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Impact of Pulmonary Arterial Hypertension on Left Ventricular Function – a Comparative Study between Scleroderma and Coronary Artery Disease

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ABSTRACT

Background: The impact of pulmonary arterial hypertension (PAH) on left ventricular performance in patients with scleroderma is still unknown. This study aims to perform a comparative echocardiographic analysis of left ventricular function between two different etiological varieties of PAH, namely PAH caused by systemic sclerosis as a representative of systemic inflammatory diseases and PAH caused by myocardial ischemia. **Material and method:** We conducted a prospective observational study on 82 patients, of which 36 were with documented PAH, with the systolic pressure in the pulmonary artery above 35 mmHg, and 46 were patients with normal pulmonary artery pressure. The study population was divided into two groups, based on the etiology of PAH: group 1 included patients diagnosed with scleroderma (n = 48); group 2 included patients with coronary artery disease (n = 35). Patients from each group were divided into two subgroups based on the diagnosis of PAH: subgroup 1A – subjects with scleroderma and associated PAH (n = 20); subgroup 1B – subjects with scleroderma without PAH (n = 28); subgroup 2A – ischemic patients with associated PAH (n = 16); and subgroup 2B – patients with ischemic disease without PAH (n = 19). **Results:** A significant difference between LVEF values in patients with PAH versus those without PAH in the ischemic group ($p = 0.023$) was recorded. Compared to scleroderma subjects, ischemic patients presented significantly lower values of LVEF in both PAH and non-PAH subgroups ($p < 0.0001$ and $p < 0.0001$, respectively). Linear regression analysis between sPAP and LVEF revealed a significant negative correlation only for the ischemia group ($r = –0.52$, $p = 0.001$) and the scleroderma 2B subgroup ($r = –0.51$, $p = 0.04$). Tissue Doppler analysis of left ventricular function revealed a significant impact of PAH on left ventricular diastolic performance in the ischemic group. **Conclusions:** Compared to patients with coronary artery disease, those with scleroderma present a less pronounced deterioration of LVEF in response to pulmonary arterial hypertension.

Keywords: pulmonary arterial hypertension, scleroderma, LVEF, coronary artery disease

INTRODUCTION

Pulmonary arterial hypertension (PAH), defined as an increase in the average pulmonary artery pressure above 25 mmHg, is triggered and maintained by a series of pathological changes based on vascular remodeling and vasoconstriction resulting from inflammatory phenomena and fibrosis, all of which ultimately result in increased pulmonary vascular resistance.[1] A number of studies have advocated for the inflammatory pathogenesis of this pathology, identifying proinflammatory cytokines such as interleukins, alpha tumor necrosis factor, and certain antibodies as promoters of PAH.[2,3]

The vascular remodeling process, invariably followed by increased pressure in the right side of the heart, ultimately leads to a series of constant changes in the right cavities, characterized by the appearance of right atrial remodeling, right ventricular hypertrophy, and tricuspid regurgitation. The association of this condition with myocardial ischemia or ventricular fibrosis leads to the development of right heart failure. Therefore, PAH resulting from the remodeling of distal pulmonary vessels leads invariably to death caused by advanced right heart failure.

Clinically, the PAH patient is generally oligosymptomatic until later stages, presenting progressive fatigue and progressive dyspnea or palpitations, which are unspecific and often overlooked. Symptoms that should raise alarm signals are syncope caused by exertion, or angina occurring as a result of left ventricular insufficiency. Clinical examinations identify in most cases the signs caused by increased pressure in the right cavities: low pulse pressure, painful hepatomegaly associated with hepatojugular reflux, turgescent jugular veins, ascites, and peripheral edema.[4,5]

The World Health Organization (WHO) classifies PAH in 5 etiological subgroups, as follows: subgroup 1 – idiopathic or familial PAH; subgroup 2 – PAH caused by left heart failure (systolic, diastolic or valvular); subgroup 3 – PAH caused by respiratory diseases evolving with pulmonary fibrosis, including bronchial asthma, pulmonary emphysema, chronic obstructive bronchopneumonia; subgroup 4 – PAH caused by chronic pulmonary thromboembolism; subgroup 5 – unclear or multifactorial pathogenetic mechanisms.[6] At the same time, a pulmonary etiology has been described in the literature, caused by left ventricular insufficiency, as the main cause for most cases of PAH.[7]

PAH is a frequent complication of several systemic autoimmune disorders such as scleroderma, studies showing that approximately 8–12% of patients with systemic sclerosis develop different degrees of PAH during the course of the disease.[8–10] Furthermore, the resulting PAH is associated with a significantly higher rate of complications and death compared to patients with other etiological forms of PAH, including those with idiopathic PAH.[11–13] PAH in scleroderma occurs as a consequence of the progressive remodeling of distal lung vessels. Progression mechanisms are incompletely known, but common precursors are considered to be represented by endothelial inflammation and dysfunction, which ultimately determines a progressive increase in pulmonary vascular resistance and pulmonary arterial pressure, leading to pressure overload in the right chambers.[14]

Left heart failure caused by ischemic coronary artery disease (CAD) is characterized by increased influx pressures in the left cavities, either due to alteration of the diastolic function or due to mitral valve insufficiency, which in turn causes post-capillary pulmonary hypertension or venous hypertension. This complex pathogenetic mechanism leads to dysfunction of the vascular endothelium and pulmonary vascular remodeling, which will inevitably lead to changes similar to those seen in patients with primary arterial pulmonary hypertension.[15–17] The impairment of left ventricle systolic function in patients with scleroderma is a controversial issue in the literature, several studies identifying a reduced number of subjects with decreased left ventricular contractility.[18] However, the left myocardium is frequently characterized by piecemeal fibrosis, secondary to both ischemia and immune inflammatory phenomena, which invariably leads to the alteration of diastolic function and, to some extent, also influences the systolic performance of the left heart.[19,20] Regarding the alteration of diastolic function in myocardial ischemia, it is known that it leads to the alteration of myocardial relaxation, which is reversible by myocardial revascularization in the initial phase, but becomes permanent in the post-myocardial infarction phase, when an altered relaxation pattern appears in relation to the ventricular remodeling processes.[21]

This study aims to perform a comparative echocardiographic analysis of left ventricular function between two different etiological varieties of PAH, namely PAH caused by systemic sclerosis as a representative of systemic inflammatory diseases and PAH caused by myocardial ischemia.

MATERIAL AND METHOD

We conducted a prospective observational study on 82 patients, of which 36 were patients with documented PAH, with a systolic pressure in the pulmonary artery above 35 mmHg, and 46 were patients with normal pulmonary artery pressure.

All patients were examined by 2D, Doppler, and tissue Doppler transthoracic echocardiography, and the following parameters were assessed: (a) for left heart cavities: left ventricular ejection fraction (LVEF), left atrium diameter, LV end-systolic/diastolic diameter, E/A ratio, DT, tissue Doppler (e' septal and e' lateral); (b) for right heart cavities: systolic pulmonary artery pressure (sPAP). Images were obtained from parasternal, apex, and subcostal views. The noninvasive assessment of sPAP was determined based on the peak velocity of the continuous Doppler tricuspid regurgitation wave, followed by the Bernoulli equation and adding the estimated right atrial pressure. Valvular regurgitation was evaluated using the Doppler color function. The LVEF was evaluated using the Simpson formula based on two-dimensional LV images during systole and diastole from apical views of 4 and 2 chambers. Mitral valve flow assessment was performed to quantify the following parameters: maximum velocity of early diastolic filling (E), maximum velocity of late diastolic filling by atrial contraction (A), and deceleration time of the E wave (DT). Tissue Doppler analysis was performed at the level of the mitral annulus, from apical 4 chambers view, to assess early diastolic velocity at the lateral ring (E' lateral) and early septal diastolic velocity (E' septal). All measurement values were obtained as an average of more than 3 heart cycles. All echocardiographic examinations were performed with a Vivid E9 echocardiographic equipment (General Electric Vingmed Ultrasound, Horten, Norway).

Statistical analysis was performed using the GraphPad Prism 7 software. To test the distribution of numerical data, the D'Agostino Pearson normality test was used; numerical data was expressed as mean ± standard or median deviation when appropriate, and qualitative data was expressed as numerical value and percentage. The Spearman or Pearson coefficient was used to illustrate linear correlation and regression analysis. The t test was used for the analysis of the two groups regarding non-pair continuous variables. The specific variables were compared using the chi-square test, and a p value below 0.05 was considered statistically significant.

This study was conducted in accordance with the revised version of the Helsinki Declaration. The study was conducted under the approval of the Ethics Commission of SCJU Tîrgu Mureş No. 17345/09.07.2018. Written informed consent was obtained from each patient prior to enrolment.

The study population was divided into two groups, based on the etiology of PAH: group 1 included patients diagnosed with scleroderma (n = 48); group 2 included patients diagnosed with CAD (n = 35). Patients of each group were divided into two subgroups based on the diagnosis of PAH: subgroup 1A – subjects with scleroderma associated with PAH (n = 20); subgroup 1B – subjects with scleroderma without PAH (n = 28); subgroup 2A – ischemic patients with associated PAH (n = 16); and subgroup 2B – patients with ischemic disease without PAH (n = 19).

RESULTS

General characteristics of the study population

From 82 study patients, 48 presented scleroderma (58.53%), and 35 (42.68%) presented CAD. In total, 36 patients were diagnosed with PAH, of which 20 (subgroup 1A – 41.66%) with scleroderma and 16 (subgroup 2A – 45.71%) with myocardial ischemia. There were no significant differences between groups regarding the body mass index (BMI, p = 0.8), or chronic tobacco use (p = 0.7). However, patients in the first group presented a significantly higher number of female subjects (p = 0.001) and a higher mean age (p = 0.009) compared to group 2 (Table 1).

LVEF and PAH

We found no statistically significant differences between the subgroups of scleroderma patients in terms of LVEF (p = 0.2182). However, there was a significant difference between LVEF values in patients with PAH versus those without PAH in the ischemic group (p = 0.023) (Figure 1). Moreover, when compared to subjects with scleroderma, ischemic patients presented significantly lower values of LVEF in both the PAH and the non-PAH subgroups (p <0.0001 and p <0.0001, respectively) (Figure 2). Linear regression analysis between sPAP and LVEF revealed a significant negative correlation only for the ischemia group (r = –0.52, p = 0.001) and the scleroderma 2B subgroup (r = –0.51, p = 0.04) (Table 2).

Tissue Doppler analysis of left ventricular function

Regarding the results of tissue Doppler measurements, a significant negative correlation was obtained between the

TABLE 1. General characteristics of the study population

	Scleroderma	CAD	p value
Age (years)	49.7 ± 6.4	57.5 ± 5.3	0.009
Female gender	67%	37%	0.001
BMI	24.7	25.6	0.8
Smoking	40%	45%	0.7

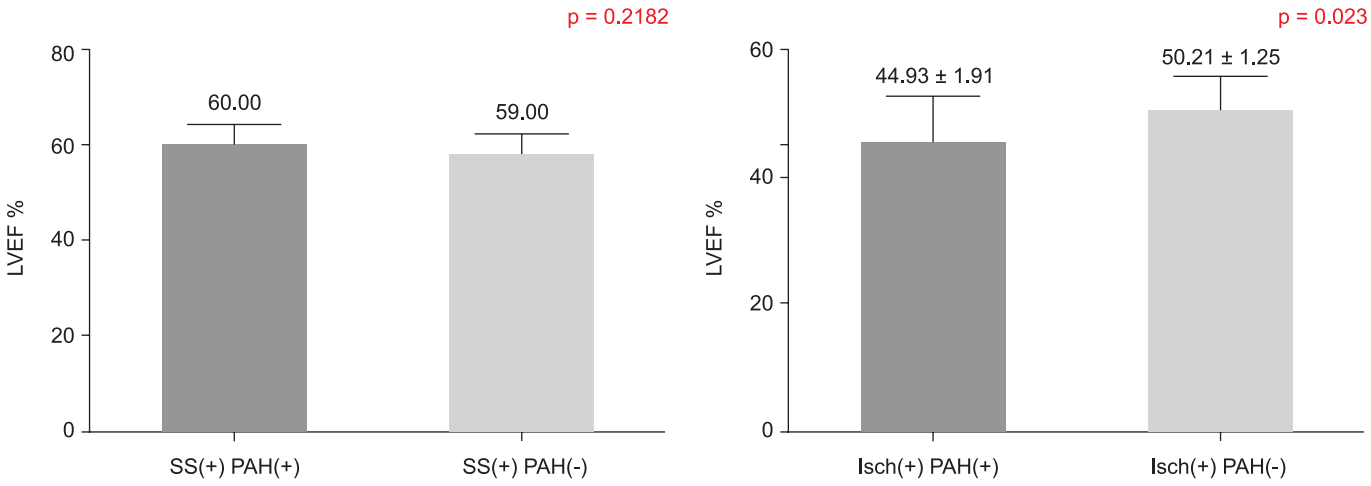

FIGURE 1. LVEF in patients with PAH vs. patients without PAH in the scleroderma group (**A**) and in the ischemic group (**B**)

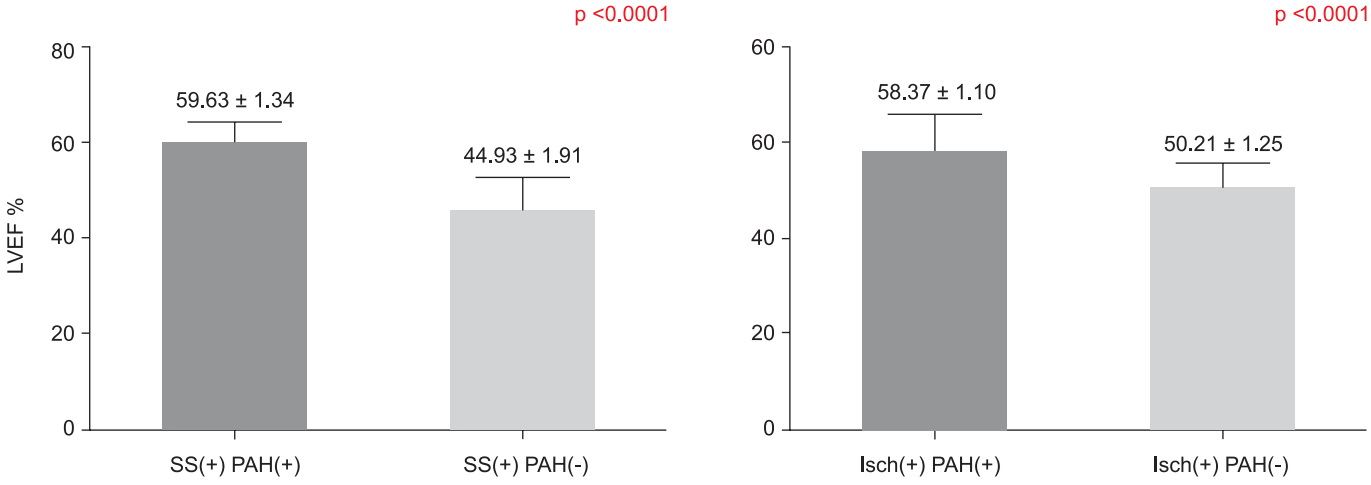

FIGURE 2. LVEF in the scleroderma group vs. the ischemic group in patients with PAH (**A**) and without PAH (**B**)

septal E' value and the sPAP value for the main group of ischemic patients (r = –0.52, p = 0.0013). In the ischemic group, we found a negative correlation between the septal E' value and the sPAP (r = –0.44, p = 0.08) for the PAH subgroup and a positive correlation (r = 0.08, p = 0.85) for the 2B subgroup, both without statistical significance.

Among patients with scleroderma, a weak positive correlation between E' lateral and sPAP was obtained for both the main group (r = 0.04, p = 0.85) and subgroup 1B (r = 0.03, p = 0.89). In contrast, scleroderma and PAH patients showed a poor negative correlation between sPAP and septal E', with no statistical significance (r = –0.09, p = 0.6) (Figure 3).

TABLE 2. Correlations between sPAP and LVEF in the study groups and subgroups

Group	r	p value
Scleroderma	0.11	0.43
Ischemia	–0.52	0.001
Scleroderma and PAH	–0.26	0.15
Scleroderma without PAH	–0.51	0.04
Ischemia and PAH	–0.45	0.08
Ischemia without PAH	–0.37	0.11

Analysis of left ventricular diastolic function

Regarding the correlations between the E/A ratio and sPAP, only the subgroup of ischemic PAH patients showed a statistically significant positive correlation (r = 0.48, p = 0.05). Neither the main group of ischemic patients (r = 0.21, p = 0.21), nor the subgroup of patients without PAH (r = –0.34, p = 0.15) showed any significant correlations. Among the patients with scleroderma, no significant correlations were found between the E/A ratio and sPAP for the main group

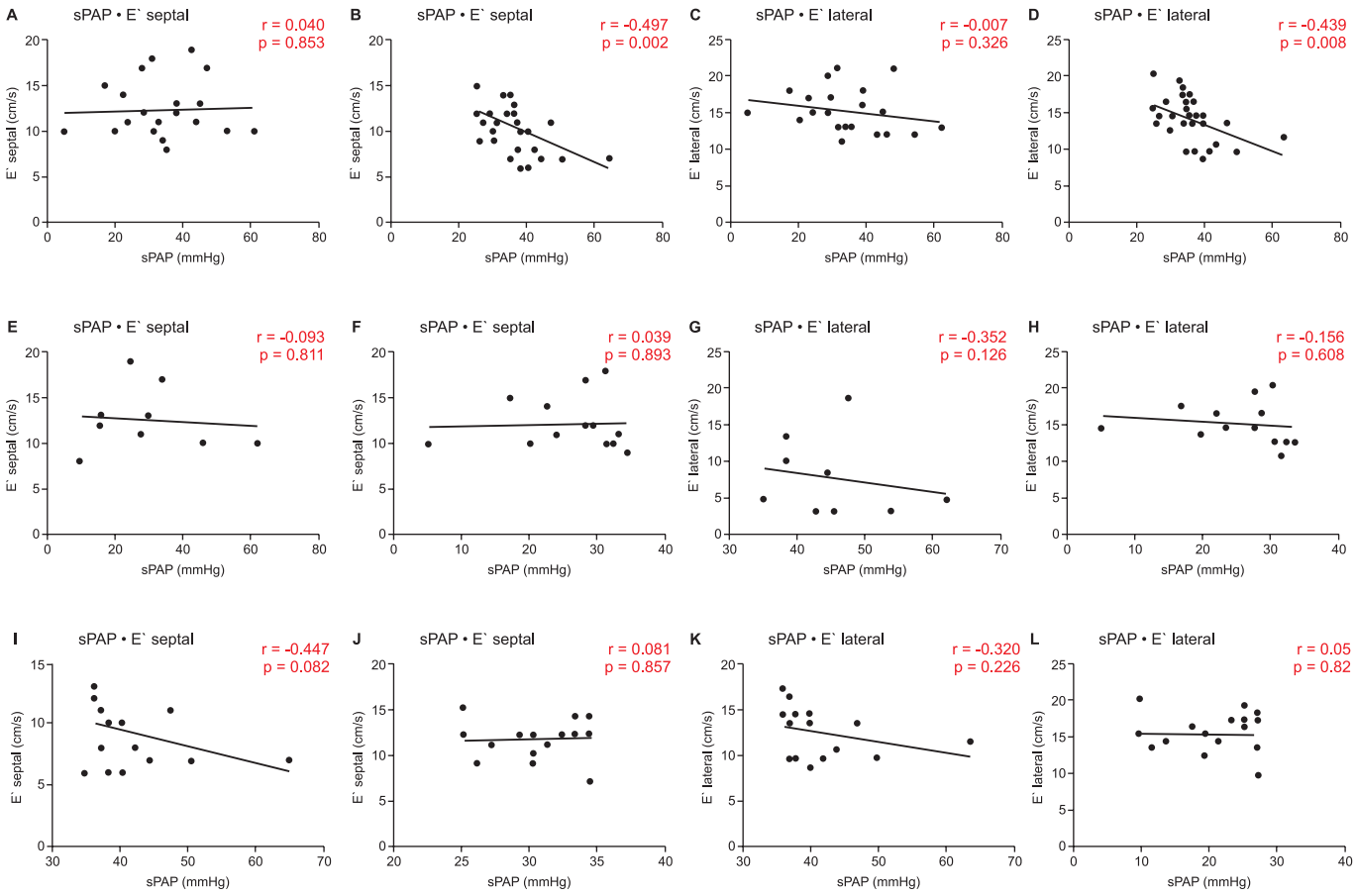

FIGURE 3. Correlation between tissue Doppler indexes (E` septal and E` lateral) and PAPs in the study groups. **A** – correlation between E' septal value and the sPAP in patients with scleroderma; **B** – correlation between E' septal value and the sPAP in patients with coronary artery disease; **C** – correlation between E' lateral value and the sPAP in patients with scleroderma; **D** – correlation between E' lateral value and the sPAP in patients diagnosed with coronary artery disease; **E** – correlation between E' septal value and the sPAP in patients with SS(+) PAH(+); **F** – correlation between E' septal value and the sPAP in patients with SS(+) PAH(–); **G** – correlation between E' lateral value and the sPAP in patients with SS(+) PAH(+); **H** – correlation between E' lateral value and the sPAP in patients with SS(+) PAH(–); **I** – correlation between E' septal value and the sPAP in patients with Isch(+) PAH(+); **J** – correlation between E' septal value and the sPAP in patients with Isch(+) PAH(–); **K** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(+); **L** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(–)

(r = 0.23, p = 0.12), or for the subgroups (r = 0.20, p = 0.29 – subgroup 1B; r = –0.44, p = 0.08) (Figure 4).

Concerning the E-wave DT, the patients from the scleroderma group did not present any significant correlations with sPAP in the main group (r = –0.23, p = 0.13), neither in the subgroups with (r = 0.20, p = 0.49) or without PAH (r = 0.14, p = 0.46). Patients in the ischemic group showed a negative correlation between DT and sPAP (r = –0.25, p = 0.17), a positive correlation in the two subgroups: with PAH (r = 0.09, p = 0.73) and without PAH (r = 0.01, p = 0.95), but without reaching the statistical threshold. Following the comparison of the mean DT value, a statistically significant difference was obtained between the study subgroups (subgroup 1A 175 ± 11, subgroup 1B 208 ± 10, subgroup 2A 190 ± 4, subgroup 2B 190 ± 3, p = 0.01) (Figure 5).

DISCUSSIONS

The purpose of this study was to evaluate systolic and diastolic ventricular function in scleroderma patients compared to those with ischemic heart disease. In this respect, we compared left ventricular systolic and diastolic function for two disorders involving different pathophysiological mechanisms. Myocardial ischemia episodes are common in the development of scleroderma, not due to epicardial coronary artery stenosis, but to microvascular dysfunction, since vascular lesions specific to scleroderma lead to a major alteration of the microcirculation.[22,23] Moreover, we attempted a comparative analysis between subgroups with and without PAH in each of the main study groups, since beyond the impact of PAH on the structure of the heart and independent of it, myocardial damage is well-

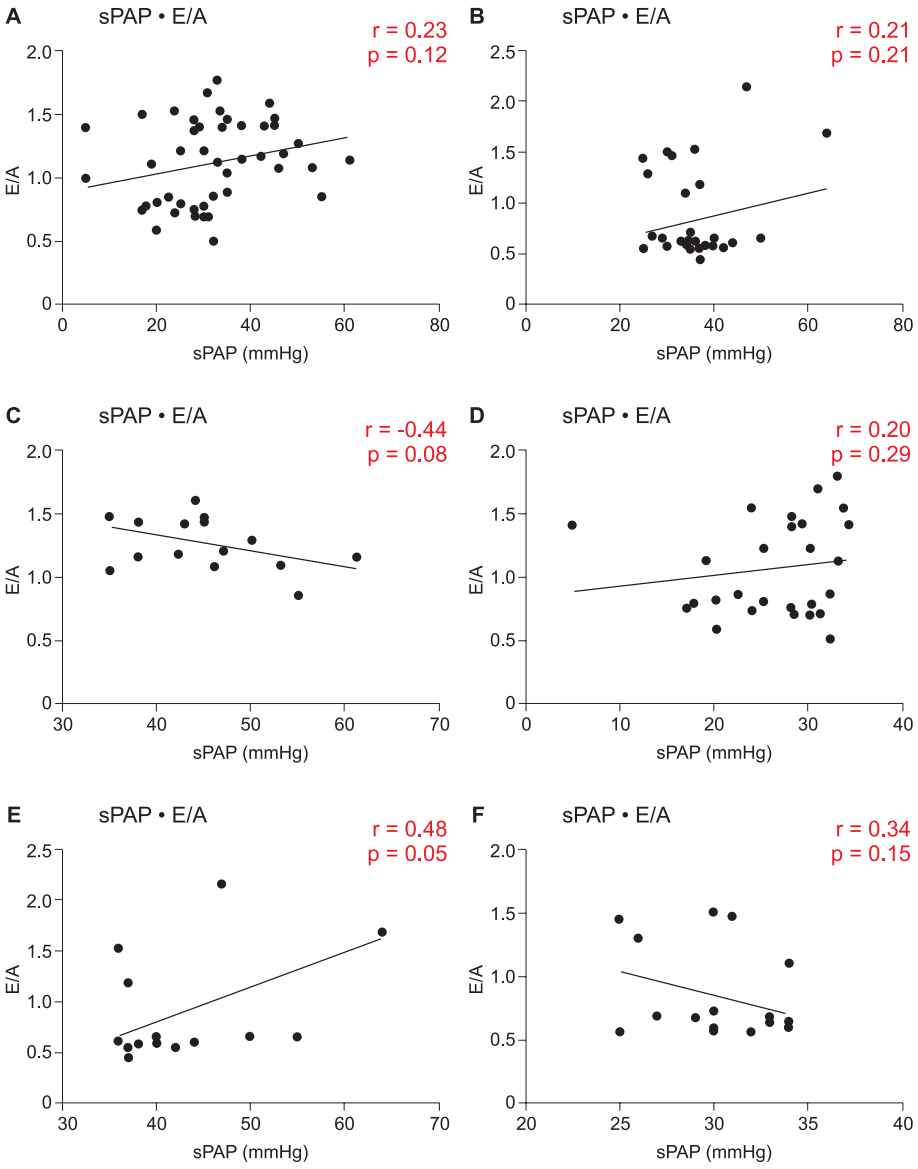

FIGURE 4. Correlation between the E/A index and PAPs in the study groups. **A** – patients with scleroderma; **B** – patients with coronary artery disease; **C** – patient with SS(+) PAH(+); **D** – patients with SS(+) PAH(–); **E** – patients with Isch(+) PAH(+); **F** – patients with Isch(+) PAH(–)

known both for ischemic patients and for those diagnosed with scleroderma.

The impairment of LVEF in patients with scleroderma is still a controversial issue in the literature, studies identifying a low percentage of subjects with impaired ventricular contractility.[24] About 40% of patients with scleroderma show relaxation disorders.[25] The results of this study revealed, as expected, a significantly more depressed ejection fraction among ischemic patients. A lower LV systolic function was observed in ischemic subjects, both when comparing the two large groups and the subgroups of the study. Ischemic subjects with PAH had the most depressed LVEF, followed by ischemic patients without PAH. There was also a significant difference among patients with scleroderma, where the associated PAH included a significant impairment of LV systolic performance. In addition, the same type of correlation was present for patients with non-PAH scleroderma, indicating that beyond the depreciating impact of PAH on LVEF, intrinsic myocardial dysfunction in scleroderma plays an important role in left ventricular systolic function.

It is known that myocardial ischemia leads to the alteration of the myocardial relaxation process, which is reversible in the early phases by restoring normal myocardial flow.[15–17] Diastolic dysfunction occurs from the first moments of myocardial ischemia, characterized by a specific

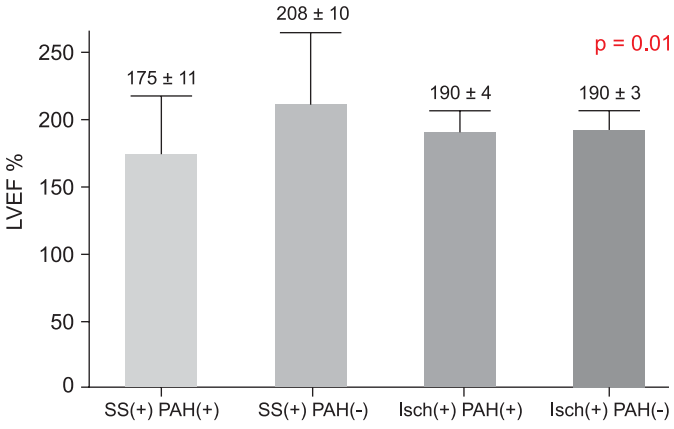

FIGURE 5. Comparative analysis of the mean DT values across the study subgroup

pattern of altered relaxation, whereas in the post-myocardial infarction phase, the same dysfunctional LV pattern is correlated with the myocardial remodeling processes.[16] In a patient diagnosed with scleroderma, diastolic dysfunction is common,[26] being correlated with the duration of the illness.[27] However, it is only identified in a minority of these patients, being underestimated in most studies conducted among subjects with systemic scleroderma.[28] One of the largest studies on LV diastolic function has identified distal dysfunction by echocardiographic evaluation in 50% of patients with scleroderma compared to 23% of patients from the control group.[26]

The present study identified the presence of altered relaxation-type diastolic dysfunction based on E' lateral and E' medial mitral valve Doppler tissue indexes in both subjects with scleroderma and subjects with ischemia. Additionally, an important negative correlation was identified between sPAP values and both indices of diastolic dysfunction for the group of ischemic patients. Mene *et al.* indicated Doppler tissue echocardiography parameters as valuable markers in identifying myocardial damage in patients with asymptomatic scleroderma.[29] The evaluation of diastolic dysfunction in patients with scleroderma in particular is clinically important, Yiu *et al.* demonstrating that the subtle diastolic dysfunction of the LV evaluated by tissue Doppler is correlated with a very low capacity and rhythm disorders in patients with scleroderma.[30]

An echocardiographic control study conducted by Meune *et al.* on 100 patients with scleroderma confirmed the increased frequency of diastolic dysfunction in patients with systemic sclerosis versus the control group; however, in patients with PAH associated with systemic sclerosis, elevated sPAP values involve a more pronounced distal alteration of the LV.[31] Our study identified the same negative correlation for the E/A ratio used as an indicator of LV diastolic function among patients with scleroderma and PAH. Furthermore, E DT evaluation identified significantly lower values for subjects with scleroderma and associated PAH, leading to the diagnosis of altered relaxation diastolic dysfunction.

CONCLUSIONS

Scleroderma, by intrinsic myocardial damage, can lead to the alteration of LV function even in the absence of PAH. Patients with PAH present a higher proportion of diastolic dysfunction both in case of associated CAD and scleroderma. However, PAH severity, assessed by the mean sPAP, correlates well with the severity of diastolic dysfunction in ischemic patients, quantified by tissue Doppler echocardiography. Compared to patients with coronary artery disease, those with scleroderma present a less pronounced deterioration of LVEF in response to PAH.

CONFLICT OF INTEREST

Nothing to disclose.

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