Fast heart, slow heart: Changes in the molecular motor myosin explain the difference

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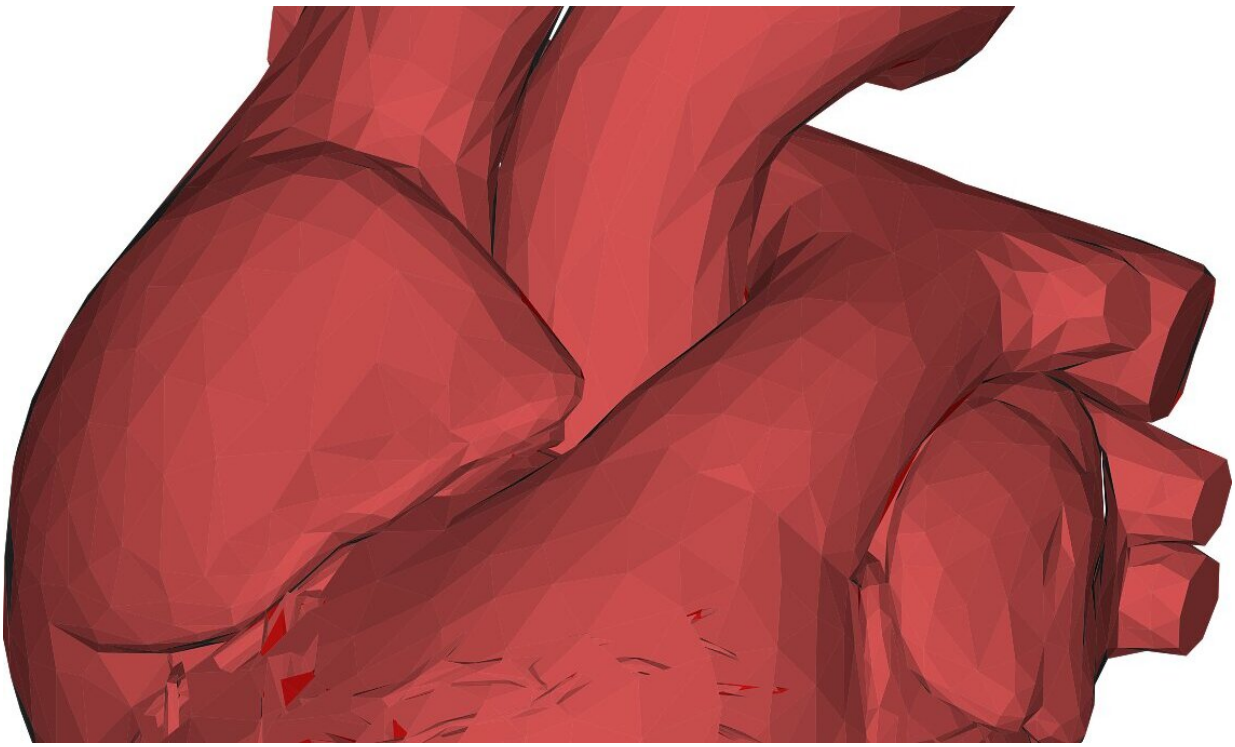

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The human heart contracts about 70 times per minute, while that of a rat contracts over 300 times; what accounts for this difference? In a new study publishing 10th June in the open-access journal *PLOS Biology*, led

by Michael Geeves and Mark Wass of the University of Kent and Leslie Leinwand from the University of Colorado Boulder, reveal the molecular differences in the heart muscle protein beta myosin that underly the large difference in contraction velocity between the two species.

Myosin is a "molecular motor"—an intricate nanomachine that forms the dynamic core of a muscle's contractile machinery, burning cellular chemical energy in the form of ATP to rapidly and reversibly exert force against cables of actin. In so doing, it pulls the ends of the muscle cell closer together, causing muscle contraction. It has long been known that the maximal rate of contraction, called V0, varies predictably among mammals: In small mammals with their high metabolic rate, V0 is higher than in larger mammals, which have lower metabolic rates.

There are multiple kinds of myosin, which serve diverse roles not only in muscle but in every other cell of the body. It is the muscle-specific forms, called sarcomeric myosins, that shows the pronounced difference in V0 between species (the V0 values of non-muscle isoforms show little in the way of between-species differences). Not surprisingly, the amino acid sequence of these sarcomeric myosins varies between species, but which of these variations is responsible for the small mammal/big mammal difference in V0?

The authors compared beta myosin (the sarcomeric myosin present in slow muscle and in heart) sequences from 67 different mammals, and found that differences in the motor domain, the region of the molecule that binds and burns ATP, were most closely correlated with differences in V0. Further analysis of two different evolutionary lineages of mammals, each containing both large and small species, led them to identify 16 sites on the molecule that were associated specifically with size difference, independent of lineage. Humans and rats differed at nine of these sites. When the authors then changed the human protein to

include the rat amino acids at these sites, the rat-human chimeric protein functioned more like the rat protein, with a doubling of motility and a faster release of the waste product ADP (the velocity-limiting step in contraction).

An increase in size is a common trend in mammalian evolution, seen in multiple lineages, including our own. "The change in V0 that we observed in the chimeric protein demonstrates that changes in these residues likely enabled the slower heart rate required in larger animals as they have evolved from small to large," Chloe Johnson one of the authors said. "The fact that the two lineages tested in this study both hit upon the same solution to slowing contraction suggests there may be few molecular options for altering beta myosin's rate of contraction."

More information: Johnson CA, McGreig JE, Jeanfavre ST, Walklate J, Vera CD, Farré M, et al. (2021) Identification of sequence changes in myosin II that adjust muscle contraction velocity. *PLoS Biol* 19(6): e3001248. doi.org/10.1371/journal.pbio.3001248

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