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CREATIVE MUSING

Scaling of Atrioventricular Transmission in Mammalian Species: An Evolutionary Riddle!

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Scaling of AV Transmission. "Scaling deals with the structural and functional consequences of changes in size or scale among otherwise similar organisms." It plays a key role in all studies on comparative mammalian physiology and morphology. Heart weight is proportionally related to body weight and can be described by a straightforward, so-called allometric equation. We studied scaling of AV transmission times (PR intervals on the ECG) in 375 mammals of different dimensions and species. Scaling of AV transmission times versus heart length (third root of weight) is statistically best described by a S-shaped curve. This implies that AV transmission time in mammals is not linearly related to heart length and does not depend solely on the length of the AV transmission system. The AV node fine-tunes AV transmission times at rest and during exercise in individuals; it protects the ventricles against high-rate atrial arrhythmias such as atrial fibrillation; and it regulates basal AV transmission times in mammalian species of varying sizes. We call the "how" and "why" of the scaling of AV transmission time in mammals an evolutionary riddle that deserves further study. *(J Cardiovasc Electrophysiol, Vol. 13, pp. 826-830, August 2002)*

scaling, comparative atrioventricular transmission, evolution, mammalian heart

Introduction

As early as 1927, Clark[1] noted that "the PR interval varies so little in different animals." In previous publications, we described the relationship between body or heart weight and the duration of the PR interval in a large number of mammalian species.[2-7] Heart weight is proportionally related to body weight,[8,9] but in going from mouse to whale we found that PR interval duration is not linearly related to heart weight.[4-7] Small mammals (mice and rats) have relatively long PR intervals that hardly differ in duration. Large mammals (horses, elephants, and whales) have relatively short PR intervals that also are of nearly equal duration. We concluded that PR interval duration does not solely depend on the transmission velocity of the cardiac impulse and/or the length of the AV transmission pathway. Other mechanisms must be involved. In this article, we present a more quantitative approach to this observation and stress the lack of known substrates for these findings.

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What is Scaling?

The term *scaling* and its meaning play a key role in all studies on comparative physiology and morphology. In 1638, Galileo Galilei[10] was the first to draw attention to the relationship between body size and shape and dimension of bones in a variety of mammalian species. As an example, he used a bone *"whose natural length has been increased three times and whose thickness has been multiplied"* to maintain the same relative strength as when it was smaller (Fig. 1). This adaptation is called *scaling,* although in Galilei's time the word "scaling" did not yet exist.

According to Schmidt-Nielsen,[9] *"Scaling deals with the structural and functional consequences of changes in size or scale among otherwise similar organisms."* In engineering, problems of changes in size often can be solved by using stronger or different materials, for example, concrete or steel instead of brick or wood. In the living world, the material used to build animal bodies is the result of eons of evolutionary processes, so scaling of structure and function must occur within the constraints of morphology and physiology of organs and organ systems. In recent years, new and interesting models of scaling laws in biology have been presented,[11,12] but to the best of our knowledge they have not been tested in relation to the electrical functions of the mammalian heart.

Most animals live in the same physical world; therefore, they function at relatively uniform temperatures and pressures.[13] Mammalian biologic systems function at about 37°C. The diameter of all mammalian cells depends on the

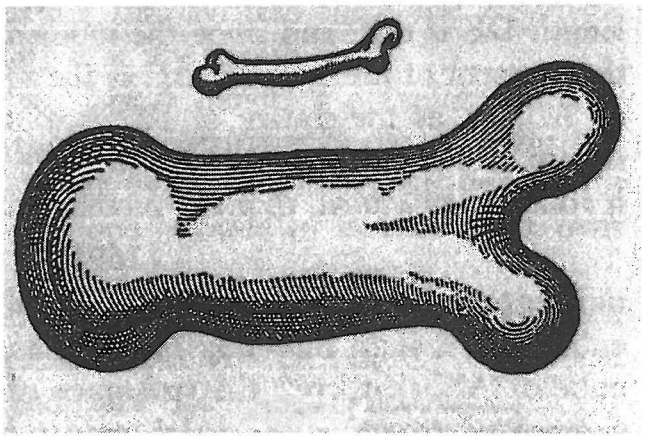

Figure 1. *Reproduction of Figure 27 in the book on Galileo Galilei (p. 126).*[10]

metabolic demands of the cells and the capability for transmembrane oxygen diffusion. Therefore, the diameter of all mammalian cells reflects the optimal relationship between cell volume and oxygen diffusion rate at their body temperatures.[14] *"Cardiac muscle is composed of individual cells that in all mammals (mouse through whale) are rather uniform in diameter (approximately 10 to 15 μ)."*[15,16] Scaling of heart size takes place, but the diameter of the mammalian cells does not seem to change. Larger mammals have more cells, not larger cells.[14] Not only is cardiac tissue composed of cells of similar diameter, but erythrocytes and glandular tissue also consist of cells that tend to be uniform in diameter.[17]

Often it is easy to explain and understand why and how scaling is occurring. Prothero[8] and Schmidt-Nielsen[9] found that in all mammals studied, heart weight was 0.6% of body weight (Fig. 2), a direct proportional relationship. Cardiac output is related to the metabolic rate and the oxygen consumption of the mammalian body with a slope of 0.81.[9] In mammals, stroke volume is directly related to heart weight. Small mammals have a relatively high metabolic rate, yet their stroke volume is directly related to heart weight with a scaling factor of 1.[9] A consequence in small mammals is that their relatively high cardiac output is not effected by a (relatively) larger heart but by a relatively higher heart rate. Systematic study of scaling of the electrical functions of the mammalian heart, such as QRS duration or AV transmission time, versus body (heart) size is a neglected part of cardiovascular electrophysiology and of scaling studies in general.[11,12] The relationship among form, size, and function in mammals[18] is of interest not only for understanding scaling aspects in biology in general, but in the case of the AV transmission system it also may add to our understanding of the contribution of AV nodal function to optimal efficacy of the circulation. In (human) health and disease, for instance, during atrial fibrillation,[19] the fundamental role of the AV node in controlling ventricular rate is well acknowledged.

Results

AV Time Versus Heart Size

1. *Small mammals:* The PR interval in a newborn mouse weighing 5 g with a heart weight of about 30 mg is 30 to 40 msec. In rats weighing 300 g with a heart weight of approximately 1,800 mg, the PR interval is 40 to 50 msec. So while body weight and thus heart weight in those rodents increase by a factor of 60 and heart length by a factor of 4, there is hardly any increase in the observed AV transmission times.[7] Extrapolating heart length to zero still would result in a PR interval close to 30 msec.
2. *Average-sized mammals*: In contrast, there is a distinct and linear increase of PR intervals from the adult rat onward to the horse, going from 40 to 350–400 msec (a factor of 10). Body weight in this group of mammals (including humans) increases from 300 g to 900 kg (a factor of 3,000) and heart length increases by a factor of 15,[5] while the AV transmission time increases by a factor of 7 to 10.
3. *Large mammals*: PR interval duration (400 msec) in elephants weighting 3,500 kg[3] and in the humpback whale weighing 30,000 kg[4] is approximately the same as in a medium-sized horse weighing 900 kg,[18] an increase by a factor of 33, while heart length increases by a factor of 2.

The combination of these findings is shown in Figure 3, which summarizes our data and those of others obtained in 375 mammals of different species with widely varying body weights and thus heart weights.[3-7,20-22] The nonlinearity of the curve is mainly due to the aberrant behavior of the whale. The minimal increase, if any, of the PR interval in small mammalian species of different sizes may yet fall within a generally applicable allometric equation. It is interesting to note that a constant PR interval at increasing body sizes can be observed within one species (the human).

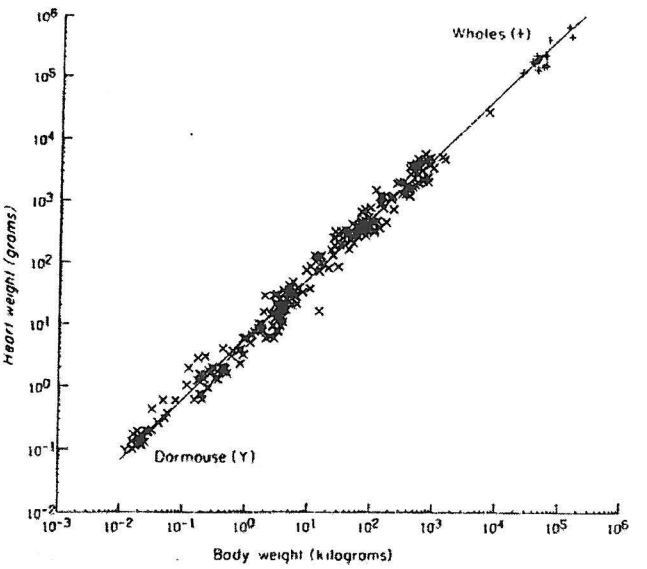

Figure 2. *Prothero's original figure from 1979.*[8] *(Reproduced with permission from Prothero J: Heart weight as a function of body weight in mammals. Growth 1979;43:139-150.)*

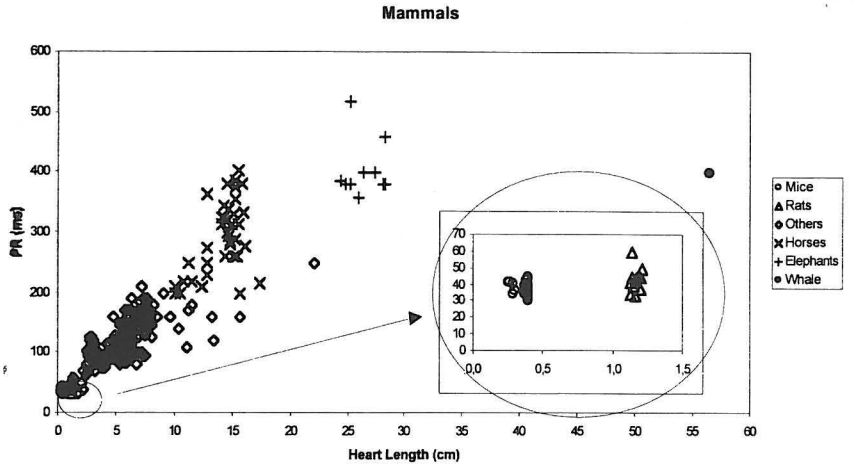

Figure 3. *PR time (in milliseconds) versus heart length (in centimeters) observed and computed in 375 mammals of different species and sizes, ranging from newborn mice to the humpback whale. See text for details.*

Mathematical Considerations

Why Heart Length?

In a gross simplification necessary for a more quantitative approach, we present the length of the pathway that the electrical impulse must travel from atria to ventricles as heart length, which we defined as the third root of heart weight (assuming a constant density of 1 $g \cdot cm^{-3}$). Using the third root of heart weight underestimates the true length of the AV transmission system (atria, AV node, His-Purkinje system). After passing the AV node, the electrical impulse traveling from atria to ventricles takes the twisted His-Purkinje road, which is present in the hearts of all mammalian species of all sizes.[23-28] This is a more complicated and definitely longer route than the straight, one-dimensional heart length we used for our data presentation. We are aware of the fact that the shape of the heart is not the same in different mammalian species. We thus introduce an unknown error that will affect the nonlinearity of the scaling data of AV transmission versus heart length. The relationship between AV transmission time and heart length may be different in different species and, therefore, may yet resemble an allometric scaling pattern.[2,29]

PR Time Versus Heart Length

The outcome of data collection of biologic magnitudes often is presented in the form of the so-called allometric equation:

$$Y = a \times X^b. \quad (1)$$

In this equation, X and Y are the involved biologic magnitudes, and a and b are constants, where b is the substantial constant and sometimes referred to as the scaling factor. The allometric equation curve is a robust presentation of most biologic scaling data.[11,12] A clear example is the heart weight versus body weight relationship described by Prothero.[8]

By taking logarithms, the equation allows for an easy estimation of the unknown constants a and b of a series of data:

$$Log\ Y = Log\ a + b \times Log\ X \quad (1a)$$

One often refers to this presentation as the regression of *Log Y* on *Log X*. The constant *Log a* represents the intercept with the (log) y-axis and b the slope of the straight line. This may pose a fundamental problem for the presentation of biologic data, because why should one always expect $y = 0$ for $x = 0$? For instance, in our case, at an extrapolated heart weight of zero, the PR interval still would be on the order of 30 to 40 msec. Van der Tweel et al.[7] demonstrated in newborn mice with hearts as small as one can obtain (±30 mg) and well-developed His-Purkinje systems[25] that the line representing the relationship between PR interval and heart length crosses the y-axes well above zero.

Therefore, from several possibilities we opted in Figure 3 for the *logistic curve* (sigmoid curve) introduced by Verhulst[30] in 1844 as "courbe logistique":

$$Y = p/\{1 + q \times Exp(-\lambda \times X)\}. \quad (2)$$

X and Y again are the involved biologic magnitudes, and p, q, and λ are the parameters of the curve. Compare a and b of Equation 1. The actual data justifying this fit have been reported previously.[4,5,7,20-22]

This formula, which describes the data shown in Figure 3, implies that at a theoretical heart length of zero, PR interval does **not** equal zero. It also describes the S-shape of the curve of the relationship between PR interval and heart length. This curve presents a possible difference between scaling of AV transmission time and other forms of scaling (allometric) of (cardiac) functions in mammals. When we discard the whale data, scaling of AV transmission still can be described by an allometric formula, but the whale data are too unique and biologically too important not to present the more complicated relationship. In either case, it leaves us with the perplexity of rather simple mathematics versus a highly complex, albeit amazingly predictable, electric behavior of the mammalian AV node.

Discussion

Mice Versus Rats, Versus Horses, Versus Whale

The curve shown in Figure 3 combines the findings of PR intervals versus heart length for 375 mammals ranging from newborn mice[7] to the humpback whale.[4] Because considerably more small mammals were studied than large animals, there is a cluster of data points at the lower end of

the curve and only a few data points at the higher end. It is interesting to note that at an extrapolated (nonexistent) heart size of zero there still would be a sizable PR interval. The whale data "weigh" heavily, but because of the biologic significance of those precious data they were included.

A puzzling observation is that in small mammals (newborn mice and rats) the PR times, apart from being quite long, hardly seem to differ even though the rat heart is 60 times bigger (heavier) than the newborn mouse heart and the distance (third root of weight) the impulse must travel between atria and ventricles increases at least fourfold. Large mammals show the opposite; horses, elephants, and our whale have relatively short PR intervals. Despite a wide difference in body (heart) weight and heart length, PR also hardly differs in duration. This observation further demonstrates that in hearts smaller than a certain size (rats) AV transmission time seemingly cannot get shorter, and in large hearts (horses, elephants, and whales) AV transmission time cannot get longer. It is interesting to note that at an extrapolated (nonexistent) heart size of zero there still would be a sizable PR interval.

A constant PR interval, at increasing body sizes, can be observed within one species. Kähler et al.[31] recently reported the development of cardiac time intervals in normal human embryos. Their data show that between weeks 20 and 42 of gestation, the PR interval remained unchanged between 55 and 60 msec. Costa et al.[32] clearly showed in premature infants that although the infants gained weight from birth until age 5 to 7 weeks, PR intervals did not increase. They remained constant at the 90-msec level, i.e., the same PR duration we found in premature babies weighing $\leq$1 kg.[6] When hearts get bigger and the His-Purkinje systems longer, AV transmission does not necessarily take more time. The conclusion is undeniable that there is no simple relationship between traveling distance and traveling time of the impulse in the mammalian AV transmission system, not only between species but also within a single species (human).

General Considerations

Macro- and micro (electron)-morphology of the myocardium, AV node, and His-Purkinje system, studied in detail for more than a century, is similar in all mammalian species of all sizes.[23-28] Electrophysiologic differences between myocardial and Purkinje cells in a variety of mammalian hearts are relatively small[33,34] and do not explain the limited increase of AV transmission time versus heart size and the overall complexity of AV nodal electrical function.[35,36] Despite its promises for the future, there is no known molecular substrate that yet explains the behavior of AV transmission scaling in mammals. Some differences in conduction velocities in atria of genetically manipulated mice were found to be related to connexin40 protein concentration in the gap junctions,[37,38] but at this time it does not seem possible to extrapolate those findings to conduction velocities in the specific conduction system in mammals of different sizes. Moreover, there is conflicting evidence in this field.[39] For now, we cannot present a substrate or explanation for the scaling of delay in the AV transmission system in relation to body weight (heart size) in mammalian species. It is possible that a species-dependent density of adenosine receptors is responsible for this phenomenon, but apart from guinea pig data there is insufficient information to support this.[40]

The Brain of the Heart

The AV node has at least three functions:

1. It warrants optimal efficacy of cardiac output by fine-tuning the delay between atrial and ventricular contraction.[41] It is fair to assume that the differences in AV transmission times between mammalian species (of different sizes) as presented here serve the same purpose.
2. Another important aspect of AV node physiology is the protection of the ventricles and thus of life itself against the effects of high-rate atrial arrhythmias such as atrial fibrillation.[42]
3. It serves (at least in humans) as a backup pacemaker in case of atrial arrest, whatever the cause.

The AV node controls the function of the heart and thus of the circulation; therefore, it plays a fundamental role in the survival strategy of all mammalian species. As such, it is fair to call this complicated evolutionary marble "the brain of the heart."

The Possible Role of Evolution

The notion of evolution to explain the PR-heart length relationship may be found in the physical effects of the mitral valve radius on the pressure gradient over the valve. We have reason to believe that (part of) the explanation can be found in Poiseuille's law. In small mammals, there must be a strongly increasing (fourth power) effect of the diminishing radius of the mitral valve opening on resistance of the mitral valve during ventricular diastole. The narrow mitral opening probably requires an increase in PR interval to allow more time for ventricular filling and to prevent excessive pressure in the left atrium. In large mammals, further lengthening of the PR interval is not necessary. Scaling of PR interval versus heart length in mammals may guarantee optimal efficacy of the circulation in very small and very large mammals. This can be viewed as the expression of a survival strategy of very small and very large mammalian species.

Conclusion

1. Morphology, electrophysiology, and biochemistry of the transmission system of the mammalian heart do not offer a straightforward answer to the problem of nonlinear scaling of AV transmission time in different mammalian species. Until now, clinical and experimental electrocardiology did not even signal the peculiar relationship between AV transmission time and heart size, let alone offer a solution for this phenomenon. AV and myocardial conduction studies have entered their molecular phase but still are far from firmly linking transmission velocities in the AV node and His-Purkinje system to gap junction proteins.[43] It is unknown exactly where the answer may be found: in the AV node proper, in the His-Purkinje system, or in both?
2. We learned from evolution that form prevails over function.[44] This fact is fundamental to our understanding of function adaptation to differences in size in mammalian species. It is exemplified by the almost identical blueprint of the heart and the AV node in all mammalian

species of all dimensions as well as in the similar size and form of mammalian myocardial cells.

3. The reasoning presented in this article leaves us with two major questions. (1) *How* is scaling of AV transmission time (adaptation of function) versus heart size effected? In other words, what is the substrate of nonlinear comparative AV transmission in mammalian species of different sizes? Billette[45] called this problem a challenge for the 21st century. It is. (2) *Why* is this unusual form of scaling observed in the mammalian AV transmission system? In other words, what is the survival strategy (hemodynamic or other) for this behavior? We will return to this evolutionary riddle in a subsequent article.

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References

1. Clark AJ: *Comparative Physiology of the Heart.* Cambridge University Press, Cambridge, 1927, pp. 49-51.
2. Meijler FL: Atrioventricular conduction versus heart size from mouse to whale. J Am Coll Cardiol 1985;5:363-365.
3. Meijler FL, Van der Tweel LH: De elektrocardiogrammen van 10 olifanten en van de orka in Harderwijk. Ned Tijdschr Geneeskd 1986;130:2344-2348.
4. Meijler FL, Wittkampf FHM, Brennen KR, Baker V, Wassenaar C, Bakken EE: The electrocardiogram of the humpback whale *(Megaptera novaeangliae)*, with specific reference to atrioventricular transmission and ventricular excitation. J Am Coll Cardiol 1992;20:475-479.
5. Wassenaar C: *Comparative Electrocardiography in Mammals.* Thesis, University of Utrecht, The Netherlands, 1993.
6. Van Wezel-Meijler G, Van Genderen HR, Meijler FL: Atrioventriculaire geleidingstijd bij te vroeg geborenen ongeveer de helft van die bij volwassenen. Ned Tijdschr Geneeskd 1997;141:244-247.
7. van der Tweel LH, Strackee J, Stokhof AA, Wassenaar C, Meijler FL: ECG of the newborn mouse *(Mus Domesticus)* with specific reference to comparative AV transmission. J Cardiovasc Electrophysiol 1999; 16:168-173.
8. Prothero J: Heart weight as a function of body weight in mammals. Growth 1979;43:139-150.
9. Schmidt-Nielsen K: Scaling. Why is animal size so important? Cambridge University Press, Cambridge UK, 1984, pp. 126 -130.
10. Galilei Galileo. In: *Dialogues Concerning Two New Sciences* (translated by H. Crew and A. de Salvio). Northwestern University Press. McGraw-Hill Paperbacks, New York, 1963, p. 126.
11. Williams N: Fractal geometry gets the measure of life's scales. Science 1997;276:34.
12. West GB, Brown JH, Enquist BJ: A general model for the origin of allometric scaling laws in biology. Science 1997;276:122-126.
13. Eckert JR, Randall D: *Animal Physiology: Mechanisms and Adaptation.* WH Freeman, San Francisco, 1983, p. 49.
14. Calder WA III: *Size, function and life history.* Harvard University Press, Cambridge, 1984, p. 87.
15. Sommer JR, Johnson EA: Comparative ultrastructure of cardiac cell membrane specializations. A review. Am J Cardiol 1970;25:184-194.
16. Sommer JR, Johnson EA: Ultrastructure of cardiac muscle. In Berne RM, Sperelakis N, Geiger SR, eds: *Handbook of Physiology. The Cardiovascular System. I. The Heart.* American Physiological Society, Bethesda, MD, 1979, pp. 113-186.
17. Teissier G: Biometrie de la cellule. Tabulae Biologicae 1939;19(Pt 1):1-64.
18. Altman PL, Dittmer DS. *Biological Handbooks: Respiration and Circulation.* Federation of American Societies for Experimental Biology, Bethesda, MD, 1971, pp. 272-236.
19. Meijler FL, Jalife J, Beaumont J, Vaidya D: AV nodal function during atrial fibrillation: The role of electrotonic modulation of propagation. J Cardiovasc Electrophysiol 1996;7:843-861.
20. Lombard EA: Electrocardiograms of small mammals. Am J Physiol 1952;171:189-193.
21. Hundley JM, Ashburn LL, Sebrell WH: The electrocardiogram in chronic thiamine deficiency in rats. Am J Physiol 1945;144:404-414.
22. Grauwiler J: Beobachtungen am Elektrokardiogramm von nicht-domestizierten Saugetiere. Schweizer Archiv für Tierheilkunde 1961; 103:397-417.
23. Meyling HA, Ter Borg H: The conduction system of the heart in hoofed animals. Cornell Vet 1957;47:419-455.
24. Rentschler S, Vaidya DM, Tamaddon H, Degenhardt K, Sassoon D, Morley GE, Jalife J, Fishman GI: Visualization and functional characterization of the developing murine cardiac conduction system. Development 2001;128:1785-1792.
25. Tawara S: *Das Reizleitungssystem des Herzens.* Gustav Fischer, Jena, Germany, 1906.
26. Truex RC, Smythe MQ: Comparative morphology of the cardiac conduction tissue in animals. Ann N Y Acad Sci 1965;127:19-33.
27. James TN: Structure and function of the AV junction. Jpn Circ J 1983;47:1-47.
28. James TN, Kawamura K, Meijler FL, Yamamoto S, Terasaki F, Hayashi T: Anatomy of the sinus node, AV node and His bundle of the heart of the sperm whale *(Physeter macrocephalus)*, with a note on the absence of an os cordis. Anat Rec 1995;242:355-373.
29. Meijler FL, Janse MJ: Morphology and electrophysiology of the mammalian atrioventricular node. Physiol Rev 1988;68:608-647.
30. Verhulst PF: Recherches mathématique sur la loi d'accroissement de la population. Nouveaux Mémoires de l'Academie Royale des Sciences et Belles-Lettres de Bruxelles. 1844;Tome XVIII.
31. Kähler C, Scheußner E, Grimm B, Schneider A, Schneider U, Nowak H, Seewald HJ: Fetal magnetocardiography: Development of the fetal cardiac time intervals. Prenat Diagn 2002;22:408-414.
32. Costa CA, Faul BC, Ledbetter MK, Oalmon MC: The electrocardiogram of the premature infant. Am Heart J 1964;67:4-14.
33. Jack JJB, Noble D, Tsien RW: *Electric Current Flow in Excitable Cells.* Clarendon Press, Oxford, 1975, pp. 292-296.
34. De Mello WC: Passive electrical properties of the atrioventricular node. Pflugers Arch 1977;371:135-139.
35. Billette J: What is the atrioventricular node? Some clues in sorting out its structure-function relationship. J Cardiovasc Electrophysiol 2002; 13:515-518.
36. Wu J, Wu J, Olgin J, Miller JM, Zipes DP: Mechanisms underlying the reentrant circuit of atrioventricular nodal reentrant tachycardia in isolated canine atrioventricular nodal preparation using optical mapping. Circ Res 2001;88:1189-1195.
37. Tamaddon HS, Vaidya D, Simon AM, Paul DL, Jalife J, Morley GE: High-resolution optical mapping of the right bundle branch in connexin40 knockout mice reveals slow conduction in the specialized conduction system. Circ Res 2000;87:929-936.
38. van Rijen HVM, van Veen TAB, van Kempen MJA, Wilms-Schopman FJG, Potse M, Krueger O, Willecke K, Opthof T, Jongsma HJ, de Bakker JMT: Impaired conduction in the bundle branches of mouse hearts lacking the gap junction protein Connexin40. Circulation 2001; 103:1591-1598.
39. Kanagaratman P, Rothery S, Patel P, Severs NJ, Peters NS: Relative expression of immunolocalized connexins 40 and 43 correlates with human atrial conduction properties. J Am Coll Cardiol 2002;41:116-123.
40. Meester BJ, Shankley NP, Welsh NJ, Wood J, Meijler FL, Black JW: Pharmacological classification of adenosine receptors in the sinoatrial and atrioventricular nodes of the guinea-pig. Br J Pharmacol 1998; 124:685-692.
41. Dagget WM, Bianco JA, Powell WJ, Austen WG: Relative contribution of the atrial systole-ventricular systole interval and of patterns of ventricular activation to ventricular function during electrical pacing of the dog heart. Circ Res 1970;27:69-79.
42. Wellens HJ, Durrer D: Wolff-Parkinson-White syndrome and atrial fibrillation. Relation between refractory period of accessory pathway and ventricular rate during atrial fibrillation. Am J Cardiol 1974;34: 777-782.
43. Jalife J, Morley GE, Vaidya D: Connexins and impulse propagation in the mouse heart. J Cardiovasc Electrophysiol 1999;10:1649-1663.
44. Gould SJ: Archetype and adaptation. Natural History 1986;95/10:16-27.
45. Billette J. Functional origin of mammalian PR interval variations: A challenge for the 21st century. J Cardiovasc Electrophysiol 1999;10: 174-177.