Response to Letter Regarding Article, “Differential Cardiac Remodeling in Preload Versus Afterload”

We would like to thank Reil et al for their interesting discussion. They argue that wall stress of mice with transversal aortic constriction (TAC) may have been higher than those of mice with aortocaval shunt (shunt), which would be supported by lack of brain natriuretic peptide expression in shunt. We believe that we can disprove the arguments and the conclusion of Reil et al for the following reasons:

1. After 1 week of increased load under both conditions, hypertrophy, as measured by left ventricular weight per tibia length, is similarly increased in both models, and this holds true for myocyte minimal fiber diameter as well (Figure 1 of our article).

2. It was recently shown under well-controlled in vitro conditions that myocardial expression of brain natriuretic peptide increases only with afterload, not with preload. Accordingly, it was shown by Yamamoto et al\(^1\) that strain of neonatal myocytes during systole significantly increased brain natriuretic peptide expression, whereas strain during diastole did not.

3. We believe that wall stress-time integral is the major determinant of load-dependent gene expression, whereas arterial elastance reflects arterial load impact on the left ventricle.\(^4\) Accordingly, Ea has been shown to be reduced in human aortic regurgitation.\(^5\) It is hard to believe that hypertrophy-inducing load of the left ventricle under the condition of severe shunt would be reduced to 42.5% of control as calculated by Reil et al. This should induce atrophy instead of hypertrophy.

The argument that the pericardium would reduce preload is interesting. However, to our knowledge, pericardial forces are largely unknown in mice. Unlike in human or large animal models, the mouse pericardium is thin. Therefore, the contribution to left ventricular end-diastolic pressure generation should be rather low. In addition, volume overload occurs in all heart chambers in our shunt model. Therefore, calculation of the transmural gradient (left ventricular end-diastolic pressure minus right atrial pressure) would lead to a low gradient, and the left ventricular pressure might be underestimated.

Finally, the argument that the isovolumetric decay of left ventricular diastolic pressure was not included in the wall stress calculation is well taken. Accordingly, to estimate the impact of inclusion of isovolumetric decay, we recalculated diastolic and total wall stress. The diastole was divided in the part of the isovolumetric decay and in the residual part, and total wall stress was newly calculated. Mean total wall stress was then 9.68±0.22 mm Hg in sham, 15.17±1.17 mm Hg in shunt (P<0.05 versus sham), and 15.43±0.66 mm Hg in TAC (P<0.01 versus sham). Mean total wall stress was increased in shunt by 57% and in TAC by 59% (P=0.86 shunt versus TAC). Therefore, inclusion of the isovolumetric decay in the calculation of diastolic wall stress does not lead to a significantly higher wall stress in TAC compared with shunt.

In conclusion, afterload leads to maladaptive hypertrophy, whereas preload has a more favorable phenotype. This results from distinct differences in hypertrophic signal activation with both forms of load despite comparable increases in stress-time integral.

Disclosures

None.

References


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