Supplementary data for the paper "*Reduced hemodynamic coupling and exercise are associated with vascular stiffening in pulmonary arterial hypertension*" by A. Bellofiore *et al.*

In addition to the frequency-domain analysis included in the paper, a time-domain analysis was used to estimate the characteristic impedance of the pulmonary vasculature. Following the approach established for the systemic circulation, $Z_{C\_95}$ was calculated as the pressure-to-flow ratio at 95% maximum flow (Mitchell, 2009). In addition, $Z_{C\_50}$ was calculated as the pressure-to-flow ratio at 50% maximum flow. The analysis was performed for the 22 subjects who completed the exercise protocol.

The correlation between characteristic impedance from frequency-domain ($Z_C$) and time-domain analysis ($Z_{C\_95}$ or $Z_{C\_50}$) was studied using a Bland-Altman analysis. The results are summarized in Figure S1. The analysis for $Z_C$ and $Z_{C\_95}$ indicated a moderate agreement between the two metrics ($R^2 = 0.272$). The bias is 0.35 WU × $m^2$, and the limits of agreement are -1.17 and 1.87 WU × $m^2$. The use of $Z_{C\_50}$ instead of $Z_{C\_95}$ resulted in an improved linear correlation with frequency-domain analysis ($R^2 = 0.401$), with only slightly improved bias (0.32 WU × $m^2$) and limits of agreement (-1.08 and 1.73 WU × $m^2$).

A comparison between frequency-domain and time-domain impedance analysis may have clinical significance. While frequency-domain analysis is considered the gold standard, the simpler time-domain approach is more commonly used in the clinical setting (Huez 2004, Wang 2011). The results presented here showed a mild agreement between the two types of analysis, which should suggest caution when using time-domain analysis clinically.

In the pulmonary circulation, $Z_{C\_50}$ may be a better approximation of the characteristic impedance than the established $Z_{C\_95}$. This may be attributed to the delay in the return of reflected waves, which is different between systemic and pulmonary circulation. In the systemic circulation, the strongest wave reflections are generated at the abdominal aortic bifurcation, relatively distant from the point where pressure and flow are measured. Pressure and flow at 95% maximum flow may be still relatively undisturbed by wave reflections (Mitchell, 2009). In contrast, in the shorter pulmonary circulation wave reflections return earlier to the proximal pulmonary artery. Measuring the pressure-to-flow ratio at an earlier time point (i.e. at 50% maximum flow) may reduce the disturbance due to reflected waves and result in a better approximation of $Z_C$. That said, the limited evidence reported here warrants further investigation.

## References

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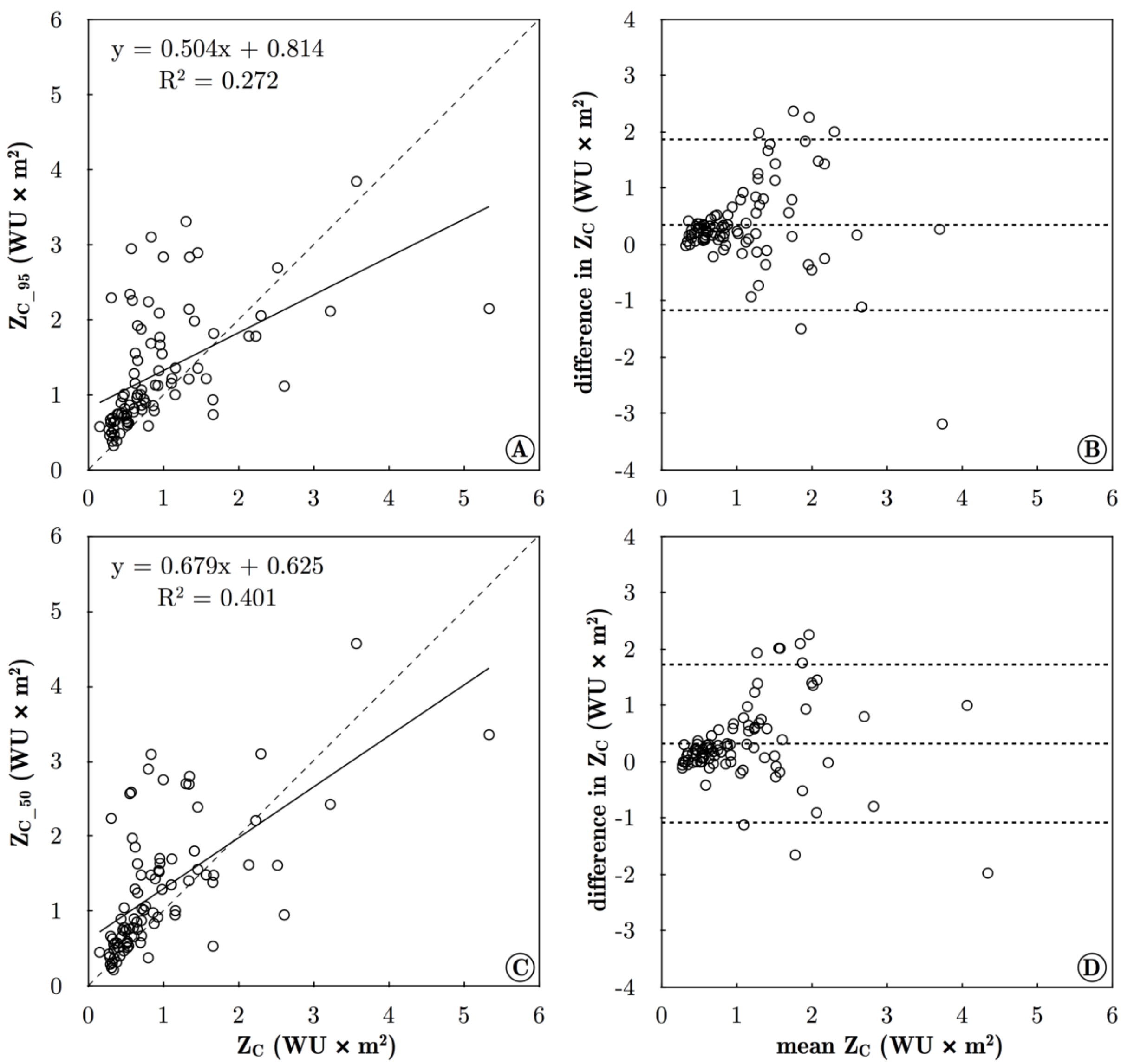


**Figure S1. Comparison of frequency-domain and time-domain analysis of pulmonary vascular impedance.**

*A)* Comparison of $Z_C$ (frequency domain) and $Z_{C\_95}$ (time-domain, at 95% maximum flow). Line of equality is included (dashed line). *B)* Bland–Altman plot of the difference between $Z_C$ and $Z_{C\_95}$. Bias and limits of agreement are displayed as dashed lines. *C)* Comparison of $Z_C$ (frequency domain) and $Z_{C\_50}$ (time-domain, at 50% maximum flow). Line of equality is included (dashed line). *D)* Bland–Altman plot of the difference between $Z_C$ and $Z_{C\_50}$. Bias and limits of agreement are displayed as dashed lines.