Identification of a Growth Factor That Rejuvenates the Heart

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Study Hypothesis
With improvements in healthcare resulting in the population increasingly skewing toward the elderly, heart failure is becoming an increasingly prevalent pathological condition worldwide.1 Aging of the heart frequently manifests as left ventricular hypertrophy and diastolic dysfunction, for which there are limited therapies.2 To address whether this condition is reversible, Loffredo et al3 hypothesized that cardiac hypertrophy in the elderly is the result of the loss of factors in the blood that preserve myocardial structure and function, and that replacement of those factors can reverse the hypertrophic condition.

How Was the Hypothesis Tested?
The authors began by performing parabiosis experiments, in which the circulatory systems of 2 animals are surgically joined. They used mice of the strain C57BL/6, which develop a human-like, age-related cardiac hypertrophy as they grow older. They tested a variety of combinations of mice—unpaired young mice (2 months of age), unpaired old mice (23 months), young paired with young, old paired with old, young paired with old, and pairs in sham parabiosis in which the animals were surgically attached (and their movements and behavior thereby limited in the same way as mice in true parabiosis) but did not have connected circulations—and euthanized them after 4 weeks of parabiosis to assess the sizes of both the whole hearts and the individual cardiomyocytes. They also measured gene expression in postmortem cardiac tissue. In some experiments, while the mice were still alive, the authors measured blood pressure with a variety of techniques, as well as circulating levels of angiotensin II and aldosterone.

The authors went on to collect blood samples from various mice and performed both metabolomic profiling and proteomic profiling using aptamer-based technology to screen for factors differentially present in young and old mice. On identifying a promising candidate factor, they first assessed the factor for its effects on cell signaling and hypertrophy-related phenotypes in cultured neonatal rat cardiomyocytes. Finally, the authors tested the factor via in vivo administration to old mice in a randomized study (factor versus saline in intraperitoneal injections), followed by assessment of cardiac size and gene expression. They performed a similar study with young mice in which cardiac hypertrophy had been induced by transverse aortic constriction.

Principal Findings
At baseline, the authors found that old mice had substantially larger hearts (as assessed by the heart weight:tibia length ratio) than young mice. After 4 weeks of parabiosis, heart size in mice in young–young pairs remained unchanged, as did heart size in mice in old–old pairs. Heart size in young mice in old–young pairs was also unchanged. In contrast, heart size in old mice in old–young pairs was significantly decreased compared with baseline old mice or old–old pairs, although not as low as young mice. Heart size in old mice in sham old–young pairs was no different than in old mice in sham old–old pairs or in baseline old mice.

These findings were replicated with respect to cardiomyocyte size; whereas old mice (whether single or in pairs) had substantially larger cells than young mice (whether single or in pairs), old mice in young–old pairs displayed cells that were significantly smaller than in baseline old mice or old–old pairs and, remarkably, were the same size as in young mice. The authors demonstrated with careful blood pressure measurements and assessment of the renin–angiotensin–aldosterone system that hemodynamic effects could not account for the changes observed in the old mice in the young–old pairs.

With respect to cardiomyocyte gene expression, the authors assessed ANP and BNP, which encode natriuretic peptides, and SERCA2, which encodes the sarcoplasmic reticulum calcium ATPase that is involved in diastolic relaxation of the heart. ANP and BNP expression were substantially decreased, and SERCA2 substantially increased in the old mice in the young–old pairs compared with all other mice.

In comparing the proteomic profiles in blood samples from young versus old mice, the authors identified 13 analytes that significantly differed in the profiles. Of these analytes, growth differentiation factor 11 (GDF11) was confirmed to be greatly reduced in the circulation of old mice compared with young mice. Accordingly, the authors used neonatal rat cardiomyocytes to demonstrate that GDF11


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has antihypertrophic effects with respect to cell signaling and other cellular properties. The authors then assessed the effects of GDF11 on administration to old mice and found that the factor (1) reduced heart size, (2) reduced cardiomyocyte size, (3) reduced ANP and BNP expression, and (4) increased SERCA2 expression—all consistent with the effects in old mice of parabiosis with young mice. They found that GDF11 did not have the same effects in young mice with cardiac hypertrophy induced by pressure overload in the setting of transverse aortic constriction.

**Implications**

Although the authors were careful to conclude that GDF11 may not account for the entirety of the antihypertrophic effect experienced by old mice parabiosed with young mice, they did demonstrate that GDF11 has an antihypertrophic effect when administered to a mouse model of cardiac aging. As a corollary, the reduced circulating levels of GDF11 observed in old mice may contribute to cardiac aging. Although GDF11 administration is evidently not effective against all types of cardiac hypertrophy, the identification of GDF11 as a rejuvenating factor opens up tantalizing possibilities for the treatment of age-related cardiac hypertrophy and diastolic dysfunction.

**Disclosures**

Dr Musunuru is a member of the Early Career Committee of the American Heart Association Functional Genomics and Translational Biology Council.

**References**

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