Review • CME

Evolution and Scaling of Atrioventricular Conduction Time in Mammals

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

This review in The American Heart Hospital Journal *is published in two parts. Part 1 deals with the role of scaling in (patho)physiology and anatomy, or the function and structure 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 (AV) conduction (Winter 2006 issue—*Am Heart Hosp J. *2006;4:53–57.). Part 2 offers a simple mathematic explanation of AV conduction time scaling based on AV hemodynamics in mammalian species of different sizes.*

Changes of the PR interval (atrioventricular delay) in relation to changes of heart size in mammalian species (scaling) confront us with a perplexing lack of understanding of an essential function of the heart. The PR interval controls the duration of late diastolic blood flow from the atria to the ventricles. There is good evidence that blood flow velocity is fairly constant in all mammalian species, meaning it does not scale. Also, in all mammalian species, the mitral orifice does not offer any resistance to atrioventricular blood flow. It follows that blood flow duration is directly dependent on the distance between the atria and the ventricles. Although the heart is not a cube, this distance is defined as the third root of heart mass. The third root of any value changes little in relation to the value itself. This simple mathematic fact is an easy explanation for PR interval behavior in relation to heart and/or body size. However, the atrioventricular intranodal electrophysiology of this behavior is not known.

During evolution, hemodynamics had to be adjusted according to the habitat in which a particular species was to survive. This adjustment was controlled by the electrical processes preceding the mechanical behavior of the heart and thus of the entire circulation. It follows that the electrical activation of the atrial myocardium and atrioventricular (AV) conduction time serves as well as controls the transport of blood from the atria to the ventricles during late diastole. The mean velocity of blood decreases only slightly with increasing body size.[1] Thus, differences in blood transport time from the atria to the ventricles mainly represent differences in distances, which depend on the size of the heart. Understanding the varying PR intervals in health during rest, excitement and exercise, and disease (e.g., mitral stenosis, AV block, preexcitation) is only possible with knowledge of the physiology of AV blood transport and ventricular filling. A number of factors have to be taken into account.

Mitral Orifice Diameter

A possible anatomic feature that could affect the AV blood transport by creating some form of resistance is the mitral opening between the left atrium (LA) and the left ventricle (LV). In a large postmortem study of fresh hearts obtained from mammals, we found a nearly proportional relationship between mitral orifice diameter and heart length (the third root of heart mass)[2]; the diameter of the mitral orifice being half the length of the heart. As the heart gets larger, the mitral orifice gets wider, implying that changes of heart size result in proportional changes of mitral diameter and do not affect the duration of AV transport of blood in mammalian species (Figure 1).

Magnetic Resonance Imaging of the Human Heart

Further insight in the visual and quantitative aspects of the transport of blood from the LA to the LV was

• 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:* Frits L. Meijler, MD, PhD, ICIN, P.O. Box 19528, 3501 DG Utrecht, The Netherlands; e-mail: denham@euronet.nl

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obtained with the use of magnetic resonance imaging (MRI) in 10 healthy adult subjects (mean mass, 83 kg; SD, 12 kg).[2,3] The human heart is representative of all mammalian hearts. Hearts differ in size but not in shape or architecture. Figure 2 shows four still frames from MRI movies available at: http://www.euronet.nl/~denham/MRI-movies. During diastole, beginning with rapid LV filling caused by (active) dilation of the LV, the mitral valve is wide open with the result that the LA and LV appear as one space. It can be seen that the mitral orifice and mitral valve do not pose any resistance to ventricular filling. The cine mode of the movie shows real-time contractions of the human heart during one full cardiac cycle. The two-chamber and short-axis views of the LV show that the rapid filling phase starts at early diastole with the opening of the mitral valve. LV volume is further increased by LA contraction—a direct visualization of the Frank-Starling mechanism in vivo.[4,5] Interesting findings arise after several viewings of the movements of the heart; for instance, the closing during LV systole and the opening of the mitral valve during LV diastole is a fascinating sight, reminding us of the closing and opening of one of the major spring tide defense barriers in the North Sea delta in the Netherlands, west of Rotterdam harbor (Figure 3). This is beyond the subject of this study, but the engineers were never aware of the mitral leaflets in operation.

LV Volume and Mitral Flow Measurements

MRI of the heart allows for LV volume measurements and quantification of the mitral flow.[2,3] In this investigation, we are mainly interested in the diastolic flow measurements. We found an average LV stroke volume of 90 mL and a cardiac output of 5.6 L. The contribution to diastolic LV volume (average of the 10 observations) was 66%±6% for early (rapid) filling and 31%±5% for the atrial contraction (late diastolic filling). As a rule of thumb, one should remember that total LV diastolic volume consists of two thirds early and one third late filling. Figure 4 shows a typical example of mitral flow quantification in an individual with a heart rate of 60 bpm, i.e., a cardiac cycle of 1000 ms (x-axis). Point 0 on the x-axis coincides with the beginning of the QRS complex on the electrocardiogram and represents the start of the cardiac cycle. The y-axis shows blood flow velocity over the mitral valve in mL/s. During LV systole there is no flow over the mitral valve; the mitral leaflets are closed because LV pressure exceeds LA pressure. LV systole ends with the beginning of rapid LV filling due to relaxation of the LV, which brings LV pressure

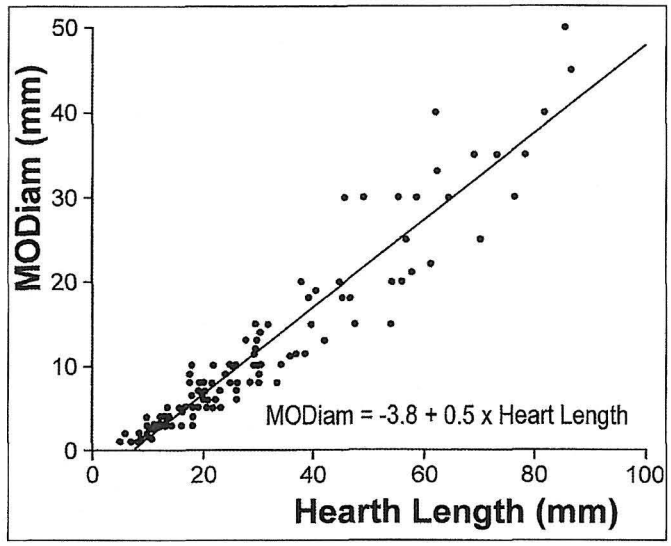

Figure 1. Relationship between mitral orifice diameter (MODiam) and heart length (cubic root of heart mass). Reproduced with permission from *Heart Rhythm*. 2005;2:188–196.[2]

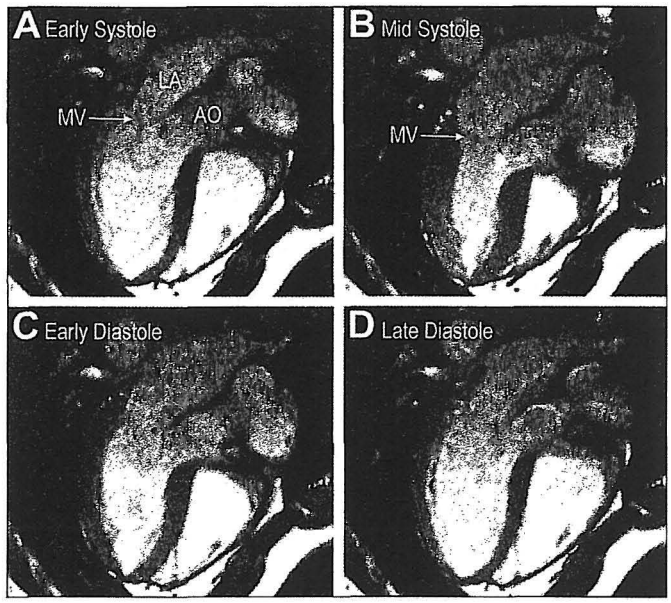

Figure 2. Four still frames from a representative magnetic resonance imaging movie (available at: http://www.euronet.nl/~denham/MRI-movies). LA=left atrium; MV=mitral valve; AO=aortic valve; LV=left ventricle. Reproduced with permission from *Heart Rhythm*. 2005;2:188–196.[2]

below LA pressure. Curve E represents the flow over the mitral valve during the rapid filling phase, and curve A represents the flow caused by the atrial contraction. The sum of the areas under curves E and A equals stroke volume. When we normalize cardiac cycle duration of our human subjects, the A wave always starts at 80% of the RR interval, while start and duration of the E waves are scattered between 35% and close to 80% of the cardiac cycle. We now

Figure 3. One of the major Dutch defense barriers against the sea (top of picture). When the tide is too high, the water level on the seaside can be compared with high left ventricular pressure during systole. The steel arms resemble the chordae tendineae. Reproduced with permission from the Netherlands Ministry of Transport, Public Works and Water Management, The Netherlands.

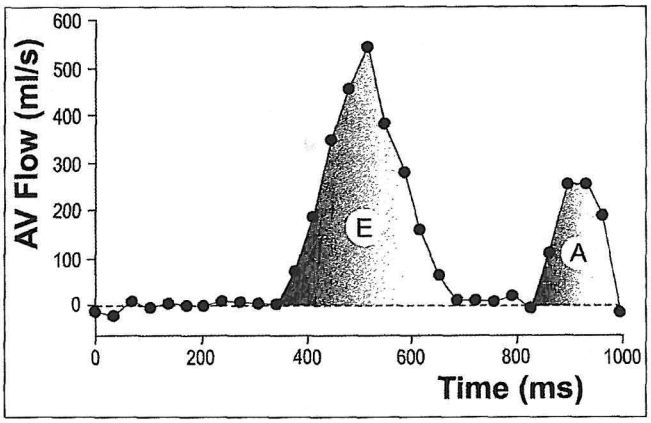

Figure 4. Atrioventricular (AV) mitral flow velocity during one cardiac cycle of 1000 ms. The time between 0 and the beginning of E represents left ventricular systole. The E curve represents the rapid filling phase during early diastole, and the A curve represents the AV flow over the mitral valve during atrial contraction—late diastolic filling. The sum of the areas under the curves equals stroke volume. Reproduced with permission from *Heart Rhythm*. 2005;2:188–196.[2]

must realize that the PR interval only controls about one third of diastolic blood flow, while approximately two thirds enters the LV *before* the beginning of the A wave and after LV systole. The A wave and the duration of AV conduction play a secondary (although vital) role in controlling the stroke volume that leaves the ventricle during systole.

In 1988, van Dam-Koopman[6] published a study on diastolic LV dimensions in atrial fibrillation using two-dimensional echocardiography. With her consent, we reproduced the most salient figure from her study (Figure 5). The x-axis represents the duration of the RR interval (ms) and the y-axis represents the LV end-diastolic dimension (mm) in a patient with a normal mitral valve. The ventricular rhythm is random during atrial fibrillation, thus all RR intervals differ in duration.[7] It can be seen that after 600 ms, maximum end-diastolic dimension (in this case considered to represent LV end-diastolic volume) is reached independently of further lengthening of the RR interval. In individuals with a sinus rhythm, the duration of LV systole determines the timing of *early* diastolic LV flow and, thus, the major part of stroke volume. However, as shown in Figure 4, *late* diastolic flow (beginning of atrial contraction) appears to occur at 80% of the cardiac cycle. The conclusions are: 1) the PR interval controls about one third of total diastolic blood flow; and 2) in patients who require sequential pacing, especially those with heart failure, the atrial stimulus should be delivered at 80% of the chosen cardiac cycle to obtain the optimal effect of the atrial contraction.

Mathematic and Other Considerations

The impetus of an almost lifelong study was to understand scaling of AV conduction (PR interval on electrocardiography) in mammalian species. Our thesis is that in evolution, electricity of the heart has been designed to control hemodynamics. For that reason, two different physical models were applied (personal communication, Dr. Frans Nieuwstadt, 2004) to estimate the time it takes to transport blood from the atria to the ventricles.[8,9] In these models, we focused on the duration of late diastolic filling by atrial contraction because that duration is relevant to scaling of the PR interval.[2] The independently obtained outcomes of both models were similar and yielded a theoretic scaling factor of one third power on heart mass for the duration of blood transport by atrial contraction into the ventricles.

In a recent study using allometric equations, a scaling factor of one fourth for PR interval (AV delay) vs. heart mass was found.[10] The difference with a one third scaling factor may reflect the use of standard Euclidean vs. fractal analysis. However, this difference may be immaterial, particularly in the context of biologic variability.[1] For the sake of clarity, we plotted the third root as well as the fourth of a series of values (Figure 6). It can be seen that the "mismatch"[11] caused by the third (and fourth) root slowly increases with the magnitude of the values on the x-axis. This simple mathematic consideration offers an additional plausible explanation for the one third vs. the one fourth scaling

factor controversy. The one third root of heart mass is a rough approximation of the distance (the heart is not a cube) between the atria and the ventricles and, thus, at a given (constant) flow velocity, the mass-dependent transportation time. AV conduction delay is much more complicated because it takes place within the AV node. The true nature of the process that causes this delay is still unknown. A further complication is the fact that when we plot the PR interval against heart mass and extrapolate the curve to heart mass at zero, it crosses the y-axis at a value clearly different from zero. The PR interval still has a value of about 40–50 ms.[12] In other words, with a theoretic heart size of 0 mm, the PR interval is >0 ms.

A metaphor for AV delay is that of a traffic roundabout that is covered from above. One can see a car (impulse) entering the roundabout (AV node) and also exiting it. The time that the car stays on the roundabout can be measured, but what happens in between is unknown. The roundabout may have a more or less complicated design, and the speed of the vehicle may vary. The same is true for the AV node; its morphology is complicated, and the speed and route of an atrial impulse going through it is unknown. Thus, our knowledge of AV node electrophysiology[13,14] or, rather, our lack thereof, does not allow for an explanation of the mechanism of AV conduction delay, let alone for the mechanism that links AV delay to the duration of late diastolic AV blood transport.

With respect to early diastolic filling, it is worthwhile to take into consideration that, according to Schmidt-Nielsen,[1] heart rate scales with body mass with a fourth root but, according to Lambert and Teissier,[15] with a third root. We find here a similar difference of appreciation associated with the PR interval. The duration of a cardiac cycle is inversely proportional with heart rate. The relationship between cycle length and contractility, called postextrasystolic potentiation, is fairly well established.[16] Small hearts as compared with large hearts have fast heart rates; thus, small hearts have short cardiac cycles accompanied by high contractility and a high speed of relaxation.[17] LV filling occurs at a high speed, made possible by fast relaxation and short AV distances. Simple mathematic principles (Figure 6) explain the so-called mismatch between PR interval and heart mass; simple rules of hemo(hydro)dynamic transport explain the duration of AV blood flow; however, the mechanisms of the linkage of AV blood flow with AV delay and of AV delay itself are still terra incognita.[18,19]

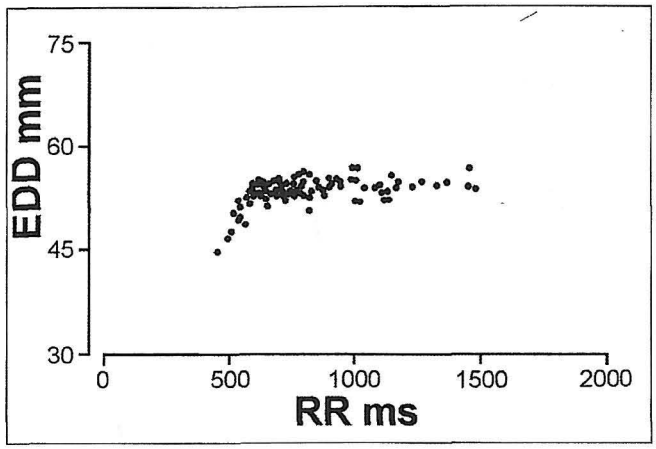

Figure 5. Left ventricular end-diastolic dimension (EDD) vs. RR intervals in a patient with atrial fibrillation and a normal mitral valve. There is no further increase in EDD after an RR interval of 600 ms. Courtesy of Dr. Ina van Dam-Koopman.[6]

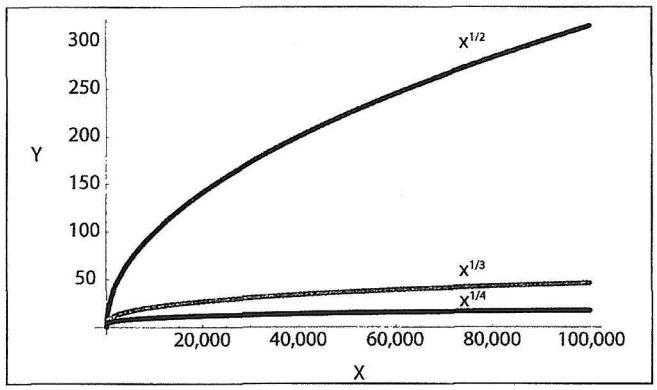

Figure 6. Plot of the square root (1/2), cubic root (1/3), and fourth root (1/4) of a series of values. The larger the value, the relatively smaller become the root results as well as their relative quantitative differences. See text for further details.

Evolution

In the previous section,[20] we distinguished between the role of electricity of the heart and hemodynamics in evolution as well as in the survival of species and individual members of a species. We postulated that for each species to survive there has to be a strong coupling between electricity and hemodynamics, because it is the circulation that enables life and promotes survival. Evolution is the driving force of the shape, size, and function of all mammals. It is of great interest that, in evolution, form prevails over function.[21] Similar organs and structures are found in mammalian species of widely different sizes and shapes.[1] Thus, the hearts of all mammals are built according to the same blueprint. In addition, all mammals have cells that are approximately the same size. Changes in body shape and size call for scaling of a number of functions, as explained above. Scaling of the PR interval has long been an enigma, but the

realization that scaling factors of one third and one fourth power offer a rather simple explanation for what we formerly perceived as a mismatch has solved this riddle—but not its physiology. Of course, considering the electricity and mechanics of the heart, we cannot separate one from the other. The time course of evolution does not allow for an experimental approach to AV nodal scaling.[22,23]

Conclusions

From an evolutionary point of view, we have to accept that for the survival of mammalian species, electricity of the heart is the servant of the mechanical behavior of the heart and, thus, of circulation. In each individual, electricity rules the heart and, in agreement with that, the PR interval controls the duration of AV blood flow. The duration of AV blood transport is related to the size (mass) of the heart, with a scaling factor of one third. This duration is controlled by the AV delay (PR interval). Scaling of the PR interval takes place in the AV node. However, the mechanism of this is unknown, as is the linkage between electric and hemodynamic scaling. The so-called mismatch between PR interval and body/heart mass is explained by simple mathematic considerations: the larger the value, the relatively smaller the third and fourth root. The same mathematic results demonstrate that the larger the heart, the relatively smaller the perceived difference between the one third- and one fourth-power scaling factor. The early diastolic filling is scattered over early diastole, while atrial contraction (late diastolic filling) occurs at 80% of the cardiac cycle. Stroke volume consists of the sum of two thirds early and one third late diastolic filling.

Summary

In the past, we and others have tried to understand the relationship between the PR interval on electrocardiography (AV conduction delay) and the size of the body and, thus, that of the heart in mammals. From the mouse to the whale, the PR interval increases 10-fold, whereas body mass increases some million-fold. This apparent mismatch is the result of so-called scaling of AV delay with body and heart mass. During evolution, circulation had to adapt to the size of mammalian species. This was made possible by the evolving form and function of their hearts. All mammalian hearts are built according to the same blueprint, but the change in size of each species demanded adaptation of the hemodynamic function of the heart. This change in function needed a proper electrical control system. Therefore, the electricity of the heart had to follow the developing hemodynamics. In each individual mammal, including the human, electricity controls the mechanical function of the heart. It follows that AV delay not only controls atrial contraction, but also the duration of late diastolic flow. The velocity of this flow does not scale; therefore, it is the same for all mammals. Distance determines the time to transport blood from the atria to the ventricles. We used two physical models demonstrating that the cubic root of heart mass can approximate this distance. When one plots the cubic root of heart mass against heart mass itself, it becomes clear why the PR interval increases so little with the increase of body size of mammalian species. Therefore, the mismatch is the result of a simple mathematic principal together with the fact that the AV delay controls the duration of late diastolic blood flow. We now understand the physiology of this late diastolic flow. However, neither the electrophysiologic processes that control AV conduction delay nor the mechanism that links AV delay to transport time of late diastolic flow are known. An important additional finding was that atrial contraction always starts at 80% of the duration of the cardiac cycle. This may be of advantage for dual-chamber pacing in patients with heart failure.

Acknowledgment: Expressing our gratitude to all friends, peers, and colleagues, as well as assistants and others, for guiding us over the nearly half century that we tried to lift a tip of the veil of atrioventricular node function in health and disease in humans and other mammals would fill a full page. However, we make the exception by thanking ***Mrs. Lise Plamodon****, Departement de Physiologie, Faculté de Medicine, Université de Montreal, Canada, for her help with the art work, and remembering our friend,* ***Dr. Frans Nieuwstadt****, professor of hydrodynamics at the Delft University of Technology, The Netherlands, whose recent untimely death is a great loss to us.*

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