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Exertional periodic breathing potentiates erythrocyte rheological dysfunction by elevating pro-inflammatory status in patients with anemic heart failure

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ABSTRACT

Background: Exertional periodic breathing (EPB) or anemia is associated with an adverse prognosis in advanced heart failure (HF). The disturbed rheological properties of erythrocytes may contribute to circulatory disorders. This study investigated whether EPB with/without anemia influences rheological/hemodynamic functions in patients with HF.

Methods: According to the WHO criteria for anemia, 168 HF patients were divided into six groups: non (N)-anemic with (n = 27)/without (n = 56) EPB, light (L)-anemic with (n = 17)/without (n = 21) EPB, and moderate/several (M/S)-anemic with (n = 21)/without (n = 26) EPB groups. These HF patients and 30 healthy counterparts performed an incremental exercise test using a bicycle ergometer. Rheological and hemodynamic characteristics were determined by slit-flow ektacytometer and bioreactance-based device/near infrared spectrometer, respectively.

Results: In the HF patients with EPB, both L- and M/S-anemic groups exhibited 1) higher plasma myeloperoxidase/interleukin-6 concentrations, 2) more blood senescent/spherical erythrocyte counts, 3) larger aggregability and smaller deformability of erythrocytes under shear flows, 4) higher systemic vascular resistance, which was accompanied by smaller amounts of blood distributed to cerebral/muscular tissues during exercise, 5) less VO_{2peak} and ventilatory efficiency, and 6) lower Short Form-36 physical/mental component scores and higher Minnesota Living with HF questionnaire score than N-anemic group. Additionally, plasma myeloperoxidase/interleukin-6 levels were directly related to erythrocyte aggregability and inversely related to erythrocyte deformability. However, there were no significant differences in pro-inflammatory factors, rheological/hemodynamic properties, and aerobic capacity between L- and N-anemic groups in the HF patients without EPB.

Conclusion: EPB potentiates anemia-related rheological/hemodynamic dysfunctions by elevating pro-inflammatory status, reducing physical fitness in patients with HF.

1. Introduction

Anemia is an important comorbidity in heart failure (HF), which is associated with a large increase in mortality [1,2]. An increased rigidity of erythrocyte has been diagnosed in patients with anemia, and this impaired deformability is negatively correlated to the hemoglobin (Hb) concentration in blood [3]. Clinical investigations have demonstrated that patients with cardiovascular diseases were frequently accompanied by the increases in erythrocyte aggregability and blood viscosity, which may enhance vascular resistance to flow shear force and heighten tendency for vascular thromboembolism [4,5].

Elevated oxidative stress and correspondingly increased pro-inflammatory cytokine levels conspicuously contribute to the development and progression in chronic HF [6,7]. Repeated, excessive exposure to oxidative stress progressively impairs the rheological properties of erythrocyte because of the lack of nuclei and organelles for *de novo* synthesis of antioxidants in erythrocyte [8,9]. Additionally, elevated oxidative stress may accelerate erythrocyte senescence, subsequently promoting the cells removed from circulation by macrophage engulfment [9,10]. However, the relationships between oxidative stress/pro-inflammatory status and erythrocyte rheological properties in HF patients with anemia have not yet been established.

Periodic breathing, an abnormal pattern of respiration that consists of alternating hyperpnea and hypopnea, has been recognized during exercise and sleep in chronic HF patients [11,12]. A recent investigation has demonstrated an elevated oxidative stress in HF patients with sleep periodic breathing (Cheyne–Stokes respiration) [13]. Whether exertional periodic breathing (EPB) influences erythrocyte rheological properties by

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modulating circulatory redox status in anemic HF patients is still unclear. Accordingly, we hypothesize that anemic HF patients with EPB exhibit higher levels of peroxide/pro-inflammatory products than those without EPB do. Moreover, the elevated oxidative stress by EPB facilitates erythrocyte senescence and rheological dysfunctions, subsequently reducing hemodynamic efficiency during exercise, ultimately depressing aerobic capacity and health-related quality of life (QoL) in the HF patients.

To answer the above questions, this investigation compared the differences in 1) plasma peroxide and pro-inflammatory cytokine levels, 2) erythrocyte senescence and shape in blood, 3) erythrocyte aggregability and deformability under shear flows, 4) hemodynamic response to exercise and aerobic capacity, and 5) generic and disease-specific QoL among anemic/non-anemic HF patients with/without EPB. The purpose of this study was to clarify whether EPB potentiates anemia-related rheological/hemodynamic dysfunctions, further exploring possible mechanisms of circulatory disturbance and exercise intolerance in the HF patients who suffer from anemia and/or EPB.

2. Methods

2.1. Subjects

This study enrolled 168 patients diagnosed with HF from August 2010 to December 2011 in the Department of Cardiology, Chang Gung Memorial Hospital, Taiwan. The HF was diagnosed if the patients had (i) a left ventricular ejection fraction (LVEF) ≤40% or (ii) LVEF >40% with episodes of acute pulmonary edema after excluding other non-cardiogenic etiologies. These patients with HF belonged to New York Heart Association functional classes II to III and had received optimal treatment for at least 12 months according to American Heart Association/American College of Cardiology guidelines. Exclusion criteria included the presence of atrial fibrillation/flutter, second/third degree heart block, history of life-threatening ventricular arrhythmias, recent unstable angina, myocardial infarction or coronary revascularization (<4 weeks), uncontrolled diabetes mellitus, severe chronic obstructive pulmonary disease, or symptomatic cerebrovascular disease within 12 months, collagen vascular disease, alcohol or drug abuse during the previous 12 months or significant renal or hepatic disease. Subjects were divided into six groups: non (N)-anemic with (n=27)/without (n=56) EPB, light (L)-anemic with (n=17)/without (n=21) EPB, and moderate–several (M/S)-anemic with (n=21)/without (n=26) EPB groups. Anemia was classified using the World Health Organization criteria: 1) light anemia, 11 g/dL≧Hb<12 g/dL in women and 12 g/dL≧Hb<13 g/dL in men; 2) moderate anemia, 10 g/dL≧Hb<11 g/dL in women and 11 g/dL≧Hb<12 g/dL in men; and 3) severe anemia, hemoglobin <10 g/dL in women and hemoglobin <11 g/dL in men [14]. Periodic breathing during exercise was identified according to the following criteria present on ventilation measurements: 1) the regularity of ventilatory oscillations was ≧3 consecutive cycles; 2) the standard deviation of three consecutive ventilatory cycle lengths was <20% of the average; 3) minimal average amplitude of ventilatory oscillation was ≧5 L; and 4) each ventilatory cycle time was proximally 1 min [11,15]. Additionally, normal control (NC) group was carefully selected to recruit 30 subjects who had no anemia (hemoglobin≧12 g/dL in women and hemoglobin≧13 g/dL in men) and cardiopulmonary/hematological disorders. The investigation was performed according to the Helsinki declaration, and was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan. All subjects provided informed consent after the experimental procedures were explained.

2.2. Graded exercise test

Subjects performed a graded exercise test on a bicycle ergometer (Ergoselect 150P, Germany). Each subject was instructed to fast for at least 8 h and to refrain from exercise for at least 24 h before the test. All subjects arrived at the testing center at 9:00 AM to eliminate diurnal effects. The exercise test comprised 2 min of unloaded pedaling followed by a continuous increase in work-rate of 10 W/min until exhaustion (progressive exercise to peak oxygen consumption, VO_{2peak}) [16]. Minute ventilation (V_E), oxygen consumption (VO_2), and carbonic dioxide production (VCO_2) were measured breath by breath using a computer-based system (MasterScreen CPX, Cardinal-health Germany). Heart rate (HR) was determined from the R–R interval on a 12-lead electrocardiogram,

Table 1
Demographic and clinical characteristics in various groups.

		HF with EPB			HF without EPB			NC
		N-anemia	L-anemia	M/S-anemia	N-anemia	L-anemia	M/S-anemia	
Anthropometrics/clinical characteristics								
Subjects	n (%)	27 (41.5)	17 (26.2)	21 (32.3)	55(53.4)	22 (21.4)	26 (25.2)	30
Gender	male/female	15/12	8/9	9/12	21/24	10/11	12/14	15/15
Age	year	60.3±2.1	62.6±2.9	63.3±2.7	60.9±3.2	60.1±3.4	61.8±3.1	59.3±2.8
Height	cm	164.2±2.5	162.1±2.1	161.9±1.9	165.6±2.1	163.0±2.6	161.1±2.0	163.0±1.9
Weight	kg	66.7±2.6	64.4±3.0	64.9±2.3	65.83±2.6	64.3±2.6	63.9±2.9	63.0±1.9
HR	beat/min	76±3	76±3	78±2	77±3	77±2	79±4	74±3
SBP	mm Hg	129±3	128±3	130±4	130±3	131±4	129±3	127±3
DBP	mm Hg	79±3	80±3	78±2	81±3	78±2	79±3	77±2
Etiology (primary cause)								
Ischemia	n (%)	15 (56)	9 (53)	12 (57)	35 (63)	11 (53)	14 (54)	0 (0)
Hypertension	n (%)	3 (11)	2 (12)	2 (10)	5 (9)	3 (12)	3 (12)	0 (0)
Cardiomyopathy	n (%)	9 (33)	6 (35)	7 (33)	16 (28)	6 (35)	9 (34)	0 (0)
HF duration	year	4.1±1.8	4.2±1.7	4.5±1.6	4.1±1.9	4.0±1.6	4.3±1.8	0±0
Echocardiography								
LVEF	%	38.2±3.5	36.9±3.1	37.5±3.9	37.5±4.0	34.5±2.9	35.2±3.6	ND
Renal function								
BUN	mg/dL	16.2±1.3	17.8±2.0	15.8±2.0	15.8±1.1	16.9±1.5	17.0±2.1	ND
Creatinine	mg/dL	1.1±0.2	1.0±0.1	1.2±0.1	0.9±0.1	1.0±0.2	1.2±0.2	ND
Metabolic biomarkers								
Cholesterol	mg/dL	187±7	185±8	180±11	190±12	188±11	186±12	ND
Triglyceride	mg/dL	125±8	118±7	116±10	118±11	124±12	122±11	ND
Glucose	mg/dL	119±6	120±7	115±8	117±6	113±5	118±8	ND
HbA1c	%	6.6±0.6	6.8±0.7	7.1±0.6	6.5±0.8	6.4±0.9	6.8±0.7	ND
Uric acid	mg/dL	7.6±0.7	7.5±0.9	8.0±1.0	7.2±1.0	8.1±0.9	7.4±0.8	ND
Medications								
Digoxin	n (%)	5 (20)	4 (22)	4 (20)	12 (21)	5 (22)	5 (20)	0 (0)
β-blocker	n (%)	25 (92)	15 (91)	20 (93)	51 (91)	20 (93)	25 (95)	0 (0)
ACE/ARB	n (%)	22 (81)	13 (78)	17 (82)	45 (81)	17 (82)	21 (80)	0 (0)
Ca^{2+}channel blocker	n (%)	18 (65)	10 (67)	13 (60)	38 (68)	14 (65)	17 (65)	0 (0)
Diuretics	n (%)	14 (50)	9 (55)	11 (51)	30 (53)	10 (48)	14 (53)	0 (0)

N-anemia, non-anemic group; L-anemia, light-anemic group; M/S-anemia, moderate/severe-anemic group; NC, normal control group; HF, heart failure; EPB, exertional periodic breathing; ND, no determination. Values are mean±SEM.