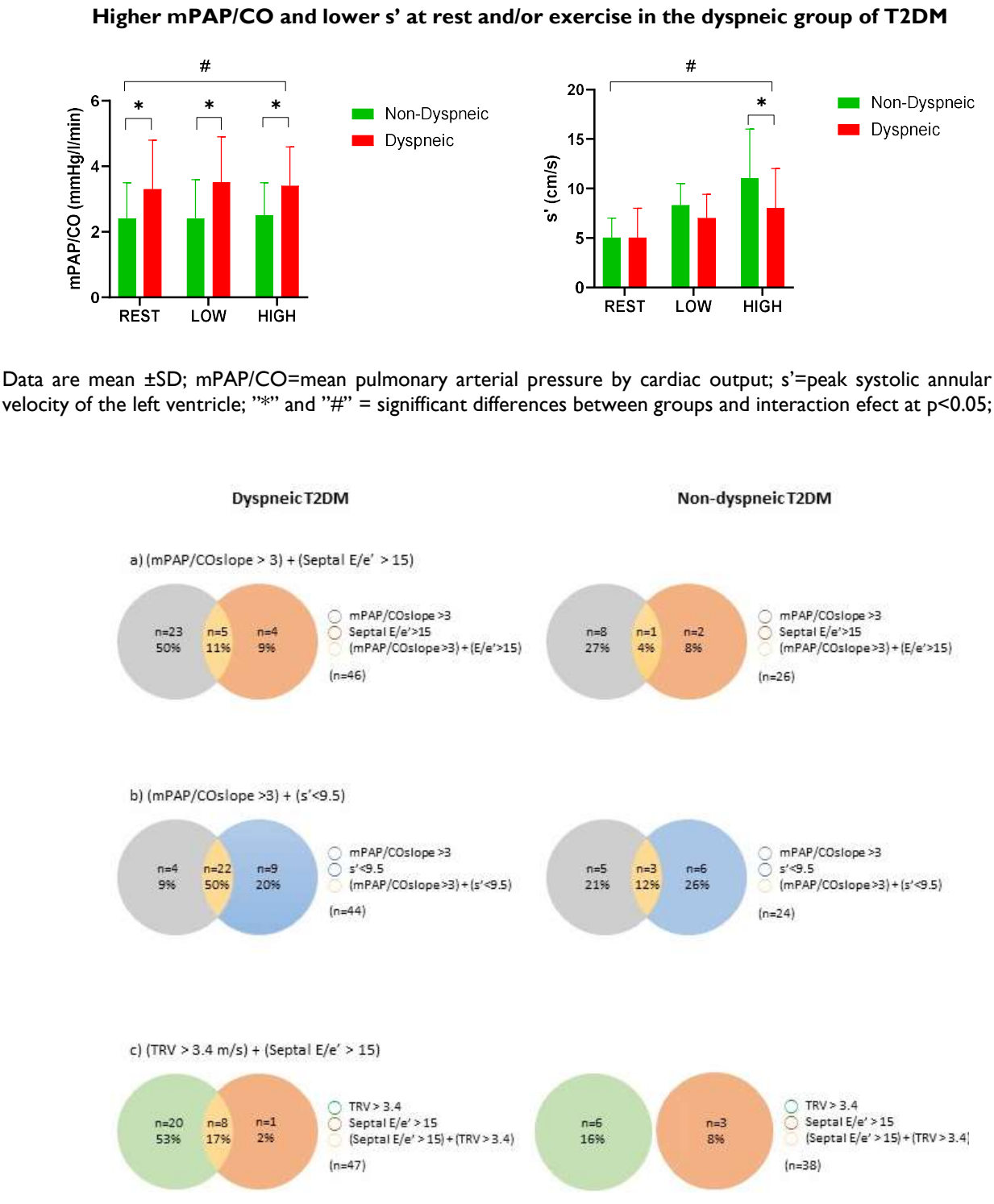
Data are expressed as mean ± SD, as median (interquartile range) or number [percentages] as appropriate. SV; stroke volume, CO; cardiac output, LVEF; left ventricular ejection fraction, E; peak velocity of early diastolic filling phase, e'; early diastolic velocity at the septal annulus, E/e'; left ventricular filling pressure, s's; peak systolic velocity at septal annulus, mPAP; mean pulmonary artery pressure. Significant differences between groups at * $P < 0.05$. Significant differences within groups at † $P < 0.05$

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.

Figure 2. Central illustration



Data are mean ±SD; mPAP/CO=mean pulmonary arterial pressure by cardiac output; 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=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 ($\mathrm{TRV} = \sqrt{\mathrm{sPAP}/4}$); Venn's diagrams=data are from high-intensity exercise;"*" and "#"=signifficant differences between groups and interaction efect at p<0.05;