Putting "At-Rest" Evaluations of the Right Ventricle to Rest: Insights Gained From Evaluation of the Right Ventricle During Exercise in CTEPH Patients With and Without Pulmonary Endarterectomy

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Over 7 decades after Isaac Starr declared that "*weakness of the right side of the heart . . . seems less important . . . in the dynamics of congestive failure,*[1]" the right ventricle (RV) has finally been afforded its due respect in many disease states. However, the definition and assessment of the seemingly simple concept of "RV function," has proven vexingly elusive. Echocardiographic assessment of RV contractile function is hindered by its crescentic, triangular shape and unique longitudinal contractile pattern and often relies on imperfect one-dimensional measurements such as the tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic velocity (S'), or RV fractional area change. All of these measures, including RV ejection fraction (RVEF) assessed by cardiac magnetic resonance (CMR), are load dependent and thus do not represent true RV contractile function. Similarly, until very recently, assessment of RV function has been described almost exclusively in patients "at rest" due to the above-mentioned limitations of imaging, which are only compounded in the exercising patient. Given that we have known for decades that evaluation of left ventricular function under stress is prognostic in coronary disease, heart failure, and valvular disease,[2–4] it is perhaps surprising that we have been unable to see across the interventricular septum to consider the benefits of stress evaluation of the right ventricle.

The current study by Claessen et al[5] in this issue of *JAHA* contributes significantly to a growing body of litera-

ture[6–8] illuminating this particular cognitive blind spot by providing insights from a novel method of RV functional assessment during exercise stress. By coupling invasive hemodynamic monitoring with CMR imaging techniques (which the authors recently validated against the direct Fick assessment of cardiac output), they were able to provide a unique assessment of RV volumes and function in conjunction with pulmonary pressure and RV load during exercise. Fifteen subjects with chronic thromboembolic pulmonary hypertension (CTEPH), 7 subjects with chronic thromboembolic disease previously treated with pulmonary endarterectomy (post-PEA) and resultant normalization of mean pulmonary artery pressure (mPAP; ≤ 25 mm Hg), and 14 control subjects first underwent cardiopulmonary exercise testing to exhaustion on an upright cycle ergometer. Twenty-four hours later, the same subjects underwent supine exercise CMR with simultaneous invasive pulmonary artery and systemic arterial pressure measurements. The exercise CMR protocol was repeated in the post-PEA patients 30 to 60 minutes after receiving a single oral dose of sildenafil.

Corroborating work from Bonderman et al in 2011 studying the effects of submaximal exercise in post-PEA patients,[9] the authors found a reduction in peak oxygen consumption and exercise capacity in post-PEA patients when compared with controls. Predictably, at rest post-PEA patients had a lower total pulmonary vascular resistance (tPVR) and higher pulmonary compliance (C_{PA}) then CTEPH patients; however, they still had higher resistance and lower compliance than normal controls. Resting RVEF and cardiac index were similar in post-PEA patients and controls whereas CTEPH patients predictably had a lower RVEF and cardiac index. With exercise, notable differences emerged in the control and post-PEA patients in the CMR-measured parameters of RV size and function. Normal controls greatly augmented their cardiac output with exercise (6.2 to 16.2 L/min) while post-PEA patients failed to augment their CO by nearly as much (6.1 to 9.5 L/min) and more closely resembled CTEPH patients (5.1 to 7.9 L/min). Whereas control patients demonstrated an increase in RVEF and reduction in RV end diastolic volume

(RVEDV), post-PEA patients again resembled the CTEPH-patient pattern with an increase in RVEDV with exercise and failure of RVEF to augment. Similarly, measures of RV load in post-PEA and normal patients diverged with exercise, again largely agreeing with the findings of Bonderman et al in 2011. Where tPVR did not change significantly in normal controls with exercise, it increased in both post-PEA and CTEPH patients. C_{PA} decreased in all groups, though the C_{PA} with exercise in normal controls was significantly higher than in post-PEA or CTEPH patients. The pressure-flow relationship (the slope of mPAP plotted against CO) was also steeper in post-PEA patients than in controls. Finally, the effects of sildenafil were noted on resting and exercise parameters in post-PEA patients. While resting parameters were unaffected, sildenafil administration in the post-PEA patients before exercise led to lower tPVR, higher C_{PA}, a decrease in the mPAP/CO slope, and an improvement in RVEF.

The findings of this study are novel and important findings, yet must be considered in the context of some limitations. First, there are notable differences in the control and CTEPH/post-PEA groups, both in regards to age and ventricular volumes. It has been known as far back as 1967 that during exercise, older subjects have a blunted reduction in PVR and steeper mPAP/CO slope when compared with younger subjects.[10,11] In a sub-analysis of the current study, the authors do reduce the age gap by investigating only the oldest half of the control subjects and find near identical relationships in hemodynamics and ventricular volume measurements as in the larger normal population group, though the age gap between controls and the other 2 age groups remains greater than a decade. We also note that these normal controls have some conspicuously abnormal parameters of ventricular size. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, the average RVEDV for women and men was 108.9 and 140.9 mL, respectively.[12] However, in the current study, the resting RVEDV mean was 161 mL. Similar elevations in LVEDV in the control group are seen in the current study (MESA mean LVEDV=109 mL for women and 142 mL for men; study control mean LVEDV=162 mL).[13] MESA also found that older age was associated with a smaller RVEDV, estimating that the RVEDV decreases by a mean of 6.6 mL per 10 years of advancing age. Thus, ≈50% of the difference between the observed RVEDV difference in the post-PEA patients (average age 62 years, resting RVEDV 128 mL) and control subjects (average age 36 years) may be explained by age, though other factors may also play a role.

A second question involves the chamber most commonly queried under stress—the left ventricle. It is noteworthy that post-PEA patients had LV dilation with stress. In these patients, the LVEDV increased from 117 mL at rest to 129 mL with stress. This diverged significantly from the control patients (162 to 156 mL) and even CTEPH patients

(112 to 102 mL). It is unclear if the PEA procedure itself altered septal or LV mechanics under exercise, or if the post-PEA patients differed in other ways from the control patients that led to LV dilation with stress (eg, subclinical ischemic disease or hypertensive heart disease). This also raises the possibility that LV end diastolic pressure may have increased to a greater degree in post-PEA patients. If this is true, then the tPVR response to exercise in post-PEA and CTEPH patients may have occurred due to different underlying hemodynamic mechanisms; namely a greater degree of the tPVR increase in post-PEA patients due to an elevation in pulmonary artery wedge pressure (PAWP) and pulmonary venous distention. While we understand the authors' reticence to perform wedge maneuvers during near-maximal exercise for safety concerns, the measurement of a PAWP would have been valuable in defining differential loading conditions between the groups, particularly in light of the LV dilation seen only in the post-PEA patients.

Finally, it is worth reiterating the author's statement that the differences in CO with exercise between the post-PEA and control groups were not driven by differences in stroke volume, but by significant differences in heart rate response. While the control group augmented their resting heart rate to 149 beats per minute (bpm) with exercise during CMR evaluation (81% maximum predicted heart rate (MPHR)), the CTEPH and post-PEA patients only mounted heart rates of 120 (76% MPHR) and 108 bpm (68% MPHR), respectively. Based on calculated MPHR, age alone does not fully account for the differences in heart rate response. Perhaps the disease state of CTEPH exerts a lasting effect on chronotropic competence as has been described in patients with pulmonary hypertension,[14] perhaps the CTEPH and post-PEA patients had reduced clearance of the beta-blocking agents (despite a 24-hour wash-out period), or perhaps pulmonary endartectomy itself predisposes to chronotropic incompetence. Regardless of etiology, it is enlightening that the reduced RV reserve of the post-PEA patients in this study is predominately actuated by chronotropic incompetence instead of a failure to augment stroke volume.

Despite these concerns, the authors' ability to measure ventricular volumes during exercise and compare this against concurrently measured hemodynamics provides powerful and provocative insights into RV and pulmonary pathophysiology. As noted above, SV augmentation with exercise is similar in post-PEA and control patients. However, the method by which the RV generates this augmented stroke volume is different for each group and is informed by evaluation of the RV end-systolic and diastolic volumes, and requires careful consideration of total RV load during exercise in all 3 groups. One method to estimate total RV load (resistive and pulsatile components) is the effective arterial elastance (Ea; end-systolic pressure divided by SV). In normotensive patients, RV

Table. Effective Arterial Elastance (Ea) and End-Systolic Elastance (Ees) Values Employed for the P/V Loop Model for Each Patient Group at Rest and With Exercise (Group Average Values Used)

	Normal Control ($V_0=10$)		Post-PEA ($V_0=-8$)		CTEPH ($V_0=14$)		Post-PEA+Sildenafil ($V_0=-8$)	
	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex
Ea, mm Hg/mL	0.11	0.21	0.43	0.69	1.11	1.53	0.38	0.52
Ees, mm Hg/mL	0.17	0.69	0.43	0.77	0.78	0.88	0.43*	0.77
Ees/Ea	1.5†	3.2	1.0†	1.1	0.7†	0.06	1.1†	1.4

CTEPH indicates chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; PEA, pulmonary endarterectomy; sPAP, systolic pulmonary artery pressure.
*Assumes no change in Ees at rest with sildenafil administration.
V0 and Ees are calculated by *presuming*† coupling ratios (Ees/Ea) of 1.5 for controls,[18] 1.0 for post-PEA patients,[19] and 0.7 for CTEPH patients.[20] Ea for normal controls calculated by mPAP/stroke volume (SV); Ea for post-PEA and CTEPH patients calculated by sPAP/SV.[15,16] V0 presumed unchanged within each patient group from rest to exercise.

end-systolic pressure can be estimated by mPAP. However, with development of even borderline pulmonary hypertension, end-systolic pressure is best estimated as systolic pulmonary artery pressure (sPAP).[15,16] Based on calculation of group-averaged Ea (mPAP/SV for controls and sPAP/SV for post-PEA and CTEPH), we can see that Ea increases during exercise in all groups (Table). The ventricular response to this afterload is quite different. In control patients, both RVEDV and RVESV decline significantly with exercise, but RVESV to a greater extent—thereby increasing SV and RVEF (RVEF=SV/RVEDV). Therefore, the increase in stroke volume in the face of reduced preload (RVEDV) and increased afterload must be due to augmented intrinsic RV contractility (termed end-systolic elastance (Ees)). In the post-PEA patients both RVEDV and RVESV actually increase, but RVESV to a lesser extent and thus stroke volume increases again. RVEF, however, remains largely unchanged. In this group, it is evident that the augmentation in stroke volume is more a result of increased preload than of an augmentation of contractility.

One can visualize this by constructing pressure–volume relationships for rest and exercise states for each patient group (shown in Figure) with only a few reasonable assumptions. First, we must assume that the ventricular volume in the theoretical state of zero pressure (V_0) is identical in rest and exercise. Second, we can calculate systolic pulmonary arterial pressure for each group from a formula validated by Chemla et al [sPAP=(mPAP/0.61)−2].[17] Finally, we assume that resting RV-pulmonary artery (PA) coupling is normal in the controls (Ees/Ea=1.5),[18] borderline in the post-PEA (Ees/Ea=1.0),[19] and given the low RVEF, uncoupled in the CTEPH (Ees/Ea=0.7)[20] to calculate a V_0 point for each group. We are then able to reasonably generate model pressure-volume loops for each patient group at rest and exercise. On first glance, it is obvious that the control patients have significantly augmented their RV contractility during exercise (Ees—dashed line) and this increase is significantly more in relative terms to the increase in associated afterload (Ea). Therefore, the coupling ratio (Ees/Ea) dramatically increases during exercise

(Figure A). However, in the post-PEA patients (Figure B), stroke volume is generated largely by increasing preload: Ees modestly increases and to a similar degree to the increase in afterload; therefore, Ees/Ea is largely unchanged. In CTEPH patients (Figure C), the RV's ability to augment contractility is further diminished with exercise and Ees/Ea actually falls. With sildenafil, post-PEA patients during exercise increase RVEDV but now RVESV is unchanged: contractility increases more relative to load, and thus Ees/Ea increases.
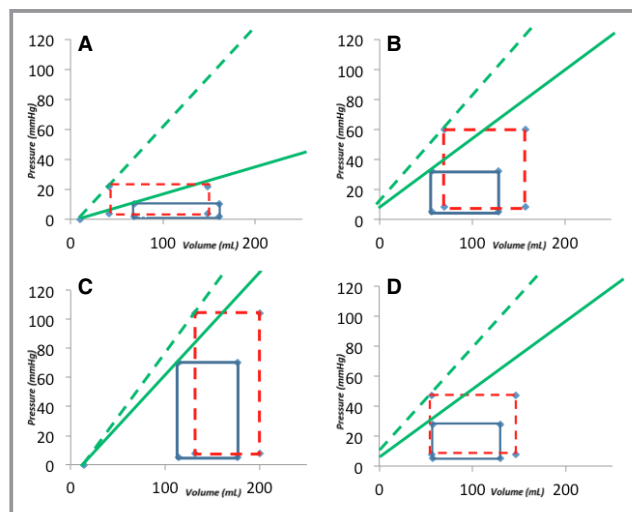
Figure. Model pressure-volume loops derived from Claessen et al[5] at rest (blue box) and exercise (red dashed box) for normal control patients (A), post-PEA patients (B), CTEPH patients (C), and post-PEA patients after sildenafil (D). Green lines denote end-systolic elastance (Ees, RV contractility) for each state (solid=rest; dashed=exercise). Ratio of Ees/Ea is assumed for each group based on prior studies.[17–20] Increasing slope of Ees denotes increasing contractility in this model. Note the control patients' ability to augment Ees with exercise, which is largely lost in the post-PEA and CTEPH patients. Sildenafil improves the ability of post-PEA patients to augment their contractility with exercise, and reduces overall RV load. CTEPH indicates chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; RV, right ventricle.

These findings by Claessen et al of differential volume changes during exercise may suggest an uncoupling of RV contractility and PA load in the CTEPH and post-PEA patients. RV-PA coupling defined by the Ees/Ea relationship is held as the gold standard of RV contractile functional evaluation,[18] though has thus far required high fidelity, clinically impractical pressure-volume catheters for assessment. If one believes that the alterations in ventricular volume and contractility responses during exercise are related, then this study may suggest that the presence of increasing RVEDV during exercise is a marker of RV-PA uncoupling, and that a concomitant rise in RVESV with exercise represents a more severe degree of uncoupling. This would provide a valuable, noninvasive method of assessing RV-PA uncoupling and perhaps offer prognostic information in right heart disease.

As imaging techniques have improved, our ability to look across the septum to consider the RV during stress has provided valuable insights into various disease states and into the physiology of the right heart system. Despite some of the above noted limitations, Claessen et al are to be commended for their development of a novel CMR technique of accurately measuring ventricular volumes during exercise, and for employing that system to clearly illuminate alterations in RV function, load, and chronotropy in patients with CTEPH and post-PEA under exercise stress. This study is evidence that high-quality exercise evaluation of the RV is possible and can provide important clinical information about our patients, and is yet another argument to put at-rest evaluations of the RV to rest.

Disclosures

None.

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