Influence of cardiomegaly on disordered breathing during exercise in chronic heart failure

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Aims

Heart failure (HF) patients breathe with a rapid shallow pattern during exercise. This study examined the relationship between cardiac size and tachypnoeic breathing in HF patients during exercise.

Methods and results

Thirty-seven HF patients [age = 55 ± 13 years, ejection fraction (EF) = $27 \pm 10\%$, New York Heart Association (NYHA) class = 2.3 ± 1.2] and 42 controls (CTL) (age = 56 ± 14 years, EF = $63 \pm 8\%$) were recruited. Participants underwent maximal exercise testing, pulmonary function testing, and chest radiography for calculation of total thoracic cavity volume (TTCV), diaphragm, heart, and lung volumes. Heart failure patients were divided into two groups: Group A = cardiac volume < median ($n = 18$) and Group B = cardiac volume $\geq$ median of the HF patients ($n = 19$). There was no difference between groups for TTCV (CTL = 8203 ± 1489 vs. Group A = 8694 ± 1249 vs. Group B = 8195 ± 1823 cm³). Cardiac volume was different between groups for both absolute (CTL = 630 ± 181 vs. Group A = 894 ± 186 vs. Group B = 1401 ± 382 cm³, $P < 0.001$ for all comparisons) and %TTCV (CTL = 8 ± 2 vs. Group A = 10 ± 1 vs. Group B = $18 \pm 5\%$, $P < 0.001$ for all comparisons). Similarly, total lung volume as a %TTCV was significantly different among the groups (CTL = 70 ± 4 vs. Group A = 65 ± 5 vs. Group B = $58 \pm 7\%$, $P < 0.01$ for all comparisons). In HF patients, there was a trend ($P = 0.10$) towards an independent association between cardiac size and tidal volume (V_T) at 75% of $\dot{V}O_2$ peak whereas this relationship was statistically significant at $\dot{V}O_2$ peak ($P = 0.02$) as patients with larger cardiac size had reduced V_T .

Conclusion

This study demonstrates the close relationship between cardiac size and breathing pattern during exercise in HF patients. These results suggest cardiac size may pose a significant constraint on the lungs during exercise and may contribute to tachypnoeic breathing.

Keywords

Tachypnoea • Ventilation • Heart size

Introduction

Classical symptomatology of chronic heart failure (HF) includes shortness of breath, particularly on exertion. Patients with HF often develop mild to moderate restrictive and to a lesser extent obstructive changes in pulmonary function.^{1–3} The aetiology of these changes has traditionally been linked to poor ventricular systolic function and reduced haemodynamic integrity; however, the clear underlying mechanism(s) remain imprecise. In fact, these changes in pulmonary function have also been attributed to weak respiratory muscles, elevated left atrial and pulmonary pressures, shifts in lung fluid balance, and heightened neuro-humoral activity.^{4–7} More recently, our laboratory has demonstrated a close anatomical relationship between the cardiac and

pulmonary systems at rest, such that HF patients with the greatest cardiac volume have the lowest static lung volumes, a relationship which was strengthened after correcting for differences in the total thoracic cavity volume (TTCV).⁸ Our laboratory has further demonstrated that increased cardiac volume is closely related to measures of forced expiratory airflows and plays an important role in the restrictive breathing patterns often reported in HF patients.⁹

Patients with HF are known to exhibit disordered breathing patterns during exercise which can include a rapid shallow pattern (tachypnoea) and oscillatory breathing.¹⁰ In addition, HF patients often breathe at reduced end-expiratory lung volume at rest which remains near residual volume throughout exercise despite significant expiratory flow limitation and adequate inspiratory

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reserve volume.¹¹ However, the specific underlying mechanisms leading to these changes in breathing pattern and altered ventilatory mechanics remain unclear.¹²

Owing to the close anatomical and haemodynamic relationships between the cardiac and pulmonary systems it is reasonable to hypothesize that significant changes in one system could have profound effects on the other, particularly during the stress of physical activity. Therefore, the focus of this study was to examine the relationship between cardiac size and breathing pattern during exercise in patients with HF. We hypothesized that increased competition for intra-thoracic space caused by increased cardiac volume associated with HF contributes to the tachypnoeic breathing pattern during exercise.

Methods

Participant characteristics

Thirty-eight patients with HF were recruited from the Mayo Clinic Heart Failure Service and the Cardiovascular Health Clinic (a preventive and rehabilitative centre) over the period 2000–2004. The inclusion and exclusion criteria for patients enrolled in this study included: patients with a history of ischaemic or dilated cardiomyopathy, stable HF symptoms (>3 months), duration of HF symptoms >1 year, left ventricular ejection fraction (EF) ≤35%, body mass index (BMI) <35 kg/m², and current non-smokers (past 15 years) with a smoking history <10 pack-years. All patients were treated with standard optimized medications for HF at the time of the study. Forty-two control participants were recruited via advertisement from the surrounding area to create a control group with a similar age, gender, and height distribution as the HF group. Control participants had normal cardiac function (EF >50%), without history of hypertension, lung disease, or coronary artery disease (CAD). All participants gave written informed consent after being provided a description of study requirements. The study protocol was approved by the Mayo Clinic Institutional Review Board; all procedures followed institutional and Health Information Portability and Accountability Act (HIPAA) guidelines.

Overview of protocol

All participants underwent maximal graded exercise testing, spirometry, and posterior-anterior (PA) and lateral (LAT) chest radiographs. Cardiomegaly was determined using the cardiac volume as a per cent of the TTCV (see the Radiographic volumetric evaluation section). The median heart size in the HF group was 12% of the TTCV. Using this median, patients with HF were divided into two groups determined by the extent of cardiomegaly as follows: Group A = patients with cardiac volume as a per cent of TTCV < median and Group B = HF patients with cardiac volume as a per cent of total thoracic volume ≥ median. Control participants (CTL) constituted the third group.

Radiographic volumetric evaluation

The PA and LAT radiographic views were used to determine the volumetric estimations of the TTCV, diaphragm (DV), cardiac (CV), and lungs (TLV) based on the assumptions of a partial ellipsoid as initially described by Barnhard *et al.*¹³ and later by Glenn and Greene as well as others.^{14–16} This methodology has been shown to be valid and reliable.^{14,15} In brief, the inner most edge of the intra-thoracic cavity and outer most edge of the cardiac silhouette on both

radiographic views were manually traced on a digitizing tablet (Accu-Grid A43BL, Numonics Corp, Montgomeryville, PA, USA) with coordinate data exported to personal computer for off-line analysis. The volumetric measures for TTCV, CV, and TLV were calculated as follows: $TTCV = (1/4\pi) D_1^* D_2^* D_3$ where D_n represents width, depth, and height of the PA and LAT views, $CV = (1/6\pi) D_1^* D_2^* D_3$ where D_n represents diameters of the atrium and ventricles in the PA and LAT views and $TLV = TTCV - (CV + DV + PBV + PTV)$ where PBV is pulmonary blood volume and PTV is parenchymal tissue volume (for details of measurements and calculations, see Olson *et al.*^{8,9}).

Measurement of pulmonary function

Spirometry evaluation included forced vital capacity (FVC) and assessment of maximal expiratory airflow including forced expiratory volume in one second (FEV₁), and mean forced expiratory flow between 25 and 75% of the FVC (FEF_{25–75}). Participants also underwent assessment of the diffusing capacity of the lung for carbon monoxide (DL_{CO}) and measurement of alveolar volume (V_A) using the single breath method. Spirometry and DL_{CO} measures were collected in accordance with the American Thoracic Society (ATS) standards.^{17,18}

Exercise testing and measurement of ventilation and gas exchange

All participants underwent a symptom-limited incremental treadmill test according to a standardized protocol. The protocol consisted of an initial treadmill speed and grade of 2.0 mph and 0%, respectively. The speed and/or grade were subsequently adjusted every 2 min to yield an approximate 2-MET increase per stage of exercise. Participants were verbally encouraged to continue the exercise protocol to maximal exertion, confirmed by a rating of perceived exertion of ≥17 on the Borg 6–20 scale or a respiratory exchange ratio of ≥1.10. Oxygen consumption (VO₂), carbon dioxide production (VCO₂), minute ventilation (V_E), tidal volume (V_T), respiratory rate (RR), and partial pressure of end-tidal oxygen and carbon dioxide (P_{ET}O₂ and P_{ET}CO₂, respectively) were measured with a metabolic measurement system through a mouth piece and pneumotach while wearing a nose clip for the entire measurement period (MedGraphics CPX/D; Medical Graphics, St. Paul, MN, USA). Respiratory exchange ratio was calculated as the VCO₂ divided by the VO₂. Manual volume calibration was performed with a 3 L syringe and gas calibration was performed with manufacturer-recommended gases of known concentration. All calibration procedures were accomplished immediately prior to each testing protocol.

Statistical analysis

All statistical analyses were accomplished using SAS v9.1 (SAS Institute Inc., Cary, NC, USA). Data were described using mean ± standard deviation (SD) or count (per cent) as appropriate. Analysis of variance was used to compare differences across the CTL and HF groups. Tukey's HSD *post hoc* analysis was applied to determine the level of significance among individual groups. Univariable and multiple variable linear regression models were used to investigate the relationship of V_T and RR (dependent variables) with VO₂ and cardiac size (independent variables) in all patients and in the subset of HF patients, both at 75 and 100% of exercise intensity.

To study the possible mediating effect of exercise level on the relationship between heart size and breathing pattern, four exercise stage observations (rest, first workload, 75% of VO₂ peak, and VO₂ peak) were pooled in the HF patients. Multivariable linear regression models with generalized estimating equations (GEE) were fit using

the data from these four time points to investigate the relationship of V_T and RR with VO_2 and cardiac size, and the interaction of VO_2 with cardiac size.¹⁹ An exchangeable correlation structure was assumed. In all participants, linear regression multiple variable models with GEE were constructed for the outcomes of V_T /TTC percentage and RR with group cardiac size and V_E /TTC and their interaction. In addition, comparisons were made between the second order polynomial curve fit between the HF groups. These models were also plotted.

Results

Population characteristics

Clinical characteristics and medications are reported in Table 1. Differences among groups include a lower BMI for the CTL group compared with Group B ($P = 0.02$) due to a lower body weight ($P = 0.009$) with a trend in the same direction compared with Group A ($P = 0.07$ for both). The CTL group also was more active compared with either patient group (compared with Group A $P = 0.01$ and compared with Group B $P < 0.001$). The CTL group had greater FVC%pred and FEV₁%pred ($P = 0.01$ and $P = 0.006$, respectively) compared with Group A. The CTL

group also had greater FVC and FEV₁ for both absolute and %pred ($P < 0.001$ for absolute and %pred comparisons) compared with Group B. Group B demonstrated lower FVC and FEV₁%pred compared with Group A ($P = 0.001$ for both). The CTL group also demonstrated larger V_A %pred compared with Group B ($P < 0.001$) and Group A also demonstrated larger V_A %pred compared with Group B ($P = 0.006$).

Radiographic evaluation

The results of the radiographic volumetric measurements are reported in Table 2. For absolute volumes, there were no differences across the groups for total thoracic volume or diaphragmatic volume. The CTL group had lower blood and tissue volume compared with Group B ($P = 0.01$). In addition the CTL group had lower cardiac volume compared with either HF group ($P < 0.001$ for both) and by design Group A was also lower than Group B ($P < 0.001$). Finally, there was no difference in lung volume between CTL and Group A, however, the CTL group was significantly higher than Group B and Group A was also higher than Group B ($P = 0.01$ and $P = 0.04$, respectively).

Table 1 Participant characteristics and patient medications

	Control	Group A	Group B	Control vs. Group A	Control vs. Group B	Group A vs. Group B
n (% Female)	42 (45)	18 (38)	19 (42)	0.78	0.59	0.85
Age (year)	56 ± 14	56 ± 12	54 ± 14	0.99	0.86	0.95
Height (cm)	170.6 ± 9.6	172.4 ± 8.6	171.6 ± 10.2	0.78	0.92	0.97
Weight (kg)	75.2 ± 13.4	82.0 ± 11.3	85.8 ± 15.9	0.19	0.02	0.67
BMI (kg/m ²)	25.7 ± 2.9	27.6 ± 4.2	29.2 ± 5.6	0.22	0.006	0.43
BSA (m ²)	1.9 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	0.29	0.10	0.89
Smoking history (pack years)	2.8 ± 7.0	1.2 ± 3.7	4.0 ± 6.6	0.62	0.79	0.37
Exercise history (min/week)	175.8 ± 153.6	72.5 ± 91.0	30.0 ± 51.4	0.01	<0.001	0.55
LV ejection fraction (%)	63.2 ± 7.8	28.6 ± 9.6	24.7 ± 10.2	<0.001	<0.001	0.36
FVC (L)	4.2 ± 0.9	4.0 ± 1.0	3.1 ± 1.1	0.79	<0.001	0.01
%Pred	105.0 ± 13.4	94.7 ± 16.2	72.9 ± 19.0	0.05	<0.001	0.001
FEV ₁ (L/s)	3.3 ± 0.7	3.1 ± 0.7	2.4 ± 0.9	0.57	<0.001	0.04
%Pred	103.5 ± 15.0	91.3 ± 15.2	70.9 ± 19.0	0.02	<0.001	0.001
VA (L)	5.7 ± 1.0	5.8 ± 1.1	5.0 ± 1.4	0.95	0.10	0.11
%Pred	98.5 ± 8.8	94.9 ± 10.6	82.6 ± 14.5	0.46	<0.001	0.003
NYHA class						
Class I	—	7 (39)	6 (32)			0.07
Class II	—	6 (33)	2 (11)			
Class III	—	3 (17)	6 (32)			
Class IV	—	2 (11)	5 (26)			
Medications [number (% of total)]						
ACE inhibitors	—	12 (67)	16 (84)			0.70
All receptor blockers	—	1 (6)	2 (11)			0.68
β-blockers	—	7 (39)	16 (84)			0.03
Digitalis	—	12 (67)	15 (79)			0.95
Diuretics	—	10 (56)	16 (84)			0.25

BMI, Body Mass Index; BSA, Body Surface Area; LV, left ventricle; FVC, Forced Vital Capacity; FEV₁, Forced Expiratory Volume in one second; VA, Alveolar Volume; NYHA, New York Heart Association; ACE, Angiotensin Converting Enzyme; All, Angiotensin II. Data are presented as mean ± SD unless otherwise noted.

Table 2 Radiographically determined volumes across groups

	Control	Group A	Group B	Control vs. Group A	Control vs. Group B	Group A vs. Group B
Absolute volumetric estimations						
Total thoracic volume (cm ³)	8203 ± 1489	8694 ± 1249	8195 ± 1823	0.49	0.99	0.58
Blood and tissue volume (cm ³)	938 ± 132	995 ± 118	1037 ± 144	0.28	0.02	0.61
Diaphragm volume (cm ³)	914 ± 298	1128 ± 472	976 ± 347	0.09	0.80	0.40
Cardiac volume (cm ³)	630 ± 181	894 ± 186	1401 ± 382	<0.001	<0.001	<0.001
Lung volume (cm ³)	5721 ± 1195	5677 ± 984	4781 ± 1485	0.99	0.02	0.08
Per cent of total thoracic cavity volume						
Blood and tissue (%)	11.7 ± 2.0	11.6 ± 1.8	13.1 ± 2.7	0.99	0.10	0.11
Diaphragm (%)	11.0 ± 2.6	12.9 ± 4.8	11.9 ± 3.4	0.12	0.62	0.62
Cardiac (%)	7.8 ± 2.2	10.2 ± 1.2	17.5 ± 4.9	0.01	<0.001	<0.001
Lung (%)	69.5 ± 3.9	65.2 ± 5.2	57.5 ± 6.7	0.009	<0.001	<0.001

Data are presented as mean ± SD.

When examining these measurements as a %TTCV, there were no differences between the groups for blood and tissue or diaphragm volumes. In contrast, the CTL group demonstrated the lowest cardiac volume when compared with either HF group ($P < 0.001$ for both) and by design Group A had a smaller cardiac volume compared with Group B ($P < 0.001$). With this, the CTL group demonstrated the largest lung volume as a %TTC compared with either HF group ($P = 0.001$ vs. Group A and $P < 0.001$ vs. Group B) and Group A was also larger than Group B ($P < 0.001$).

Functional capacity

The rest and exercise gas exchange and ventilation across groups are presented in Table 3. At rest, the CTL group had lower $\dot{V}_{CO_2}$ compared with Group B ($P = 0.01$). The CTL group also had lower $\dot{V}_E$ due to reduced RR compared with Group B ($P = 0.04$ and $P = 0.02$, respectively). At a matched submaximal percentage of peak exercise (75% peak), the control group had higher $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ compared with both patient groups ($P \leq 0.001$ for all four comparisons). Also at 75% peak intensity, the CTL group demonstrated a higher $\dot{V}_E$ compared with either Group A ($P = 0.02$) or Group B ($P = 0.001$) primarily mediated by increased V_T ($P = 0.001$ compared with Group B). Further, both patient groups demonstrated an elevated $\dot{V}_E/\dot{V}_{CO_2}$ compared with the CTL group ($P < 0.001$). At peak exercise, the patient groups demonstrated reduced $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ compared with the CTL group ($P < 0.001$ for all four comparisons). The CTL group demonstrated an elevated $\dot{V}_E$ ($P = 0.01$ compared with Group A and $P < 0.001$ compared with Group B). The reduced $\dot{V}_E$ in Group A compared with the CTL group was primarily mediated by a reduced RR ($P = 0.001$) whereas the reduced $\dot{V}_E$ in Group B was primarily mediated by a reduced V_T ($P < 0.001$). Comparing the two HF groups, Group A demonstrated a lower RR ($P = 0.03$) with higher V_T ($P = 0.003$) resulting in no difference between these two groups for total $\dot{V}_E$ ($P = 0.13$). Also at this intensity, Group B

demonstrated an elevated $\dot{V}_E/\dot{V}_{CO_2}$ compared with the CTL group ($P = 0.01$).

Relationship between heart size and breathing pattern during exercise

The results of the multivariable linear regression suggest that in HF patients, at 75% of $\dot{V}_{O_2}$ peak there was a trend (-58 mL/min per $+10\%$ cardiac size, $P = 0.10$) towards cardiac size being independently associated with V_T at this exercise intensity after adjusting for $\dot{V}_{O_2}$. In addition, at $\dot{V}_{O_2}$ peak V_T was statistically significant (-315 mL/min per $+10\%$ cardiac size, $P = 0.02$). Between all groups, across all time points of exercise, and after adjusting for $\dot{V}_{O_2}$, cardiac size was significantly related to reduced V_T in the HF patients ($P = 0.03$). The relationship between V_T as a per cent of TTCV volume and $\dot{V}_E$ as a per cent of TTCV volume among the HF patients is highlighted in Figure 1A by using the second order polynomial expression of the curve fits. This analysis demonstrates that the HF patients V_T increased along similar trajectories where, at higher exercise intensities, those patients with larger cardiac sizes (and therefore reduced intra-thoracic space needed for lung volume expansion) demonstrated significant leveling off of V_T .

Further analysis by multivariate linear regression suggests that in HF patients, at 75% of $\dot{V}_{O_2}$ peak there was a trend (3.0 breaths/min per $+10\%$ cardiac size, $P = 0.10$) towards cardiac size being independently associated with RR at this exercise intensity after adjusting for $\dot{V}_{O_2}$. Also, at $\dot{V}_{O_2}$ peak RR was statistically significant (4.8 breaths/min per $+10\%$ cardiac size, $P = 0.04$). The relationship between RR and $\dot{V}_E$ as a per cent of TTCV volume among the HF patients is highlighted in Figure 1B by using the second order polynomial expression of the curve fit. Again, this suggests that the RR increased along similar trajectories where at higher exercise intensities, those patients with larger cardiac volumes demonstrated elevated RR as a compensatory mechanism to maintain adequate $\dot{V}_E$.

Table 3 Gas exchange and ventilation across groups during exercise

	Control	Group A	Group B	Control vs. Group A	Control vs. Group B	Control vs. Group C
Rest						
VO ₂ (mL/kg/min)	3.8 ± 0.6	3.9 ± 0.9	4.0 ± 1.2	0.91	0.64	0.91
VCO ₂ (mL/min)	246.4 ± 63.7	283.4 ± 66.7	290.6 ± 59.9	0.10	0.04	0.94
V _E (L/min)	10.0 ± 2.9	12.1 ± 3.6	11.6 ± 2.4	0.04	0.14	0.86
RR (breaths/min)	14.7 ± 4.1	15.8 ± 5.4	17.6 ± 4.5	0.65	0.06	0.47
V _T (mL/min)	727.4 ± 310.1	762.2 ± 286.1	665.4 ± 154.4	0.90	0.70	0.54
V _T /TTCV	8.9 ± 3.5	8.9 ± 3.8	8.4 ± 2.5	0.99	0.87	0.89
V _E /VCO ₂	40.2 ± 4.8	42.9 ± 7.6	40.9 ± 6.4	0.24	0.90	0.56
MAP (mm Hg)	90.5 ± 12.2	82.5 ± 12.0	87.5 ± 15.6	0.08	0.69	0.47
75% of peak exercise						
VO ₂ (mL/kg/min)	24.4 ± 5.8	16.1 ± 5.6	14.0 ± 5.3	<0.001	<0.001	0.50
VCO ₂ (mL/min)	1690.4 ± 544.3	1197.3 ± 404.8	1101.2 ± 496.9	0.002	<0.001	0.83
V _E (L/min)	46.8 ± 14.0	38.2 ± 10.3	34.7 ± 8.9	0.04	0.002	0.66
RR (breaths/min)	25.8 ± 4.9	24.6 ± 4.2	27.1 ± 6.4	0.68	0.65	0.31
V _T (mL/min)	1841.6 ± 539.9	1584.4 ± 455.9	1342.7 ± 408.0	0.16	0.001	0.30
V _T /TTCV	22.5 ± 5.2	18.2 ± 4.3	16.4 ± 3.6	0.005	<0.001	0.49
V _E /VCO ₂	28.0 ± 3.1	32.9 ± 5.9	33.7 ± 6.9	<0.001	<0.001	0.33
MAP (mm Hg)	98.8 ± 23.3	91.8 ± 13.8	89.4 ± 24.5	0.49	0.28	0.94
Peak exercise						
VO ₂ (mL/kg/min)	32.1 ± 7.8	20.9 ± 7.6	17.4 ± 7.1	<0.001	<0.001	0.34
VCO ₂ (mL/min)	2745.2 ± 879.0	1890.9 ± 638.2	1644.9 ± 794.0	0.001	<0.001	0.63
V _E (L/min)	81.7 ± 26.2	63.5 ± 20.7	54.0 ± 16.3	0.01	<0.001	0.42
RR (breaths/min)	35.9 ± 6.7	30.1 ± 4.5	35.0 ± 7.9	0.001	0.63	0.03
V _T (mL/min)	2285.4 ± 596.8	2086.4 ± 546.7	1572.5 ± 426.9	0.40	<0.001	0.02
V _T /TTCV	28.0 ± 6.5	24.0 ± 5.1	19.3 ± 3.9	0.03	<0.001	0.03
V _E /VCO ₂	29.7 ± 3.2	34.2 ± 7.6	35.2 ± 6.5	0.01	0.001	0.86
MAP (mm Hg)	103.0 ± 19.1	95.1 ± 20.4	87.1 ± 27.5	0.40	0.03	0.51

VO₂, volume of oxygen consumed; VCO₂, volume of carbon dioxide produced; V_E, minute ventilation; RR respiratory rate; V_T, tidal volume; TTCV, total thoracic cavity volume; MAP, mean arterial pressure. Data are presented as mean ± SD.

Discussion

Primary findings

Patients with HF often demonstrate altered breathing patterns during exercise. These alterations include tachypnoea (rapid shallow breathing) in which patients tend to reduce end-expiratory lung volume and breathe rapidly near residual volume despite adequate inspiratory reserve volume. The mechanism(s) underlying this change in breathing pattern during exercise remains unclear but may be related to the increase in heart size with worsening disease status. The results of this study suggest a close relationship between cardiac volume and changes in tidal volume and respiratory rate during exercise. The findings suggest that a progressive increase in cardiac volume may play a role in the change of breathing architecture during exercise and may potentially contribute to symptoms of dyspnoea and fatigue.

Pulmonary function in heart failure

It is known that patients with HF demonstrate reduced pulmonary function at rest and during exercise. In particular, HF patients often

demonstrate restrictive²⁰ and to a lesser extent obstructive²¹ changes and thus it is apparent that detrimental changes in cardiac function frequently contribute to changes in pulmonary function. These changes have been attributed to a number of mechanisms including respiratory muscle weakness,^{4,22,23} changes in lung fluid balance and overt pulmonary oedema,^{5,24} and neuro-hormonal changes.^{5,6,25} Because the cardiac and pulmonary systems are linked haemodynamically, mechanically, and spatially, one would anticipate that changes in one system would influence the other. In fact, increases in cardiac volume within the closed thoracic cavity have been shown to negatively influence resting lung volumes and pulmonary function in patients with HF.^{8,9}

Influence of cardiomegaly on lung volume and pulmonary function at rest

The lungs are more compliant than the heart and thus an increase in cardiac volume within the thoracic space may limit the ability of the lungs to fill adequately. Hosenpud *et al.* demonstrated that patients with severe HF who underwent cardiac transplant had a significant improvement in lung volumes and pulmonary function.

Figure 1 (A) Relationship between tidal volume as a per cent of total thoracic cavity volume ($V_T/TTCV$) and ventilation as a per cent of total thoracic cavity volume ($V_E/TTCV$) in heart failure patients (Group A = cardiac size < median and Group B = cardiac size > median) for all time points of exercise. This figure demonstrates the impact of heart size on V_T for a given level of V_E during exercise. (B) Relationship between respiratory rate (RR) and ventilation as a per cent of total thoracic cavity volume ($V_E/TTCV$) in heart failure patients (Group A = cardiac size < median and Group B = cardiac size > median) for all time points of exercise. This figure demonstrates the impact of heart size on RR for a given level of V_E during exercise.

These authors attributed these improvements in large part to the reduction of cardiac volume and thus a reduction in the thoracic space occupied by the heart.²⁶ Using the one-dimensional measure of the cardiothoracic ratio, Agostoni *et al.*²⁷ have recently suggested that cardiomegaly contributes to reduced alveolar volume. More recently, our laboratory calculated a three-dimensional estimate of cardiac volume and demonstrated a

close negative relationship between increased cardiac volume and total lung volume.⁸

With regard to pulmonary function, it would be anticipated that reduced lung volumes may reduce the effectiveness of the elastic recoil component of exhalation due to insufficient stretch of the lungs and would manifest as reduced maximal volumes and expiratory flows including FVC and FEV₁. As such, our laboratory

recently demonstrated that HF patients with the largest cardiac volume have significantly reduced FVC and FEV₁ compared with control participants or HF patients with less severe disease.⁹

Breathing pattern during exercise in heart failure

In an effort to meet ventilatory needs, patients with HF tend to have an augmented breathing frequency in the face of a reduced tidal volume. This is often accentuated during increasing intensity of physical activity and worsening disease severity.^{12,28} In healthy individuals, normal changes in breathing pattern during exercise include a primary increase in tidal volume with increasing intensity up to ~50–60% of the vital capacity. However, HF patients tend to have a reduced vital capacity at rest and use a smaller percentage of this vital capacity during exercise, resulting in a plateau of tidal volume closer to 40% of vital capacity.¹² This change in tidal volume dynamics during exercise would require an increase in breathing frequency to adequately meet the ventilatory needs necessitated by the increase in activity level.

Under normal conditions, in healthy individuals, tidal volume is increased by encroaching primarily on the inspiratory reserve volume. This is in contrast to patients with HF in that these patients exhibit reduced end-expiratory lung volume at rest and during exercise resulting in a low-lung volume breathing pattern.¹² With this, during exercise these patients continue to breathe at extremely low lung volumes despite significant room to increase the tidal breath and ventilation by encroaching on the inspiratory reserve volume. As shown in Table 3, there was no significant difference in V_E, between the two HF groups at peak exercise. However, the breathing architecture that led to the total V_E at peak exercise was different. Specifically, Group B demonstrated a significantly reduced V_T compared with Group A with a concomitant higher RR to compensate. This rapid shallow breathing pattern results in a significant amount of non productive expiratory effort.^{12,29} Further, this tachypnoeic breathing pattern differs from the recently recognized periodic breathing at rest or exercise oscillatory breathing.^{10,30} These two forms of Cheyne–Stokes respiration are characterized by a cyclic hyperpnoea and hypopnoea without apnoea whereas the more commonly recognized central sleep apnoea results in cyclic hyperpnoea with subsequent apnoeic pauses in ventilation.^{31,32}

Despite the understanding of these breathing patterns in the HF population, the underlying mechanisms leading to this tachypnoeic pattern remain unclear. It has been suggested that pulmonary oedema and the resultant changes in lung compliance may stimulate pulmonary J receptors responsible for the development of tachypnoea in experimental animal preparations.^{33,34} Specifically, Paintal demonstrated, in an anaesthetized cat preparation on artificial ventilation, that pulmonary congestion produced by occlusion of the aorta or left a-v junction, injection of alloxan, or the addition of chlorine to the inspire resulted in stimulation of the pulmonary J receptor nerve endings. However, the pattern of nerve excitation was variable and as such it was concluded that the actual stimulus for the endings is more likely a rise in interstitial pressure or volume via a rise in pulmonary capillary pressure.³³ Although it is known that pulmonary pressures increase during exercise, this

increase is also known to be highly variable in patients with HF and thus the impact that changes in pulmonary pressure had on breathing pattern in this study remain unclear.³⁵ However, the direct relationships between tidal volume and cardiac size demonstrated in the present study suggest that the increased cardiac volume may contribute to a significant constraint on the tidal volume expansion during exercise. In particular, those patients who had the largest cardiac volume demonstrated the lowest per cent increase in tidal volume from rest to exercise.

Clinical implications

Cardiomegaly is common in HF, particularly as the severity of the disease progresses. Understanding the complex interactions between the cardio-pulmonary systems is integral in the treatment of these patients. Clearly, cardiomegaly represents one target where individualized therapeutic strategies would be of great benefit.

Authors' roles

T.P.O.: Database management, data analysis, data interpretation, and manuscript preparation. B.D.J.: Data acquisition, database management, data interpretation, and manuscript preparation.

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