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Review • CME

Evolution and Scaling of Atrioventricular Conduction Time in Mammals

Frits L. Meijler, MD, PhD;[1] Jan Strackee, PhD[2]

This review will be published in two parts. Part 1 deals with the role of scaling in (patho)physiology and anatomy, or the structure and function of organs and organ systems in relation to body size of mammalian species. An intriguing aspect of scaling is the relation between heart size and the duration of atrioventricular conduction. In Part 2, to be published in the next issue of The American Heart Hospital Journal, *we will offer a simple mathematic explanation of atrioventricular conduction time scaling based on atrioventricular hemodynamics in mammalian species of different sizes.*

Scaling can be defined as the adjustment of a structure, a function, or an organ to the size of the mammalian body. An example is the size of the heart in relation to the size of the body. The duration of the PR interval on the electrocardiogram (atrioventricular delay) in relation to the size of the heart is a perplexing example of scaling. During evolution, mammalian species changed their shape, size, and function while adapting to the habitat in which they had to live and survive. This review deals with the problem of the apparent mismatch in scaling of the atrioventricular delay (PR interval) in relation to the size of the mammalian heart from mouse to whale.

God made the basic shapes of things, and then let evolution take over to produce the world's diversity.[1]

The title of this paper may not look appealing, but the riddle of comparative mammalian atrioventricular (AV) conduction is certainly a fascinating problem. Apart from the scientific challenge, appreciating this problem may be useful in daily clinical practice. Cardiology is not about recognizing stamps in a collection; cardiology is the art of understanding the (patho)physiology of the heart and circulation and, if possible, correcting abnormalities. The AV node and AV conduction in mammals are prominent parts of this puzzle.

Cardiologists, as do other people, take their hearts for granted. They usually focus on the hearts of their patients, but it may be of interest and even worthwhile to go beyond the routine clinical practice. Our circulation distributes oxygen to and removes metabolic waste from the tissues of our body. To keep all our cells freshly oxygenated, our hearts pump about 350 L of blood an hour, over 8000 L every day, three million L in a year—enough to fill four Olympic-sized swimming pools.[2] This is at rest. During exercise, e.g., race rowing, the young and healthy human left ventricle may deliver 25 L of blood per minute against a pressure of 100 mm Hg on the average. The performance of the healthy human heart is prodigious—and it has to be.

Several factors enable the mammalian heart to do its duty at low energetic cost. One of those factors is the fine-tuning of the time lapse between the contractions of atria and ventricles. This paper deals with the mechanisms that control this time lapse, the AV delay or PR interval on the electrocardiogram (ECG). The AV delay represents the time taken by the electric impulse generated in the sinoatrial node to propagate from the atria to the ventricles. It consists of: 1) the time to conduct the electric impulse over the atrial myocardium; 2) the

• From the Interuniversity Cardiology Institute of the Netherlands (ICIN), Utrecht, The Netherlands;[1] and the Laboratory of Medical Physics, University of Amsterdam, Amsterdam, The Netherlands[2]

• Address for correspondence: Dr. Frits L. Meijler, ICIN, P.O. Box 19528, 3501 DG Utrecht, The Netherlands; e-mail: denham@euronet.nl

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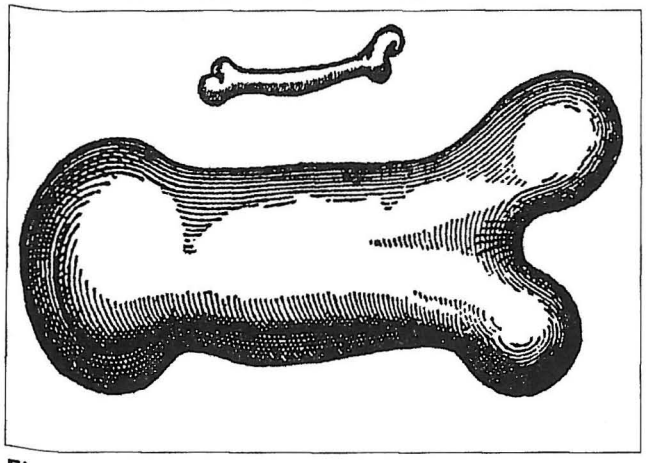

Figure 1. The bones of Galileo Galilei. Reproduction with permission from *Dialogues Concerning Two New Sciences*. Crew H, de Salvio A, trans. New York, NY: McGraw-Hill; 1963:125–126.[9]

transmission time of the impulse through the AV node; and 3) the time for conduction of the impulse over the His-Purkinje system. The major part of AV delay takes place within the AV node. There is no (or hardly any) variability of conduction velocity over the atrial myocardium or over the His-Purkinje system, so for all practical purposes, AV delay and its physiologic changes take place in the AV node.

The AV node plays a vital role in health and disease:

- It warrants an optimal efficacy of cardiac output by fine-tuning the delay between atrial and ventricular contraction.[3,4]
- It protects the ventricles and thus life itself against the effects of high-rate atrial arrhythmias, such as atrial fibrillation. For instance, without this protection, in patients with Wolff-Parkinson-White syndrome the accessory pathway may act as a short circuit between atria and ventricles, which may result in high-frequency ventricular rhythms and even ventricular fibrillation.[5,6]
- It serves as a back-up pacemaker in case of atrial arrest of whatever origin or AV block.[7,8]

In fact, the AV node controls the electric and mechanical functions of the heart and thus of the circulation of every mammal. As such, it also plays a fundamental role in the survival strategy of all mammalian species. In humans this complicated, evolutionary marvel has the size of an orange pit.

Scaling

In 1638, Galileo Galilei[9] was the first to draw attention to the relationship between body size (shape) and the dimension of bones in a variety of mammalian species (Figure 1). This relationship is called *scaling*, although in Galilei's time the word "scaling" had not yet been coined. We may notice scaling in many aspects of the nonliving and the living world around us.[10] It is a general principle of structures and bodies with similar purposes but different sizes. Three parameters can be changed when the size of a structure changes: 1) the dimension (e.g., thicker or thinner walls); 2) the material (e.g., brick, wood, or steel); and 3) the design. Compare the Brooklyn Bridge (Figure 2A)[11] with a bridge over one of the Amsterdam canals (Figure 2B).

When sizes change, the building constraints have to follow. The same principles apply to living nature; however, here we notice that despite dramatic changes in size and shape, materials and basic design do *not* change. Mammalian hearts, from 30 mg in a newborn mouse up to 900 kg in the blue whale, are all built using the same blueprint and the same material.[12,13] Even the bricks (the myocytes) are constant in size and substance.[14,15]

In biology, "Scaling deals with the structural and functional consequences of changes in size or scale among otherwise similar organisms."[10] The principles of biologic scaling are beautifully explained in Schmidt-Nielsen's book on scaling of animals. He writes: "Real organisms usually are not isometric, even when organized on similar patterns. In biology, such nonisometric scaling is often referred to as allometric."[10] Knowledge of scaling can be helpful for understanding the effect of size on form and function of organs and organ systems in living organisms in both fauna and flora. With respect to the size of animals, one considers mainly their mass (weight). Examples of scaling in cardiology include the relations between heart mass and body mass,[10,16] between stroke volume and body (heart) mass,[10] and between heart size and AV conduction time (delay).[17–19] While this article avoids the mathematics of the scaling principle, it is noteworthy that in all mammals, including humans, the heart mass is about 0.6% of body mass.[10,16] In other words, heart mass scales proportionally with body mass. A human heart has a mass of around 400 g, and the heart of a whale of 30,000 kg weighs approximately 180 kg.

In contrast, arterial blood pressure and diastolic and systolic pressures in the atria and ventricles do *not* scale, i.e., they have a scaling factor of zero.[10] This means that blood pressure is more or less the same for all mammalian species. The same holds true for hemoglobin concentration, and thus for the oxygen capacity of mammalian blood. Both are *independent* of body size. Red cell diameters, moreover, are rather uniform for all mammals.[20] So sizes of organs and

organ systems may scale but functions may or may not scale—and this makes biologic scaling even without a mathematic description a complicated matter.

Scaling of AV Delay

One of the most striking features of scaling of the heart is the relationship between size of the heart, usually expressed by its mass, and the length of the PR interval, thus the duration of the AV conduction delay (illustrated in Figure 3). As early as 1927, after the introduction of the ECG by Einthoven,[21] Clark[22] was the first to notice a "mismatch"[23] between the size of the body and the duration of the PR interval. He asserted that "the PR interval on the ECG varies so little in different animals." For instance, the PR interval for humans ranges between 150 and 200 milliseconds,[15] and in elephants and whales it is somewhere between 350 and 500 milliseconds.[24,25] From mouse to whale, AV delay increases only 10-fold, whereas body mass increases one million-fold. How to explain this mismatch—and what does it mean for the survival of mammalian species?

Because the changes in the PR interval are rather small as compared with changes of heart (body) size,[22] the "how" and "why" of scaling of AV delay in mammals present an evolutionary riddle.[26] To lift the veil of comparative AV conduction, we must take into consideration that in evolution, diastolic hemodynamic function (early and late diastolic filling of the ventricles) and electric delay in the AV node and heart cycle duration (R-R interval) are mutually dependant. (Although scaling is as important for all vertebrates as for mammalian forms of life, we limit our discussion here to scaling of AV delay in the mammalian heart.) To understand the relation between size and function of the mammalian heart, it is necessary to take a number of aspects of AV node morphology and physiology into consideration.

AV System Structure

It is generally accepted that dimension and architecture of the AV conduction system (atrial myocardium, AV node, His bundle, bundle branches, and Purkinje network) dictate the duration of the electric AV delay.[27,28] A variety of factors, such as autonomic nerve control, can influence AV conduction velocity,[29,30] and thus AV delay. One expects that those factors would differ in different mammalian species. Electrophysiologic and/or morphologic and morphometric differences among atrial myocardium, AV nodal, and/or Purkinje cells in differently sized mammals are, however, hardly apparent. On the contrary, size and function of all those cells

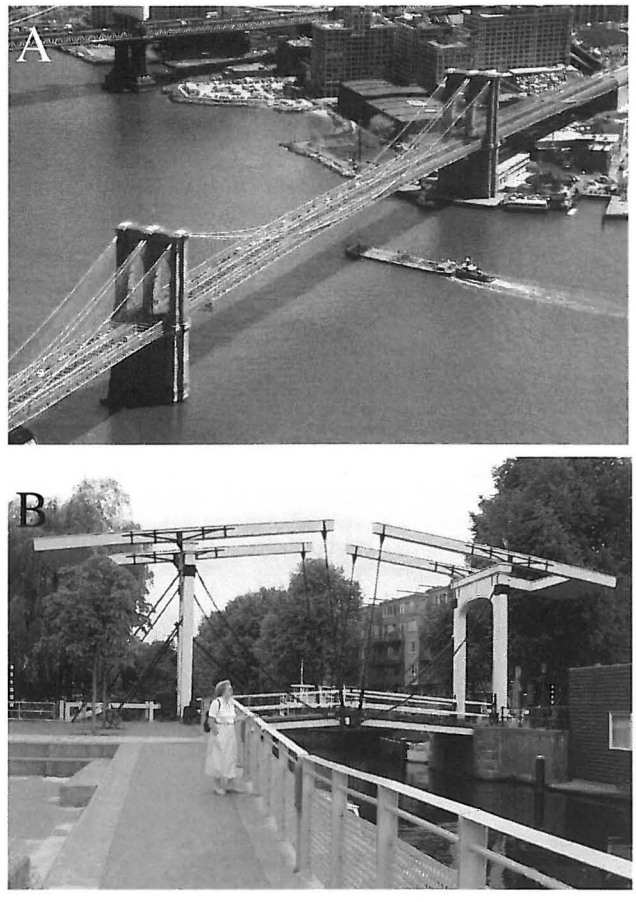

Figure 2. A) Aerial view of the Brooklyn Bridge over the East River between Manhattan and Brooklyn, New York. The bridge was built in the second half of the 19th century with granite blocks. For further details see *The Great Bridge. The Epic Story of the Building of the Brooklyn Bridge*. New York, NY: Simon & Schuster; 1972.[11] Reproduced with permission from www.tropicalisland.de/travel_newyork.html. B) A classic Amsterdam bridge over one of the canals in the old city. These bridges were and still are built with wood. Compare the dimensions and choice of material of both bridges—an example of architectural scaling.

are strikingly similar,[12,13] if not identical. There is also a striking similarity of size and morphology among mammalian cardiac myocytes,[14] which allows one to assume that the viscoelastic properties of ventricular myocardial tissue during diastole also will be similar or identical in all mammalian species[31,32] and therefore will not affect diastolic ventricular volume changes. So, for all practical purposes, it seems justified to forget about structural, cellular, and maybe even molecular differences to explain scaling of AV delay in mammalian species. We must conclude that scaling of AV delay is a function of AV node physiology.[33,34]

AV System Function

Conduction velocity in the subnodal conduction system is probably roughly the same, about 2–5

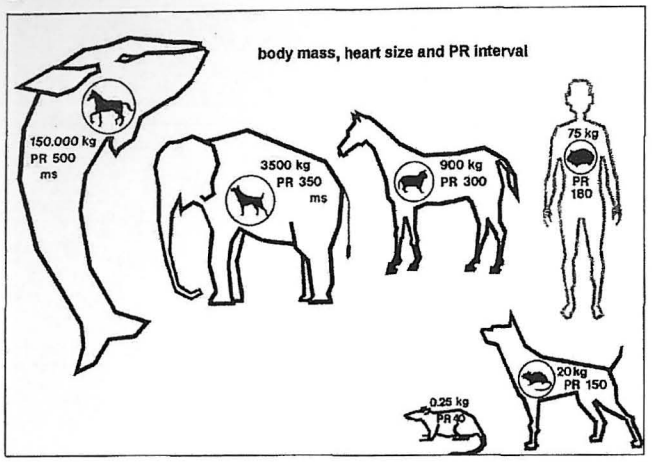

Figure 3. Drawing made by the late Dr. Robert F. Rushmer in 1990 of scaling of mammals, their hearts, and their PR intervals (ms). The mass of the heart is presented as a mammal of similar weight. For instance, a blue whale of 150 tons has a heart with the weight of a horse; a human has a heart with the weight of a guinea pig, and so on.

m/sec,[35] for all mammals. This velocity is so high that, possibly with the exception of the whale, the length of His bundles and bundle branches hardly contributes to the total mammalian AV conduction delay.[29] Conduction velocity in atrial myocardial strips is about 0.5 m/sec; thus, the key to varying AV delay for differently sized mammals must reside in the AV node itself, although the duration of atrial excitation (duration of P wave on the ECG) also plays a minor role. It is clear that the physical capability of an individual mammal and the survival of mammalian species depend on the hemodynamic performance of the heart. In other words, in evolution, the electricity of the heart is master and at the same time servant of the mechanical behavior of the heart.

AV conduction is an electric process that controls the time lapse between the beginning of atrial contraction and the start of left ventricular contraction. This time lapse allows for the transport of diastolic blood volume from the left atrium to the left ventricle. We know that without the support of the atrial contraction (as in atrial fibrillation) blood flow from atria to ventricles can sufficiently be sustained.[36,37] Therefore it appears to be possible to maintain a rather normal life solely on early, rapid ventricular filling. For mammalian species to survive, however, especially under strenuous conditions such as fright and flight, the contribution of atrial contraction to diastolic ventricular filling is vital.[38,39] As early as 1922, Wiggers and Katz[40] estimated that atrial systole contributes about 35% to ventricular filling when the AV delay, given the size of the heart, is well tuned—neither too short nor too long. Others found values of about 25%.[41]

A change in left ventricular stroke volume has to be accompanied by a change in diastolic blood flow from the atria into the ventricles. From the relatively small differences in PR intervals in widely differently sized mammals[19,22] and the proportionality of heart size and stroke volume,[10] one may assume that changes in diastolic blood flow occur at the same small diastolic pressure differences between atria and ventricles[42] in all mammals. In a rat, for instance, a small atrial volume passes a narrow mitral opening; in an elephant a large volume passes a wide mitral opening. If indeed the diastolic pressure differences between atria and ventricles are small and similar, the question to be answered is: why should it take longer for a larger atrial volume to pass a larger mitral valve opening than for a smaller atrial volume to pass a corresponding smaller one?

Conclusion

From this first part of our review we see that in mammals the PR interval (AV delay) changes little in comparison with changes in heart and body size. We can conclude that these small changes in AV conduction time regulate the fine tuning of the time lapse between atrial and ventricular contractions in mammals of all sizes. This time lapse controls late diastolic blood flow from the atria to the ventricle, which is vital for the survival of mammalian species. In the second part of this review, we will explore a simple mathematic explanation of AV delay scaling among mammalian species.

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