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SHORT REPORT

Pulmonary Arterial Pressure Changes Under Dobutamine Stress Echocardiography in Non-Anemic Iron Deficient COPD Subjects

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Purpose: Non-anemic iron deficiency (NAID) is common in COPD, and could induce functional/structural changes in the pulmonary vascular bed. Thus, we aimed to study, during resting and ambient oxygen conditions, the systolic pulmonary arterial pressure (sPAP) changes during dobutamine stress echocardiography (DSE) for NAID+ compared to NAID- subjects with COPD.

Patients and Methods: We analyzed 24 patients with COPD and evaluated their clinical parameters, including lung function and serum iron profile, followed by the changes in the sPAP under DSE.

Results: Ten subjects with NAID+ were compared with fourteen NAID- subjects for sPAP measurement. At baseline, only left atrial volume was significantly different between groups (30±4 vs 23±5 $mL_{*}m^{2}$), respectively (p-value=0.002). For the right side, tricuspid annular plane systolic excursion (TAPSE) was similar between-groups (22±2 vs 20±4, p-value >0.05), at baseline. The sPAP (mmHg) changes were also not significantly different between groups (pre 32±14 vs peak 48±14 for NAID+ and pre 29±7 vs peak 43±10 for NAID-, Group p-value=0.400, Time p-value <0.0001, and Interaction p-value=0.606).

Conclusion: COPD subjects with NAID do not show increased sPAP responses during DSE, compared with iron-replete subjects.

Keywords: COPD, iron deficiency, pulmonary hypertension, stress echocardiography

Introduction

Non-anemic iron deficiency (NAID) is a common metabolic disorder, affecting between 18% and 48% of subjects with chronic obstructive pulmonary disease (COPD).[1,2] Among the known pulmonary vascular effects of NAID are intracellular oxidative stress dysregulation,[3] pulmonary arterial smooth muscle proliferation,[4] and hyperreactive hypoxic pulmonary vasoconstriction (HPV).[5] Thus, NAID could be associated with increased systolic pulmonary arterial pressure (sPAP) under resting conditions in COPD subjects.[6] Hypoxia (and iron deficiency) could stabilize the hypoxia induced factor 1-α and trigger HPV.[4,5] In spite of this, little attention has been given to the hemodynamic effects involved in the pulmonary vascular bed in COPD subjects with NAID; in fact, COPD subjects are prone to abnormal increases in sPAP under certain conditions, eg, exacerbations, sleep-associated hypoxemia or exercise.[7]

NAID has been associated with lower physical activity and exercise capacity in COPD.[2,8] Moreover, iron supplementation led to increased exercise capacity.[9] In "healthy" people with NAID, iron supplementation led to a reduction in sPAP during exercise, independently of hypoxia.[5] As pulmonary arterial bed regulation has an important role for exercise performance, the impact of NAID for sPAP responses under increased pulmonary blood flow conditions is critical to expand our knowledge in this field.

Thus, the current study was performed primarily to explore sPAP responses in COPD with or without NAID, under dobutamine stress echocardiography (DSE), with the main hypothesis of a significantly higher increase in sPAP under

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DSE in the NAID group compared to the iron-replete group. The secondary endpoint was baseline left and right ventricular performance differences between the groups.

Methods

This is an observational, single-center, parallel-group and prospective study, including patients from March to December 2021. The subjects were recruited at the COPD clinic from the University Hospital (HUMAP) after local Ethics Committee on Research Involving Human Beings approval, from the Federal University of Mato Grosso do Sul (number 20527619.2.0000.0021), and all patients provided written informed consent. Subjects were invited to participate during two visits. The first visit was intended to verify inclusion/exclusion criteria, blood analysis, and lung function tests. The second visit was scheduled for the DSE.

Inclusion criteria were COPD subjects with at least two months stable disease and with optimized bronchodilator therapy. Exclusion criteria included chronic oxygen therapy, previous myocardial infarction, anemia (<12 g% for woman and <13 g% for men),[10] serious cardiac arrhythmia, non-effective increase in heart rate during DSE, and intercurrent comorbidities, such as bronchial asthma, thyroid pathology, heart failure, neoplasia, lung resection, uncontrolled hypertension, or diabetes. The criteria for NAID in COPD subjects are controversial and there is no global consensus.[2,6,10] Notwithstanding, we used the most accepted criteria for COPD, including functional and definitive NAID; Definitive NAID was defined as a ferritin level lower than 100 ng/mL and functional NAID included subjects with a ferritin level between 100 and 299 ng/mL and transferrin saturation (TS) <20%. Lung function included pre- and post-bronchodilator spirometry and the carbon monoxide diffusion capacity, both following the ERS/ATS criteria[11] and Brazilian predictive values.[12,13]

The standard and stress echocardiography were performed in a climatized room; two-dimensional, M-mode, and Doppler echocardiography were performed according to the American Society of Echocardiography.[14] The subjects were admitted during the morning and under food fasting. A venous line catheter was inserted in the median basilic vein. Images and parameters were collected with a standard device (EPIQ 7C, Philips, USA). The initial examination consisted of the left ventricular (LV) measures, including the left atrial indexed volume (LAV). LV ejection fraction was measured by the Teichholz and Simpson methods. In addition, LV diastolic function was performed by tissue and pulsed-Doppler echocardiography. Detailed methods for assessment of LV diastolic function have been previously published,[15] and included: (i) peak velocity of early diastole (E), peak atrial contraction velocity (A), and the E/A ratio, obtained by pulsed-wave Doppler on the mitral valve; (ii) Tissue pulsed-wave Doppler of the septal and lateral portions of the mitral annulus in diastole (E´) and the E/E´ ratio. The baseline and peak tricuspid reflux velocity (TRV) were obtained through continuous-wave Doppler at the right ventricle (RV) inlet, and the sPAP was measured by the peak gradient between the RV and the right atrium from the peak TRV, after right atrium pressure (RAP) acquisition and using the Bernoulli equation ($sPAP = (TRV)^2 + RAP$). RAP was estimated from the inferior vena cava diameter and collapsibility. Right ventricular systolic function was assessed at baseline with the tricuspid annular plane systolic excursion (TAPSE). All patients underwent continuous dobutamine infusion, under continuous monitoring of systemic arterial pressure (SAP), heart rate (HR), and peripheral oximetry (SpO_2) (DIXTAL DX 25215, Dixtal, 2008). Dobutamine was increased at increments of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 3-min intervals up to a maximum of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, seeking to achieve 85% of the maximal predicted HR. In order to reach the predicted submaximal HR, we also used handgrip exercise and atropine (up to a maximum dose of 2 mg), from the dobutamine dose of 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[16] The echocardiography was performed by a cardiologist-sonographer, blinded for blood analysis results, with wide experience in COPD echocardiograms. Thus, all records were considered technically acceptable.

All data are presented as mean±SD. For prediction of the minimum sample size, we used recently published data on reliability of sPAP through DSE.[17] Considering a between-subjects average ferritin difference of 100 ng/mL, and a within-subject mean ± SD difference of −1.2±8.0 mmHg for peak sPAP, 10 subjects in each group are necessary to reach a power of 0.8, in a two-tailed study, with significance adjusted for a p-value <0.05, in a two-way repeated measure ANOVA design. Categorical variables were submitted to the Fisher statistical approach and the Shapiro–Wilks method was used to evaluate the distribution profile of the sample. In addition, the Student t or Mann–Whitney *U*-tests were performed where appropriate for group comparisons.

Results

Twenty-four subjects were eligible and performed all the tests. Ten NAID+ and fourteen NAID- subjects were evaluated for primary and secondary endpoints. The subjects (mean±SD) were aged 65±11 vs 66±9 years, respectively, and were similar for gender, body mass index (BMI), Charlson Comorbidity Index (CCI), and smoking status (p-value >0.05 for all, Table 1). Similarly, FEV_1 (47±19 vs 48±13%predicted) and frequency of comorbidity/medication use were not significantly different between groups (p-value >0.05 for all, Table 1).

For the LV evaluation, only the LAV index (mL_*m^2) was significantly different for NAID+ vs NAID- subjects (30±4 vs 23±5 respectively, p-value=0.002, Table 1). Tissue Doppler E´ lateral (cm/s) was marginally non-significant between-groups (11±4 vs 8±2, p-value=0.07, Table 1). For the right side, TAPSE (mm) was similar between-groups at baseline (22 ±2 vs 20±4, p-value >0.05, Table 1). The sPAP changes (baseline-to-peak, mmHg) were also not significantly different between-groups (pre 32±14 vs peak 48±14 for NAID+ and pre 29±7 vs peak 43±10 for NAID-, Group p-value=0.400, Time p-value <0.0001, and Interaction p-value=0.606, Table 2 and Figure 1B). HR, TRV, and SAP responses were also

Table 1 Clinical Features, Blood Analysis, Lung Function, and TT Echocardiography for Selected Data. Comparative Data Between COPD with and without NAID

Data	NAID + (n=10)	NAID – (n=14)	*p*-value
Clinical features			
Age(yrs)	65±11	66±9	0.655
Gender M/F (n)	4/6	5/9	0.990
BSA (m^{-2})	1.7±0.1	1.8±0.2	0.528
BMI (kg m^{-2})	27±5.0	27±5.7	0.886
Smoking (p/y)	49±40	45±34	0.930
CCI (score)	3.5±1.1	3.9±1.1	0.454
Blood analysis			
Hb (g/dL)	14±2	15±2	0.614
Serum Iron (μg/dL)	71±31	94±25	0.004
Ferritin (ng/mL)	113±92	368±258	0.001
Transferrin Sat (%)	20±7	30±9	0.003
Creatinine (mg/dL)	0.9±0.4	0.9±0.2	0.912
Glucose (mg%)	101±20	133±67	0.374
Glicosilated Hb (%)	6.1±0.9	6.7±2.0	0.800
Lung function			
FEV1 (% pred)	47±19	48±13	0.930
FVC (% pred)	80±13	81±15	0.891
FEV1/FVC (%)	44±13	47±12	0.668
DLco (% pred)	37±6	47±6	0.060
DLco/VA (% pred)	61±13	72±21	0.476
TT Echocardiography			
LV Ejection fraction (%)	66±4	65±5	0.354
TAPSE (mm)	22±3	20±4	0.229
LAV index (mL/m^2)	30±4	23±5	0.002
E/A	0.8±0.3	0.9±0.4	0.496
TD E´ lateral (cm/s)	11±4	8±2	0.070
E/E´	9.4±6.6	8.7±3.2	0.578
Comorbidity			
SA Hypertension (%)	70	57	0.678
Diabetes Mellitus (%)	10	28	0.357
Coronariopathy (%)	20	0	0.550
Dislipidemia (%)	70	50	0.421

(*Continued*)

Table 1 (Continued).

Data	NAID + (n=10)	NAID – (n=14)	*p*-value
Medications			
SABA (%)	60	29	0.211
LABA (%)	70	79	0.665
LAMA (%)	40	29	0.663
IC (%)	60	78	0.392

Note: Significant $p < 0.05$ comparing NAID+ vs NAID-.Statistically significant if p-value <0.05.
Abbreviations: BSA, body surface area; BMI, body mass index; CCI, Charlson comorbidity index; DL_{CO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV_1/FVC, ratio on forced expiratory volume in 1 s and forced vital capacity; LV, Left ventricular; IC, inspiratory capacity; TAPSE, tricuspid annular plane systolic excursion; LAV, Left atrial volume; E/A, peak velocity of early diastole/peak atrial contraction velocity; E/E´, peak velocity of early diastole/peak atrial contraction velocity/Tissue pulsed-Doppler of the lateral portions of the mitral annulus in diastole; LABA, long-acting β_2-agonist long-action betamimetic antagonist; LAMA, long-acting muscarinic antagonist; SABA, short-action betamimetic antagonist.

Table 2 Cardiovascular and Oxygenation Results for Dobutamine Stress Echocardiography

Variables	NAID + (n=10)		NAID – (n=14)		*p* value	*p* value	*p* value
	Baseline	Peak	Baseline	Peak	Group	Time	Interaction
HR (beat min^{-1})	72±13	138±9	71±13	146±13	0.396	<0.0001	0.171
SpO_2 (%)	92±5	93±5	94±4	95±2	0.195	<0.0001	0.625
SAP, mm Hg	143±22	147±26	137±19	149±27	0.818	0.091	0.425
TRV, cm s^{-1}	2.5±0.5	3.2±0.5	2.4±0.4	3.1±0.4	0.540	<0.0001	0.797
sPAP, mmHg	32±14	48±14	29±7	43±10	0.400	<0.0001	0.606

Note: Statistically significant if *p*-value <0.05.
Abbreviations: HR, Heart rate; SpO_2, peripheral oximetry; SAP, Systolic arterial pressure; TRV, Tricuspid regurgitation velocity; sPAP, Systolic pulmonary arterial pressure; NAID, Non-anemic iron deficiency.

not significantly different (p > 0.05 for both, Table 2 and Figure 1A, C and D). Of note, SpO_2 increased significantly for the two groups over time (p-value <0.0001, Table 2).

Discussion

To the best of our knowledge, this is the first study to assess sPAP changes under DSE in COPD subjects with NAID. Our preliminary results do not support a role for NAID in increases in sPAP under clinically stable, ambient oxygen, and resting conditions. Further evaluations during exercise are warranted to understand the role of NAID in the pulmonary vascular bed as a limiting factor for exercise intolerance, independently of well-established peripheral muscle impairment due to NAID.

DSE is underused for evaluation of the sPAP responses in COPD. Recently, DSE has been used to detect occult pulmonary arterial hypertension in the presence of normal sPAP under standard echocardiography, with satisfactory diagnostic accuracy compared to invasive methods.[18] DSE has the advantage that it can be administered to patients unable to perform exercise. However, in the COPD population, exercise has the advantage of triggering (I) unambiguous hypoxemia, or, at least, (II) a fall in the pO_2 of venous blood during exercise, that might act as a stimulus to HPV, which is possibly exacerbated in the presence of iron deficiency.[5]

Our study was not designed to detect the incidence of PAH in COPD with NAID; thus, the small sample of our study preclude conclusions that could confirm the results of Plesner et al with regard to the increased frequency of PAH in COPD with NAID under standard echocardiography and resting conditions.[6] Considering a TRV > 2.90 m/s diagnostic for PAH,[6] both groups had the same frequency of baseline PAH (~20%). We should consider, however, that in the Plesner et al study, the authors included only COPD subjects with definitive NAID (Ferritin <100 ng/mL).[6]

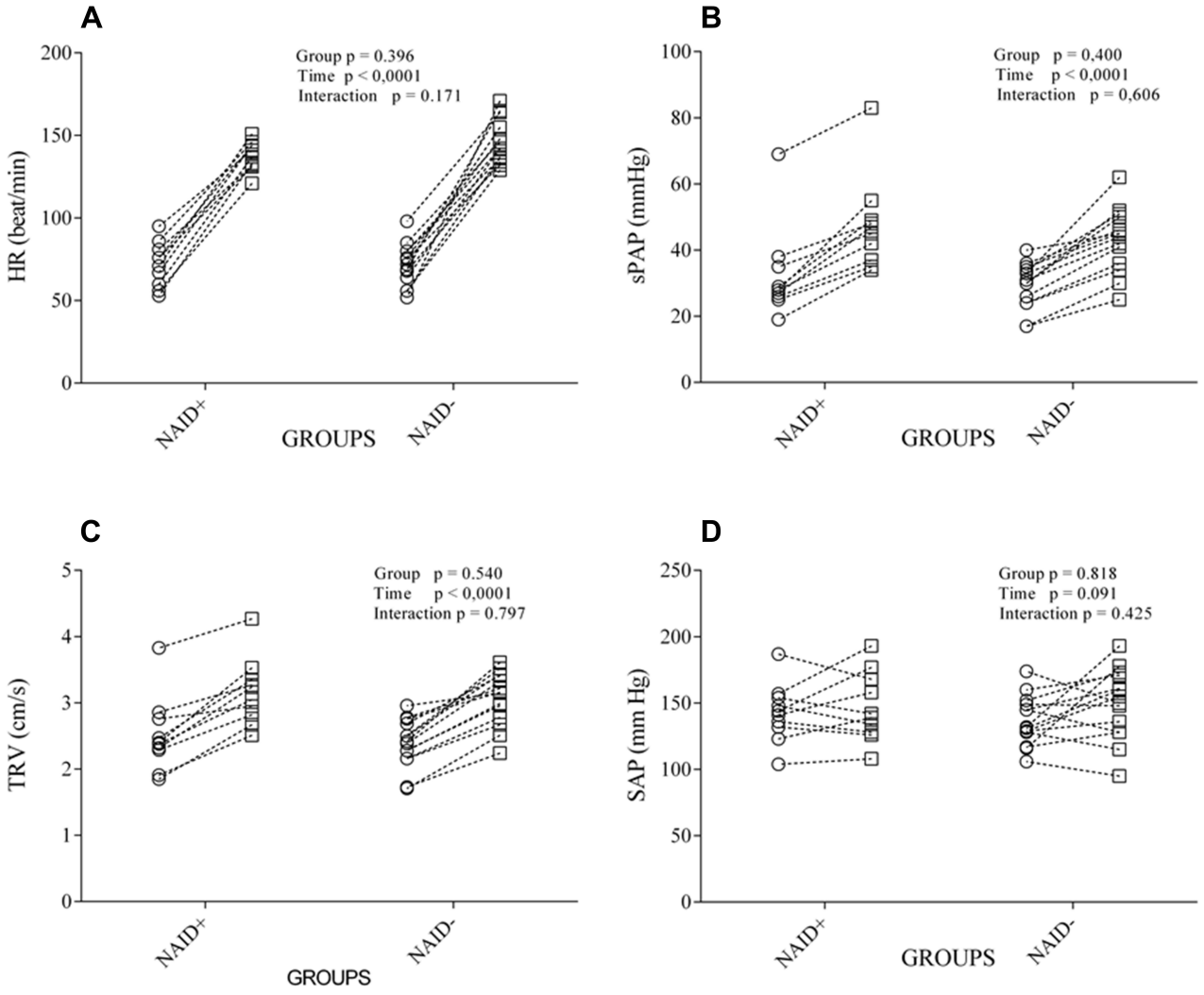

Figure 1 Baseline-to-peak DSE results for heart rate (HR, (**A**)), systolic pulmonary arterial pressure (sPAP, (**B**)), tricuspid regurgitation velocity (TRV, (**C**)), and systemic blood pressure (SAP, (**D**)) according to the groups. Circles=baseline and squares=peak.

The finding of an increased LAV in the NAID+ group is difficult to evaluate, considering the small number of subjects and absence of invasive measurements. Although iron deficiency could induce myocardial energetic disturbance secondary to mitochondrial dysfunction, inducing reduced ventricular reserve,[19] a previous study did not show abnormal cardiac filling pressures in NAID+ subjects.[20] Moreover, TAPSE, SAH frequency, and LV diastolic function were all similar in both groups. As limitations of this study, we point out the small number of subjects, and the possibility of overestimation of NAID diagnosis owing to the inclusion of functional NAID.[6] In addition, pharmacologically induced maximal heart rate under DSE does not characterize the complex mechanisms of exercise intolerance. However, a tachycardia-related increase in sPAP under DSE could predict occult pulmonary arterial hypertension,[21] eventually even highly correlated with invasive methods.[18] Of note, subjects with "early" pulmonary arterial hypertension but yet with normal or near-normal resting hemodynamics, could present with an abnormal PAP when stressed by an increase in pulmonary blood flow.[22,23]

As a preliminary conclusion, NAID in COPD subjects does not induce increased sPAP responses under resting conditions and during dobutamine stress echocardiography. Future studies should include exercise with invasive or non-invasive methods for better understanding of the impact of NAID on pulmonary arterial resistance and its contribution to exercise limitation.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

This study follows ethical standards recommended by the revised statement of Helsinki and the Ethics Committee on Research Involving Human Beings from the Federal University of Mato Grosso do Sul (Approval number 20527619.2.0000.0021). All patients provided written informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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