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Response to comments and opinions by Kremer et al regarding our original manuscript "Volume calibration with cardiac MRI vs hypertonic saline for right ventricular pressure-volume loops with exercise: Impact on ventricular function and ventricular-vascular coupling"

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We appreciate the interest that Kremer et al have shown in our work. We are pleased to rebut their criticism of our report on the impact of the hypertonic saline (HS) calibration of pressure-volume loop metrics for assessing ventricular function and ventricular-vascular interactions.

A key limitation of any single beat method is that the ESPVR, which is known to be curvilinear,[1] is derived from data obtained at a single operating condition. Whether based on a single beat[2] or an ensemble average of multiple beats with the same degree of volume loading,[3] the pressure-only method assumes a linear relationship between the end-systolic point and an estimated Pmax, which yields V_0, the volume intercept of the linear approximation. Under these conditions, as detailed in the supplement to our communication,[4] while calculation of Ees requires pressure and volume data, coupling (Ees/Ea) can be calculated from pressure alone according to the "pressure-only" method in which Ees/Ea = (Pmax/ESP)−1. Thus, clearly, HS-based volume calibration is just as good as the more accurate cardiac magnetic resonance (CMR)-based volume calibration for computing coupling.

However, as detailed in the supplement to our original communication;[4] the HS-based calibration overestimated end-systolic volume, which led to a significant underestimation in right ventricular ejection fraction, ventricular contractility (Ees) and exercise contractile reserve (ΔEes) (Figure 1). In all cases, the bias was less than 10% (Figure 1). These were and are our main conclusions, which do not depend on the "mathematical inevitability" of Ees/Ea being independent of volume.

While beyond the scope of our study, the volume calibration method also affects other important pressure-volume metrics, including preload recruitable stroke work (SW), potential energy (PE), and pressure-volume area (PVA), where PVA = PE + SW and SW/PVA (is often used to assess mechanical efficiency.[5]

Far from nuance, the approximations inherent in single beat methods and the commonly used pressure-only approach to computing Ees/Ea have real consequences for quantitative assessment of right ventricle (RV) function and PV-pulmonary vascular interactions. We sincerely appreciate Kremer and colleagues' communication and stand by our conclusion that the HS method of volume calibration, which is critical to clinical implementation of pressure-volume analysis, is sufficient for measuring ventricular-vascular interactions, including contractility, coupling, and contractile reserve, but not for either absolute RV volumes or RV ejection fraction.

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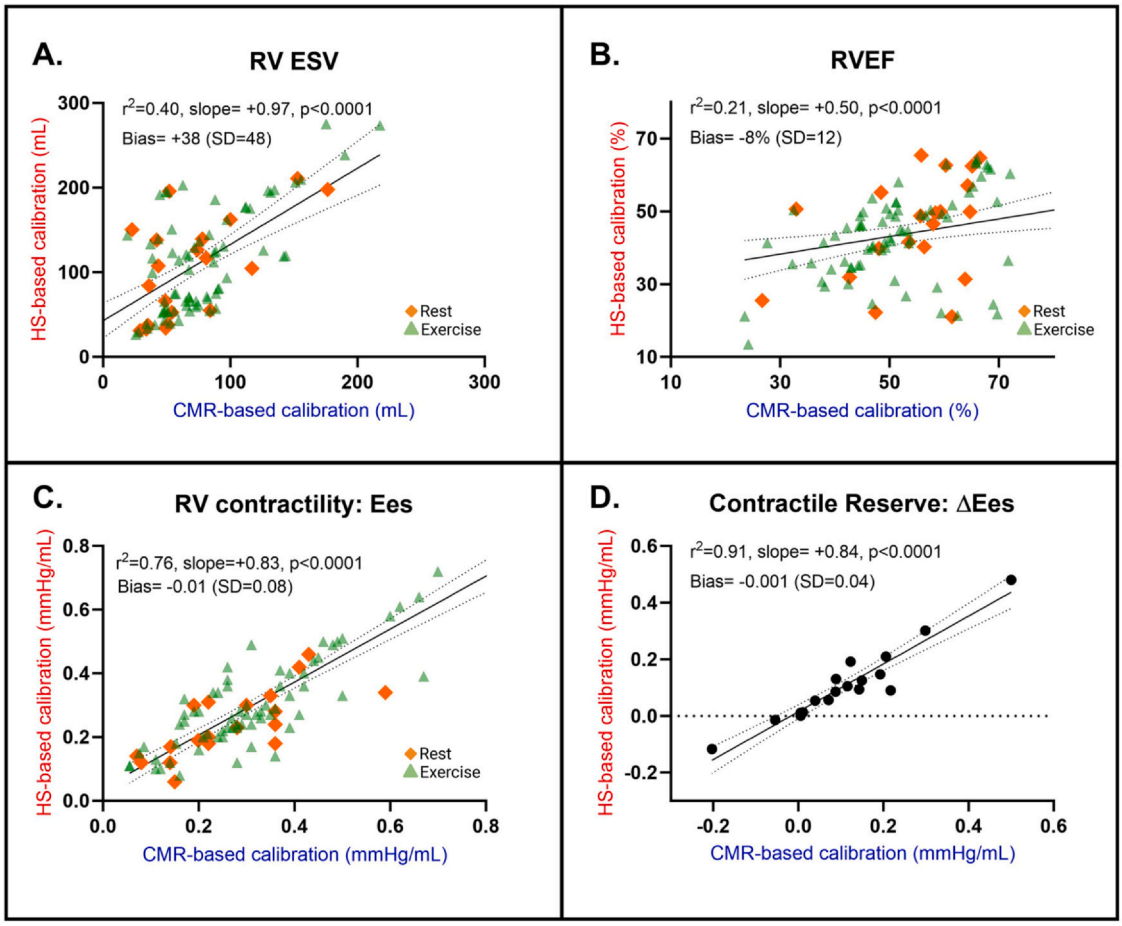

Figure 1 Correlation of key metrics of right ventricular pressure volume loops: hypertonic saline (HS) vs cardiac magnetic resonance (CMR) volume calibration method. $n = 82$ for **A**, **B**, **C**; $n = 19$ for D (peak exercise-rest). Peak exercise stage: 25 W for five, 50 W for six, 75 W for three, and 100 W for five participants. *Abbreviations*: Ees, end-systolic elastance; HS, hypertonic saline; CMR, cardiac MRI; RV, right ventricle; ESV, end-systolic volume; RVEF, right ventricular ejection fraction.

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