Editorial

Exercise Echocardiography as a Screening Tool in Systemic Sclerosis

In this issue of *The Journal*, Quinn, *et al* describe the utility of exercise echocardiography (EE) in the identification of patients with systemic sclerosis (SSc) deemed high risk for the development of pulmonary arterial hypertension (PAH)[1]. In a single-center observational study, the authors demonstrated that a significantly higher percentage of SSc patients with a persistently positive EE, as defined by an increase in right ventricular systolic pressure (RVSP) ≥ 20 mmHg with exercise, subsequently developed pulmonary hypertension (PH) compared with those who had persistently negative EE. The majority of patients with a baseline positive EE were found to have a persistently positive EE over time. However, interestingly, a proportion of those patients did not develop resting PAH. Similarly, 3 patients with baseline negative EE developed PAH shortly after initial testing, possibly representing a false-negative result. Because invasive hemodynamics with right heart catheterization (RHC) was not performed unless clinically indicated and was also performed up to 6 months following EE, it is difficult to ascertain the meaning of the present findings. Certainly, other SSc-specific features or biomarkers of increased risk in combination with positive EE need to be identified; however, lack of standardization in annual testing limits identification in this present study. In contrast, a negative EE may be helpful in identifying a group protected from developing PH in the future. This finding, if confirmed in larger studies, could lead to improved early detection strategies for patients with SSc at highest risk for development of PAH, and potentially other at-risk populations with connective tissue disease.

The current study is an extension of an original 2008 manuscript, also by Steen, *et al*, in which SSc patients at risk for PAH underwent EE to determine whether exercise-induced elevations in RVSP could elucidate those at greatest risk[2]. A major limitation of that study was designation of exertional elevation in RVSP ≥ 20 mmHg above a normal baseline as clinically significant, without any established consensus on accepted cutoff values; a limitation that is carried forward in the present study. The authors argue that the designation of a positive EE defined as RVSP ≥ 20 mmHg is more conservative than prior recommendations of RVSP ≥ 15 mmHg[3]. Current guidelines, however, recommend against this definition of exercise-induced PH (ex-PH), and in fact have removed this group entirely from the updated clinical classification owing to a lack of consensus on exercise protocols and key measurements required to establish the definition of ex-PH[4]. Further, there has been recent change in the invasive hemodynamic definition of PAH[4], with mean pulmonary arterial pressures of ≥ 20 to < 25 mmHg representing an intermediate form of disease that is high risk for emerging PAH. However, there has not been a corresponding change to the definition of abnormal RVSP or delta change in RVSP with exercise by noninvasive methods, including EE.

To reliably assess exertional pulmonary hemodynamics, there must be correlation with invasive RHC to differentiate between pulmonary vascular versus left heart disease – an important consideration that therefore limits the clinical significance of the present findings. The use of a dichotomous RVSP cutoff in the determination of a positive result without RHC correlation therefore is nebulous. Additionally, +EE patients underwent RHC within an average of 6 months, which not only limits correlation with noninvasive estimates but also potentially introduces selection bias. Undoubtedly RVSP elevation occurs along a continuum, is subject to issues with technical acquisition due to the complex geometric configuration of the RV chamber and should also be considered in conjunction with some element of cardiac output or flow. Standard echocardiographic variables of RV function such as tricuspid annular plane systolic excursion (TAPSE), which have previously been shown to be predictive of mortality in SSc[5], were not acquired in the present study. Further, the rapid drop in RVSP noted immediately following cessation of exercise may also lead to misclassification of positive and negative EE results by failing to identify those with high RVSP:flow relationships[6].

Further, as demonstrated in the current study and prior studies of patients with SSc, various forms of PH can

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develop including PH related to left heart disease and PH related to lung disease in which the role for PAH-directed therapy is not established[7,8]. Despite EE being proposed as a screening tool, conventional echocardiographic techniques were not used in the present study, such as consideration of diastolic changes with exercise that may contribute to elevation in RVSP. Diastolic dysfunction is known to be highly prevalent in SSc[9], and may be unmasked by exercise in this population as previously shown[10,11,12]. Thus, the utility of EE in patients with SSc who have significant interstitial lung disease at baseline or concomitant left heart disease, for example, is less clear. Last, it is difficult to ascertain the overall implications of these findings of a negative EE when 3 patients developed resting PAH shortly after a negative study. The lack of routine followup EE at prescribed intervals could lead to misclassification and ascertainment bias. Therefore, larger cohorts of patients with SSc are needed to power the negative and positive predictive value, sensitivity, and specificity of EE as a screening tool.

The concept of early detection techniques to assess for cardiopulmonary complications in SSc is exceedingly important and has a number of clinical implications that could affect the outcome of patients with SSc at risk for PAH. Cardiac involvement is prevalent in SSc and is clinically overt in approximately 10–30% of patients, depending on the diagnostic technique used[13,14,15]. Subclinical cardiac involvement, however, has been estimated at > 70%[16], and therefore the prevalence may be underestimated, depending greatly on clinical suspicion and appropriate application of screening and diagnostic tools. Cardiopulmonary manifestations in this population are associated with increased morbidity and mortality, primarily due to the development of right ventricular (RV) dysfunction and associated PAH[14,17]. Despite routine clinical and echocardiographic monitoring, risk prediction of cardiac involvement and PAH in SSc remains poor[18]. We have previously shown that RV contractile abnormalities may be present when conventional echocardiographic measures are otherwise normal, regardless of noninvasive estimation of pulmonary pressures[19], and that these metrics are predictive of mortality[20] and responsive to PAH-directed therapies[21]. Although 2-dimensional echocardiography is a useful noninvasive modality in PH given its high specificity and high positive predictive value[22], there may be improved screening accuracy in high-risk SSc patients when echocardiography is used in conjunction with pulmonary function testing, N-terminal pro-B-type natriuretic peptide levels[23], and other clinical factors[23,24,25]. Unfortunately in the present study, there was no standardization of adjunctive testing performed such as pulmonary function testing, 6-minute walk test, or laboratory data that could be used simultaneously to help identify those SSc patients with high-risk features of emerging PAH.

Despite current guidelines that discourage the clinical classification of ex-PH, there is a growing body of evidence suggesting that ex-PH represents an important group of high-risk patients that require close serial monitoring for emerging RV failure and resting PAH. Apart from detection of ex-PH, EE is an important noninvasive modality that allows for assessment of RV contractile reserve, an independent predictor of mortality and poor prognosis[26]. Future longitudinal studies are required, however, to determine the utility of EE as a screening tool across a broad spectrum of patients with SSc at variable risk for PAH. Firmly establishing EE as a predictive tool in this at-risk population also requires establishment of test characteristics including expected biologic variability, reproducibility, sensitivity, specificity, negative and positive predictive values, and most importantly, correlation with simultaneous invasive hemodynamics with exercise. A particular strength of the present study is the longitudinal followup of patients, and the demonstration of the overall value of persistently positive versus persistently negative EE in the prediction of resting PAH. These findings serve as an important foundation for further studies with potential to affect clinical outcomes in SSc.

Quinn, *et al*[1] report the novel finding that SSc patients with persistently positive EE are at increased risk of developing resting PAH during a mean 4-year followup period. While the objectives of this study are exceedingly important, there are a number of methodologic limitations that limit clinical implications and change in practice.

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The authors are supported by the Scleroderma Foundation (MM, SCM), CHEST Foundation (MM), US National Institutes of Health/ National Heart, Lung, and Blood Institute U01HL125175 (MM), and R01HL114910 (MM, SCM). Address correspondence to Dr. M. Mukherjee, Johns Hopkins University Division of Cardiology, 301 Mason Lord Drive, Suite 2400, Baltimore, Maryland 21224, USA. E-mail: mmukher2@jhmi.edu

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J Rheumatol 2020;47:643–5; doi:10.3899/jrheum.191249