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Assessment of Thoracic Blood Volume by Computed Tomography in Patients with Heart Failure and Periodic Breathing

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Abstract

Background—Periodic breathing (PB) is often observed in patients with HF at rest, with sleep and during exercise. However, mechanisms underlying abnormal ventilatory control are not entirely established.

Methods—Eleven subjects with HF (10M, age=69±12yr) and 12 age-matched controls (8M, age=65±9yr) participated in the study. PB was defined as a peak in the 0.003–0.04Hz frequency range of the flow signal during 6-minutes of awake resting breathing. Thoracic blood volumes (V_t , thorax; V_h , heart; V_p , pulmonary), mean transit times (MTT) and extravascular lung water (EVLW) were quantified using computed tomography.

Results—PB was observed in 7 subjects with HF and was associated with worse functional status. The HF PB-present group had thoracic blood volumes nearly double those of control and HF PB-absent (volumes reported as ml·m⁻² BSA, p-values vs. healthy; Healthy=813±246, HF PB-absent=822±161, p=0.981, HF PB-present=1579±548, p=0.002). PB was associated with longer pulmonary MTT (Healthy=6.7±1.2 seconds, HF PB-absent=6.0±0.8 seconds, HF PB-present=8.4±1.6 seconds; p=0.033 HF PB-present vs. HF PB-absent). EVLW was not elevated in the PB group.

Conclusions—Subjects with HF and PB at rest have greater centralization of blood volume.

Keywords

periodic breathing; thoracic fluid volumes; computed tomography; mean transit time; extravascular lung water

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Introduction

Periodic breathing (PB) is defined as cyclic oscillations of ventilation.⁵ These oscillatory breathing patterns have been observed in patients with heart failure (HF) during sleep, exercise, or awake at rest.^{5–7} Cheyne-Stokes respiration is similarly defined but includes periods of apnea and is often associated with central sleep apnea (CSR-CSA).⁶ Oscillatory ventilation during exercise is termed exercise oscillatory ventilation (EOV) or exercise oscillatory breathing (EOB).^{7,8} Each of these examples of PB is due to instability of ventilatory control and has been associated with poor prognosis.⁹

Pulmonary congestion increases with severity of heart failure. An increase in blood volume in the pulmonary circulation affects respiratory system function. First, increased blood volume increases pulmonary pressures, which may promote increased extravascular lung water (EVLW).¹ Second, increased blood volume within the heart and pulmonary circulation limits the expansion of the lungs, resulting in decreased lung volumes, abnormal breathing patterns and high work and cost of breathing.^{2–4}

Despite the relationship between periodic breathing patterns and adverse prognosis, the underlying pathophysiological mechanisms are not well understood.¹⁰ We previously observed a relationship between pulmonary wedge pressure and PB.⁵ Increased pulmonary venous pressures and pulmonary congestion have been shown to cause tachypneic hyperventilation in animal models.¹¹ We previously conducted a study to evaluate pulmonary congestion and thoracic blood volumes in heart failure.¹² After we observed that subjects with HF exhibit PB at rest in this study, we conducted further analysis to determine whether a relationship between pulmonary congestion and periodic breathing exists in HF. We evaluated thoracic blood volumes, mean transit times, and EVLW in subjects with and without PB by computed tomography (CT). We hypothesized that subjects with the greatest centralization of blood volume would have prolonged circulatory times, more EVLW and greater likelihood of PB.

Methods

Subjects

Eleven patients with HF (mean±SD; age=69±12yr, ht=178.0±9.5cm, wt=92.2±12.6kg) were recruited from the Heart Failure Clinic and the Cardiovascular Health Clinic in the Department of Cardiovascular Diseases at Mayo Clinic in Rochester, MN. Subjects with HF were non-obese, non-smokers, NYHA classes I–III with no history of renal, respiratory, or metabolic disease. Twelve pre-screened healthy individuals (mean±SD; age=65±9yr, ht=168.5±9.3cm, wt=70.8±12.8kg) were recruited as controls. Subjects provided written consent after being informed of all study requirements. All procedures and protocols were approved by the Mayo Clinic Institutional Review Board.

Periodic Breathing

Periodic breathing, a cyclic waxing and waning of tidal volume, was determined from the flow signal during resting breathing. Spirometry was assessed according to ATS guidelines using pneumotachograph-based pulmonary function equipment (Medical Graphics Corp

model 1070, St. Paul, MN).¹³ The flow signal was recorded at a sampling frequency of 1000 Hz in LabChart 8 (ADInstruments, Sydney, Australia) during 6 minutes of resting breathing. The power spectrum in the frequency domain was generated from a transformation of the time domain flow signal. The presence of a distinct, well defined peak in the 0.003–0.04 Hz range was indicative of PB.^{3,14} PB was confirmed visually in the time domain signal by the presence of multiple consecutive oscillations of ventilation.⁵

Compartmental Blood Volumes

All subjects were imaged at total lung capacity using the same scanner (SOMATOM Definition Force, Siemens, Erlangen, Germany). The Medspira Breath Hold System (Medspira, Minneapolis, MN) was used to ensure that subjects maintained total lung capacity throughout the scan. Thoracic CT scans were used to align the ECG-gated contrast perfusion scan. Scanning techniques and calculations have been described previously in detail.¹² Briefly, from the thoracic scan, a region of interest (ROI) was chosen that included the vena cava (VC), pulmonary artery (PA), pulmonary vein (PV) and aorta (AO). Simultaneously, iodinated contrast (0.33 ml per kg body weight; mean contrast volume = 26.7 ml) was infused intravenously at the antecubital fossa, and scanning was initiated. A scan (11 slices per scan, 4.7 mm per slice) was taken during each diastole over a period of 30 seconds. The volume of blood within a specific compartment was calculated by multiplying the blood flow (cardiac output) by the time it takes for a given amount of contrast to move through that compartment (mean transit time, MTT). Cardiac output was calculated as mass of contrast injected (116.7 mg Iodine/kg body weight) divided by the area under curve from the pulmonary artery after converting CT attenuation to contrast concentration. Mean transit time from the pulmonary artery to the pulmonary vein (MTT_{PA-PV}) and from the vena cava to the aorta (MTT_{VC-AO}) were compared between groups.

Extravascular Lung Water

The presence of EVLW was determined from thoracic CT scans. Lung tissue was segmented from adjacent tissues and large blood vessels using MATLAB built-in active contour algorithms (Mathworks, Inc, Natick, MA). Only pixels within the attenuation range of air (–1000 HU) and water (0 HU) were included in the analysis. The mean lung density was calculated from the attenuation distribution within the segmented areas. EVLW was calculated as fluid content (FC) from the mean lung density (MLD) as $FC = (MLD + 1000) / 10$.¹⁵

Statistical Analysis

Further analysis of previously published data was conducted to evaluate a potential relationship between periodic breathing and thoracic blood volumes¹². Subjects were divided into three groups: healthy controls (healthy), subjects with heart failure who did not exhibit PB at rest (HF PB-absent), and subjects with HF who did exhibit PB at rest (HF PB-present). Demographic differences between all three groups were compared using a one-way analysis of variance (ANOVA) and a Kruskal-Wallis non-parametric test. Echocardiographic variables (HF PB-absent vs. HF PB-present) were compared using a Mann-Whitney U test.

Differences in thoracic blood volumes, EVLW, and mean transit times were tested using an ANOVA and Bonferroni post-hoc tests.

Results

Subject Characteristics

Demographics and medications used by the subjects at the time of the study are reported in Table 1. Echocardiographic measures were obtained from subjects' electronic medical record. One subject with heart failure did not have an echocardiogram in the last year (mean time from echo to study: 2.6 ± 1.7 months). The subjects with HF were predominantly male, with greater BMIs compared to controls. PB was observed in 7 of 11 subjects with HF and 0 of 12 controls. The HF PB-present group was younger, had worse NYHA functional class, and lower left ventricular ejection fraction than the HF PB-absent group. Subjects in the HF PB-present group had significantly higher mean NT-proBNP concentration.

Compartmental Blood Volumes

Thoracic, pulmonary and heart blood volumes in the HF PB-present group were nearly twice that of both other groups (Figure 1). This relationship held when normalized to BSA (volumes are reported in $\text{ml}\cdot\text{m}^{-2}$, p-values are relative to the healthy group; V_t , Healthy= 813 ± 246 , HF PB-absent= 822 ± 161 , $p=1.000$, HF PB-present= 1580 ± 548 , $p=0.001$; V_p , Healthy= 412 ± 126 , HF PB-absent= 434 ± 58 , $p=1.000$, HF PB-present= 748 ± 188 , $p<0.01$; V_h , Healthy= 402 ± 148 , HF PB-absent= 388 ± 108 , $p=1.000$, HF PB-present= 831 ± 373 , $p=0.003$). The MTT of blood from the pulmonary artery to the pulmonary vein and from the vena cava to the aorta tended to be slower in the HF PB-present group compared to the HF PB-absent and control groups. However, only the MTT from PA to PV was significantly different between HF PB-absent and HF PB-present (PA to PV, Healthy= 6.7 ± 1.2 seconds, HF PB-absent= 6.0 ± 0.8 seconds, HF PB-present= 8.4 ± 1.6 seconds, $p=0.033$ vs. HF PB-absent; VC to AO, Healthy= 13.8 ± 2.4 seconds, HF PB-absent= 11.6 ± 1.4 seconds, HF PB-present= 16.7 ± 4.8 seconds).

Extravascular Lung Water

Fluid content in the lungs was not significantly different between groups (Table 2). The HF PB-absent group tended to have higher fluid content than both the HF PB-present group and the controls.

Discussion

The purpose of this study was to evaluate the relationship between thoracic fluid volumes, mean transit times, EVLW, and periodic breathing in heart failure. We made the novel observations that the HF PB-present group had significantly increased thoracic, pulmonary and heart blood volumes, as well as prolonged MTT as assessed by CT. In addition, despite markedly different blood volumes between groups, there was no difference in EVLW as assessed by CT.

Augmented thoracic blood volumes and mildly elevated extravascular lung water contribute to reduced lung volumes and flows, which may promote a more rapid and shallow breathing pattern.¹² This would increase physiologic dead space and V_E/V_{CO_2} . Less efficient CO_2 removal from the lungs would result in a greater atmospheric to alveolar CO_2 difference, which has been shown to occur with periodic breathing.⁸ Other possible mechanisms by which periodic breathing may develop in heart failure include prolonged transit time between the lungs and the chemoreceptors or elevated pulmonary pressures causing tachypneic hyperventilation and a narrowed CO_2 reserve (eupneic $PETCO_2$ – apneic threshold $PETCO_2$).^{10,11} Interestingly, we demonstrated that subjects with HF and periodic breathing did not have increased EVLW, suggesting that despite evidence of more severe volume overload, this HF group may have had more pulmonary vessel remodeling. As HF progresses, and the vasculature remodels in response to continued stretch and high pulmonary pressure, there may be a corresponding decrease of fluid flux into the extravascular space.

Importantly, we cannot determine from these findings whether there is a causal relationship between thoracic blood volumes and periodic breathing. It is possible that both are symptoms of severe heart failure. However, the large differences in thoracic blood volumes between heart failure groups call for further study.

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Figure 1. Blood volumes in the A) thoracic compartment B) pulmonary circulation and C) heart were increased in the HF-PB present group compared to the two other groups ($p < 0.05$).

Table 1

Subject characteristics.

	Healthy	HF PB-absent	HF PB-present
Demographics			
Subjects	12	4	7
Females	4	1	0
Age (years)	65 ± 8.5	72 ± 11.5	67 ± 11.5
Height (cm)	168.5 ± 9.3	177 ± 11	178.5 ± 8.5
Weight (kg)	70.8 ± 12.8	92.8 ± 15.3 [‡]	91.8 ± 10.8 [‡]
BSA (m ²)	1.8 ± 0.2	2.1 ± 0.22	2.1 ± 0.17 [‡]
BMI (kg/m ²)	24.7 ± 2.6	29.5 ± 3.7 [‡]	28.7 ± 1.7 [‡]
FVC (l)	4.0 ± 1.0	3.5 ± 1.3	4.3 ± 0.8
FVC (% predicted)	105.0 ± 9.0	77.3 ± 13.4	94.1 ± 14.0
FEV1 (l)	3.1 ± 0.9	2.6 ± 1.3	3.0 ± 0.7
FEV1 (% predicted)	105.4 ± 11.0	75.5 ± 19.2	86.1 ± 17.0
MAP (mmHg)	87.9 ± 6.6	85.4 ± 12.4	83.9 ± 10.1
Cardiac Output (l/min)	5.0 ± 2.3	4.2 ± 2.5	4.0 ± 1.4
eGFR (ml/min/1.73m ²)	77.1 ± 16.3	62.6 ± 3.2	77.8 ± 21.6
Hb (g/dl)	13.7 ± 1.2	14.9 ± 2.4	12.8 ± 1.5
NT-proBNP (pg/ml)	58.6 (25–177)	653.5 (94–1197)	1522.3 (122–3819) [‡]
NYHA class I	0	2	1
NYHA class II	0	2	3
NYHA class III	0	0	3
NYHA class IV	0	0	0
Echocardiographic measures			
EF (%)	—	35.5 ± 3.6	30.7 ± 9.0
LV internal dimension (mm)			
diastolic	—	62 ± 5.6	62 ± 6.1
systolic	—	52 ± 5.5	52 ± 8.8
E/A	—	0.63 ± 0.08	1.78 ± 0.99
E/e'	—	11.0 ± 4.3	14.8 ± 4.1
PA pressure (mmHg)	—	20 ± 4.4	36 ± 9.0 [*]
Medications			
Ace-inhibitors	0	2	3
ARBs	0	2	2
Beta blockers	0	4 [‡]	6 [‡]
Digitalis	0	0	2
Diuretics	0	1	6 ^{‡*}

Values are reported as mean±SD. BSA, body surface area; BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; MAP, mean arterial pressure; EF, ejection fraction; E/A, ratio of early to late filling velocity; E/e', ratio of early mitral inflow velocity to early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; NT-proBNP N-terminal prohormone of brain natriuretic peptide, reported as mean (range); ARBs, angiotensin II receptor blockers.

[†]P<0.05 between HF PB-present and healthy

[‡]P<0.05 HF PB-absent and healthy

^{*}P<0.05 HF PB-present and HF-PB absent

Table 2

Extravascular lung water in heart failure and healthy individuals with and without periodic breathing. Data are presented as mean $\pm$ SD.

	Healthy	HF PB-absent	HF PB-present
Fluid content, FC (%)	15.55 $\pm$ 3.18	19.60 $\pm$ 3.91	17.00 $\pm$ 2.68