Atrioventricular conduction in mammalian species: Hemodynamic and electrical scaling

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OBJECTIVES The purpose of this study was to investigate scaling of the duration of late diastolic left ventricular (LV) filling in relation to AV conduction time (delay) (PR interval on the ECG) in mammals.
BACKGROUND From mouse to whale, AV delay increases 10-fold, whereas body mass increases one million-fold. The apparent "mismatch" results from scaling of AV delay versus body and heart mass.
METHODS We measured (1) mitral orifice diameter in 138 postmortem hearts of 48 mammalian species weighing between 17 g and 250 kg and (2) transmitral diastolic flow using magnetic resonance imaging (MRI) recordings of 10 healthy human individuals. (3) We visually inspected early and late diastolic LV filling. (4) We developed two physical models to explain scaling of late diastolic LV filling time.
RESULTS (1) Diameter of the mitral orifice proportionally relates to heart length (third root of heart mass). (2) Atrial contraction starts at a fixed instant (± 80%) of the (normalized) cardiac cycle and contributes 31% ± 5% to LV filling. (3) MRI shows that during diastole, the left atrium (LA) and LV form a single space. (4) The physical models relate the duration of late diastolic LV filling directly to heart length, the third root of heart mass.
CONCLUSIONS (1) Late diastolic (LV) filling time scales with heart length (third root of heart mass). (2) No "mismatch" exists between AV delay and heart size. (3) Knowledge of the actual starting time of atrial contraction may contribute to better treatment of patients with heart failure. (4) The findings suggest that in evolution of mammalian species, hemodynamics commands electrical behavior of the heart.

KEYWORDS Evolution; Scaling; Atrioventricular conduction; Ventricular filling; Atrial contraction
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"Nothing in biology makes sense except in the light of evolution."[1]

Introduction

The metabolic rate and thus the rate of oxygen consumption in mammals change according to body size.[2,3] The circulation distributes oxygen, removes metabolic waste, and thereby is essential for the survival of all mammals and all mammalian species. An efficient circulation requires an optimally functioning heart. Electrical activation triggers cardiac contraction and has adapted to body and heart mass. For instance, small hearts have rapid heart rates and short AV delays (PR intervals); large hearts have slow rates and relatively long AV delays. From mouse to whale, AV delay increases 10-fold, whereas body mass increases a million-fold.[4] The apparent "mismatch" results from scaling of AV delay versus heart size. In biology *"Scaling deals with the structural and functional consequences of changes in size or scale among otherwise similar organ-*

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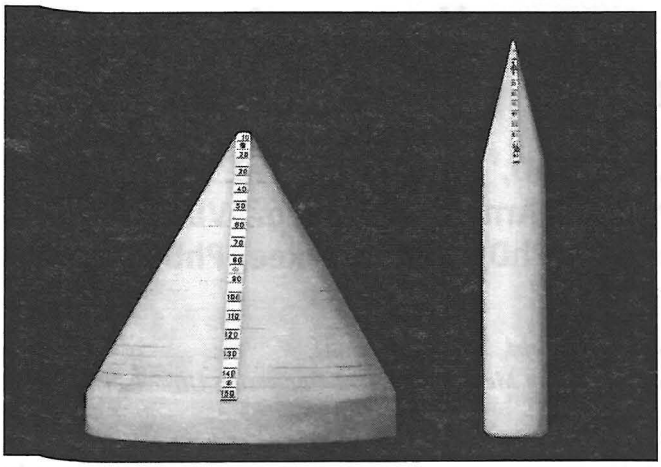

Figure 1 Cones used to measure the mitral orifice diameter. Calibration is in millimeters.

isms."[5] In a publication based on allometric analysis of the relationship between PR interval and body size, a 0.25 scaling exponent with body and thus heart mass was found.[6] Heart mass is 0.6% of body mass.[5,7] In 1927, Clark[8] had already emphasized that the change in AV delay in mammals is relatively small compared with the difference in size of the body and thus of the heart. How little the PR interval changes when hearts get bigger or smaller is amazing.[9]

Conduction velocity in the subnodal specialized conduction system is approximately 2 to 5 m/s,[10] probably roughly the same for all mammals studied. This velocity is so high that, with the possible exception of the whale, the length of the His bundles, bundle branches, and Purkinje system can hardly contribute to mammalian AV delay changes.[11] Thus, the key to varying AV delay resides in the AV node. The delay between the beginnings of atrial and ventricular contraction allows for the atrial contraction to contribute an extra 25% to 35% to ventricular filling.[12,13] Although life during atrial fibrillation can be sustained without extra ventricular filling,[14,15] the contribution is vital for mammalian species to survive, especially under strenuous conditions such as fright and flight.[16–18] Thus, postulating an evolutionary relation between the hemodynamic function of the atrium (late diastolic filling of the ventricles) and AV delay seems logical.

A change in left ventricular (LV) stroke volume must be accompanied by a change in (diastolic) atrial blood flow into the ventricle. From the relatively small differences in PR intervals in widely differently sized mammals[4,8] and the 1:1 relationship between stroke volume and heart size,[5] one can assume that changes in (late) diastolic blood flow occur at the same small diastolic pressure differences between atria and ventricles[19] in all mammals. For instance, in a rat, a small atrial volume passes a narrow mitral opening; in an elephant, a large atrial volume passes a wide mitral orifice. The question to answer is why it takes more time for a larger versus smaller atrial volume to pass a larger versus smaller mitral valve opening, respectively. In this study, we relate scaling of left heart hemodynamic function as assessed from mitral orifice diameter and magnetic resonance imaging (MRI) measurements to scaling of AV delay as previously described.[4,6,20,21]

Methods

Mitral orifice diameters

At the veterinary school of medicine in Utrecht, we performed a postmortem study of mitral orifice diameters in hearts weighing between 17 g and 250 kg from 138 different-sized mammals of 48 different species. Animals that died of cardiac disease were excluded from the study; otherwise, the causes of death varied and, as far as could be ascertained, had no effect on the heart. For logistical reasons, the time between the moment of the animal's death and the actual time of the measurements varied but was never longer than 24 hours. Measurements of body mass, heart mass, and diameter of the mitral valve orifice were made at room temperature. Anatomic studies[22] and our own visual inspections show that, during diastole, the mitral orifice has a circular shape. We used two different-sized lightweight calibrated PVC cones for different-sized hearts (Figure 1). After the LA was removed, a cone was positioned in the mitral orifice by hand until the cone fit snugly, avoiding any appreciable force. Figure 2 shows an LA view of the human mitral orifice, based on three-dimensional echocardiographic reconstruction, confirming the *in vivo* circular shape of the mitral valve ostium.

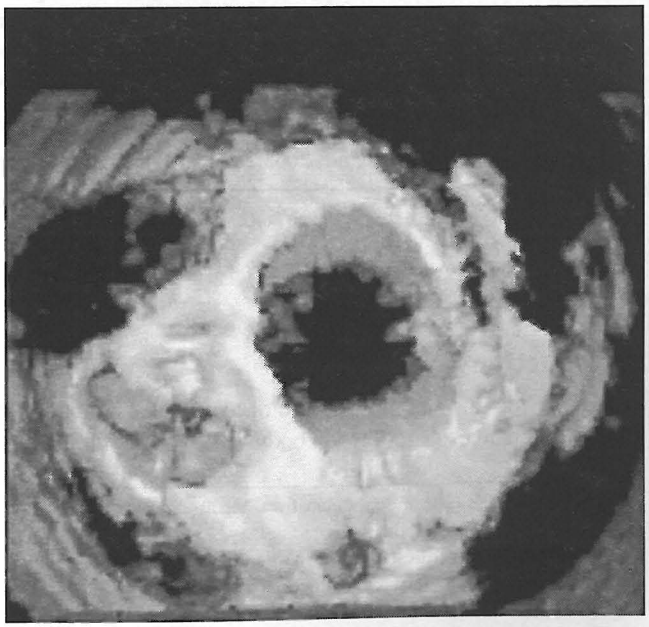

Figure 2 Left atrial view of a human mitral valve orifice, based on three-dimensional echocardiographic reconstruction. (Courtesy of Dr. H.F.J. Mannaerts, Department of Cardiology, Free University Medical Center, Amsterdam, The Netherlands.)

MRI, LV volume, and mitral flow quantification

Ten healthy volunteers (9 men and 1 woman; age 33–67 years, mean 54 ± 10 years) were recruited for MRI examination. All of the volunteers did not have myocardial or cardiac valvular disease. All examinations were approved by the Medical Ethical Committee of the Leiden University Medical Center, The Netherlands. All volunteers gave informed consent. MRI was performed with a 1.5-T scanner (ACS-NT15 Gyroscan with Powertrack 6000 gradient system, Philips Medical Systems, Best, The Netherlands), using the body coil for transmission and a five-element phased-array cardiac coil placed on the chest for signal reception.

LV volumes were determined as follows. Scout images, two- and four-chamber acquisitions, and complete short-axis acquisitions were obtained in conformance with standard cardiac MR protocols[23] using balanced fast field echo.[24] From the short-axis data, end-diastolic LV volume was determined for each patient by drawing epicardial contours manually using the MASS software (Medis, Leiden, The Netherlands) for volume calculation. Flow was measured at the mitral valve[25] using three-directional velocity encoding.[26] MRI delivers accurate data of transmitral blood flow. Retrospective cardiac synchronization was used. Thirty phase images were reconstructed for one cardiac cycle, for flow measurements and for the short-axis data.

Analysis of late ventricular diastolic filling time

We used two possible physical/mathematical models for analysis of time-dependent late LV filling[27] (F.T.M. Nieuwstadt, Personal Communication April 2004). The models are presented in the Appendix.

Results

Mitral orifice diameters

Body mass of the animals ranged from 0.017 to 250 kg. Heart mass ranged from 1.2 to 2,050 g. The diameter of the mitral orifice ranged from 1 to 65 mm. Table 1 summarizes the actual data of body mass, heart weight (mass), and diameter of the mitral orifice that fully satisfied all quality criteria. Figure 3 shows a nearly proportional relationship between the diameter of the mitral orifice (MODiam) and heart length (third root of heart mass). The diameter of the mitral orifice was half the heart length.

MRI, LV volume, and mitral Flow quantification

Imaging

One representative set of MRI movies taken from one of the 10 individuals is available at the following web address:

Table 1 Overview of postmortem mitral orifice diameter data obtained in a collection of mammalian hearts

Type of animal	BM (kg)	HM (g)	MOdiam (mm)
Bat	0.017	1.23	1.5
Pygmy mongoose	0.022	0.22	2.0
Tamarin	0.031	0.34	1.0
Monkey (pygmy oeistiti)	0.059	0.51	1.0
Squirrel (ground s.)	0.080	0.65	1.5
Monkey	0.098	5.98	3.0
Tamarin	0.120	0.63	2.0
Cat	0.130	1.00	4.0
Mouse (gerbil)	0.155	1.05	2.5
Cat	0.162	1.61	3.0
Cat	0.170	1.81	4.0
Cat	0.182	2.10	4.0
Tupaia	0.195	2.76	3.0
Tupaia	0.195	1.95	4.0
Degu	0.215	2.34	3.0
Rat	0.215	2.48	5.0
Rat	0.220	1.27	3.0
Rat	0.220	0.98	3.0
Rat	0.227	0.94	2.0
Otter	0.250	2.80	4.0
Rabbit	0.250	4.27	3.0
Otter	0.260	2.50	4.0
Guinea pig	0.270	1.66	3.0
Meerkat	0.280	3.06	3.0
Rat	0.280	1.29	3.0
Rat	0.292	1.24	3.0
Guinea pig	0.325	4.45	3.0
Rabbit	0.330	2.19	3.0
Rat	0.330	1.55	3.0
Woolly monkey	0.340	4.34	5.0
Mouse	0.253	0.12	1.0
Otter	0.370	3.91	5.0
Guinea pig	0.393	2.25	3.0
Bear (brown b)	0.405	1.80	3.0
Pygmy mongoose	0.420	5.91	6.5
Rabbit	0.420	2.68	3.0
Rabbit	0.430	2.58	4.0
Ferret	0.470	6.00	4.0
Monkey	0.538	4.25	5.0
Ferret	0.585	9.27	5.0
Guinea pig	0.630	6.13	5.0
Monkey	0.657	8.21	6.0
Ferret	0.695	8.41	6.0
Fox (fennec)	0.720	15.57	8.0
Ferret	0.725	4.76	5.0
Monkey (baboon)	0.760	18.90	8.0
Meerkat	0.770	6.97	7.0
Meerkat	0.800	7.40	5.0
Rabbit	0.800	4.65	5.0
Rabbit	0.810	4.23	4.5
Rabbit	0.850	2.46	5.0
Ferret	0.920	10.60	5.0
Fox (fennec)	0.930	18.00	7.0
Rabbit	1.050	2.63	4.0
Mara	1.200	13.71	9.0
Fox	1.250	12.71	5.0
Monkey	1.250	15.06	10.0
Kangaroo	1.260	11.35	6.0
Rabbit	1.270	7.31	7.0
Lemur	1.295	10.66	10.0
Rabbit	1.300	5.50	9.0
Guinea pig	1.321	5.80	10.0

Table 1 (continued)

Type of animal	BM (kg)	HM (g)	MOdiam (mm)
Monkey	1.350	16.95	10.0
Monkey	1.380	7.30	8.0
Rabbit	1.530	8.95	5.0
Rabbit	1.612	9.93	5.0
Rabbit	1.680	5.47	8.0
Rabbit	1.720	12.16	7.0
Rabbit	1.800	8.81	7.0
Rabbit	2.030	8.05	8.0
Rabbit	2.100	28.00	8.0
Rabbit	2.200	6.65	5.0
Lemur	2.215	27.65	9.0
Rabbit	2.250	9.14	6.0
Rabbit	2.260	10.35	5.0
Rabbit	2.270	10.08	8.0
Otter	2.345	32.23	15.0
Rabbit	2.500	17.94	6.0
Sheep	2.570	25.19	11.5
Lemur	2.610	26.00	15.0
Hare	2.790	39.89	10.0
Otter	2.800	26.30	13.0
Rabbit	2.830	12.71	5.0
Wallaby	2.840	28.42	14.0
Rabbit	2.910	7.50	7.0
Sheep	2.990	57.00	11.5
Opossum	3.140	25.35	10.0
Otter	3.140	28.82	10.0
Meerkat	3.330	37.41	8.0
Orangutang	3.500	27.50	10.0
Antelope	3.500	63.00	15.0
Armadillo	3.670	17.98	10.0
Monkey	3.800	46.37	11.0
Wallaby	3.900	15.93	10.0
Sloth	4.500	25.93	12.0
Antelope	4.750	75.00	13.0
Mara	4.880	50.33	11.5
Alpaca	4.900	67.00	19.0
Rabbit	5.220	17.64	8.0
Rabbit	5.260	23.68	8.0
Wallaby	5.900	60.70	18.0
Rabbit	6.200	21.20	13.0
Kangaroo	6.500	92.61	18.0
Otter	6.500	54.78	20.0
Wallaby	7.000	28.00	9.0
Monkey	7.400	62.30	15.0
Seal	7.500	120.00	30.0
Capybara	8.000	96.00	30.0
Antelope (indian a.)	8.100	90.00	20.0
Antelope (indian a.)	8.300	102.00	18.0
Wallaby	9.000	108.03	15.0
Fox (polar f.)	10.800	50.01	15.0
Cerval	11.500	69.00	28.0
Sheep (moufflon)	15.000	158.00	15.0
Springbok	15.400	177.00	20.0
Antelope	16.000	185.00	25.0
Sprinkbok	19.000	161.00	20.0
Kangaroo	21.700	244.00	33.0
Hyena	22.000	347.00	25.0
Antelope (indian a.)	23.000	170.00	30.0
Antelope (indian a.)	25.000	230.00	22.0
Sea lion	31.000	195.00	21.0
Alpaca	34.800	202.00	30.0
Antelope (impala)	35.000	240.00	40.0
Deer	39.000	268.00	30.0
Antelope (impala)	41.000	550.00	40.0
Deer	44.000	450.00	30.0
Zebra	44.500	650.00	45.0
Deer	45.000	480.00	35.0
Reindeer	70.000	625.00	50.0
Orangutang	78.000	330.00	35.0
Dolphin (striped d.)	85.000	393.00	35.0
Tiger	141.000	846.00	50.0
Koodoo	190.000	2050.00	55.0
Bear (brown b)	193.000	1482.00	65.0
Zebra	250.000	1500.00	60.0

Ordering according to body mass. BM = body mass; HM = heart mass; MOdiam = mitral orifice diameter.

http://www.euronet.nl/~denham/MRI-movies. The cine mode shows real-time contractions of the human heart. The two-chamber and short-axis views of the LV show that, after early filling, LV volume is increased further by LA contraction. The mitral orifice does not seem to pose any resistance to transmitral blood flow. Figure 4 shows four still frames taken from the two-chamber MRI movie. Panel A shows early systole of the LV, with beginning of closure of the mitral valve (MV, indicated by arrows). Panel B shows the LV and LA at mid systole, with the mitral valve fully closed. Panel C shows the LV and LA in early diastole during the rapid filling phase (Figure 5E). Panel D shows the LV during atrial contraction (Figure 5A). The mitral leaflets are visible in the upper panels (A, B) and thus during LV systole. The mitral leaflets are not visible during diastole. The increase in size of the aorta and LA at mid systole can be seen. With some effort, the closed aortic valves at early diastole can be seen (panel C). During diastole, LA and LV form a single space.

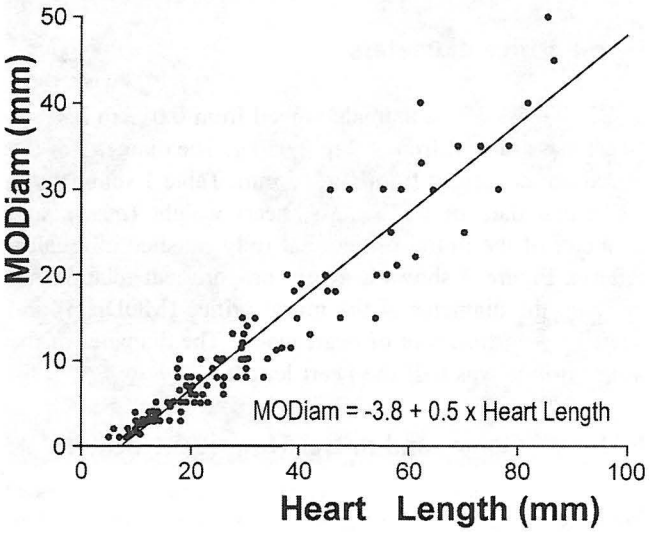

Figure 3 Relationship between mitral orifice diameter (MODiam) and heart length (third root of heart mass).

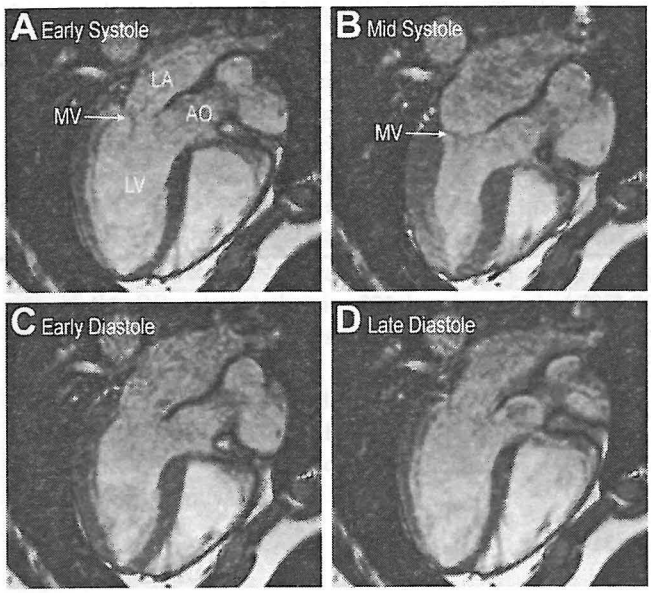

Figure 4 Four still frames from two-chamber MRI movie of a beating human heart. Left atrium (LA), left ventricle (LV), aorta (AO), and mitral valves (MV) are indicated. **A:** Early systole. **B:** Mid-systolic frame. **C:** Early diastole (E in Figure 5). **D:** Late diastole (A in Figure 5). See text for details.

Volume and flow measurements

MRI of the heart allows for LV volume measurements during the entire cardiac cycle. Table 2 presents the actual data per individual. The average stroke volume was approximately 90 ml and cardiac output 5.6 L. The contribution to LV volume flow (average of the 10 observations) was 66% ± 6% for early (rapid) filling and 31% ± 5% for atrial contraction (late filling). Figure 5 shows a typical example of flow velocity over the mitral orifice.

Diastolic filling of the (left) ventricle is caused by E (relaxation of LV myocardium, resulting in the so-called (early) diastolic rapid LV filling) and A (contraction of atrial myocardium causing late diastolic LV filling).[28,29] The sum of the areas under the curves (E+A) is the actual volume entering the LV during diastole.

An unexpected finding was that, in each individual, at a normalized cardiac cycle duration, atrial contraction always starts at about 80% of cardiac cycle length. Figure 5 gives the E and A waves in an individual who had a cycle length of 1,000 ms. The A wave starts at just over 800 ms. When we normalize the cardiac cycles of all 10 individuals to 1,000 ms or 100%, we find in each instance that the A wave starts approximately 800 ms after the beginning or at 80% of the cardiac cycle (Figure 6). By contrast, beginning and end of the rapid filling (E) phase was unpredictable in the cardiac cycle. Thus, in each individual, the starting time of the atrial contraction in the cardiac cycle is fixed, irrespective of the beginning or end of the rapid filling (E) phase. In other words, in healthy hearts the starting time of atrial contraction and thus duration of late diastolic LV filling are closely related to the duration of the cardiac cycle.

Analysis of late ventricular diastolic filling time (see Appendix)

When, during ventricular diastole, we approximate the combined atrial and ventricular cavities by a cylinder with a cross-sectional area equal to mitral orifice area, we find the diameter of the mitral orifice to be proportional to heart length (Figure 3). It follows that mitral orifice area is proportional to heart length squared. Flow equals volume per unit of time, that is, proportional to the cube of heart length, but it also equals velocity times mitral orifice area. If, as made plausible by Schmidt Nielsen,[5] blood flow velocities during ventricular diastole across mammalian species are similar, it then follows that filling time is proportional to heart length. Mathematical derivations[27] (F.T.M. Nieuwstadt, Personal Communication April 2004) indicate that late diastolic filling time by atrial contraction should scale with heart length, thus with the 1/3 power of heart (body) mass.

Discussion

Mitral orifice diameter

The results support a linear relationship between the diameter of the circular mitral orifice (Figure 2) and heart length in the mammalian hearts studied (Figure 3). The finding makes unlikely an influence of the (normal) mitral orifice on duration of PR intervals. Also, the minimal pressure difference between atria and ventricles during diastole indicates the mitral orifice likely does not impose any resistance against atrial blood flow to LV.[19] Assuming this small pressure gradient applies to all mammals and that our diameter measurements of the mitral orifice are representative, the mitral orifice likely does not pose any hindrance to early and/or late diastolic filling of the LV. Thus, the mitral

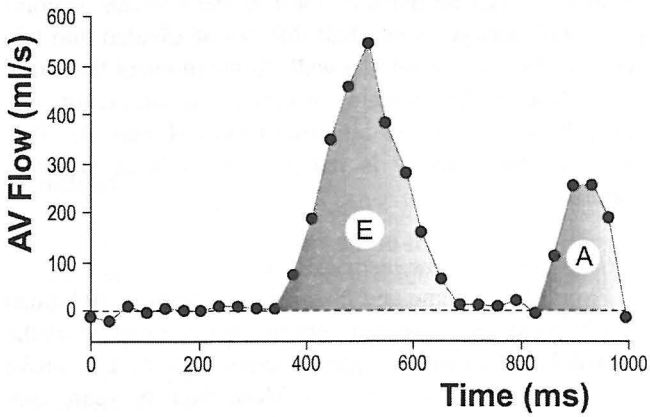

Figure 5 Flow quantification over the mitral valve. *E* is flow during left ventricular rapid filling phase. *A* is flow into the left ventricle during atrial contraction. The sum of the areas under the curves *E+A* equals stroke volume. See text for details.

Table 2 Body mass, absolute and relative contribution of early and late diastolic filling to end-diastolic left ventricular volume, and flow over the mitral valve during one cardiac cycle; stroke volume (ml), and cardiac output (L/min) in healthy human subjects

Patient no.	Body weight (kg)	Volume during early filling (ml/cycle; relative contribution in %)	Volume during late filling (ml/cycle; relative contribution in %)	Volume over MV (ml/cycle)	Volume per minute over MV (l/min)
1	68	60 (65%)	21 (24%)	87	5.7
2	83	68 (68%)	32 (32%)	100	8.1
3	95	62 (75%)	25 (30%)	83	6.3
4	86	67 (61%)	33 (30%)	109	5.9
5	97	87 (75%)	28 (24%)	116	6.7
6	77	65 (64%)	29 (29%)	100	5.2
7	64	42 (62%)	23 (34%)	68	4.5
8	74	36 (57%)	25 (40%)	59	3.9
9	92	56 (61%)	29 (31%)	92	4.0
10	95	55 (69%)	30 (38%)	79	5.9
Average	83	60 (66%)	28 (31%)	89	5.6
Standard deviation	12	14 (6%)	4 (5%)	18	1.3

Volumes over the mitral value (MV) can differ from E + A (Figure 5) because of overlap of E and A or minimal flow between E and A.

orifice likely is not involved in evolutionary regulation of (late) LV filling time or the PR interval.

MRI observations

Imaging

The lack of influence of the mitral orifice is confirmed by our MRI observations of human heart performance. The technique allows visualization of the beating of the (human) heart clearly and in "pseudo-real time." If the appropriate projection is chosen, systolic and diastolic LV volume changes can be observed. It is impressive to observe the rapid early filling of the LV by its myocardial relaxation. The PR interval controls the optimal timing of the atrial kick, which contributes significantly to filling of the ventricles and causes a short active stretch of the LV wall, beautifully showing *in vivo* operation of "Starling's Law of the Heart."[30,31] During diastole, the LA and LV can be compared with a large lecture hall that can be divided into two separate rooms by a folding wall. At the moment the mitral valve closes at the beginning of ventricular contraction, one space becomes divided into two rooms (Figure 4). This event almost certainly is independent of heart size and mammalian species.

MRI volume and flow measurements

From MRI volume and flow measurements in 10 human healthy volunteers, we can confirm that contraction of the normal LA contributes approximately 30% to LV stroke volume. (Figure 5A, Table 2). More than 80 years ago, Wiggers and Katz[12] were amazingly precise with their 35% estimate in dogs. Other investigators using different methods obtained slightly different but not conflicting data.[13] The LA needs time and force to eject its blood into the already partly filled LV. Because atrial and ventricular pressures do not scale, LA and LV diastolic pressures likely are the same in all mammals, regardless of the dimensions or mass of the heart. On the other hand, stroke volume does scale proportionally with body (heart) mass, which implies the actual atrial contribution to end-diastolic LV volume also scales. Different volumes at the same pressure need a different LA contraction force.[29,32] The difference between atrial and ventricular wall thickness of small and large hearts does not explain the scaling of PR interval in mammals. It can account only for scaling of the duration of the P wave. In the same article, Wiggers and Katz[12] already were aware of the different time course of right atrial and LA contraction, caused by the fact that the sinoauricular node is located in the right atrium.

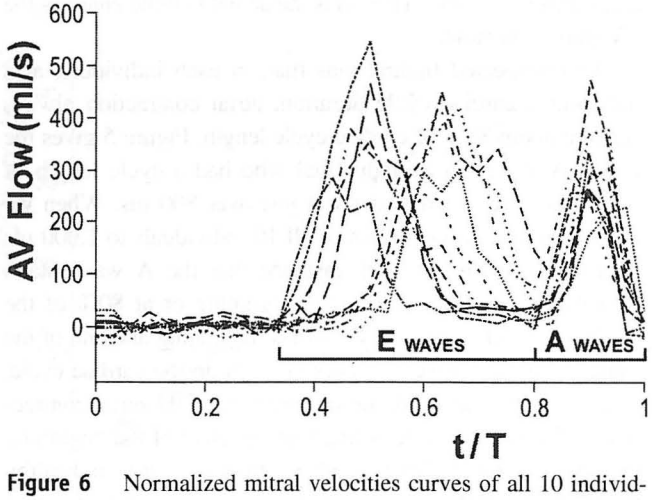

Figure 6 Normalized mitral velocities curves of all 10 individuals. E waves are scattered over the first part of the diastole of the cardiac cycle. In contrast, A waves all start at 80% of the cardiac cycle.

A phenomenon unnoticed until now was the finding that atrial contraction seems to start at a fixed instant (at ~80%) after the beginning of the normalized cardiac cycle (Figures 5 and 6). This finding implies that in any individual, the beginning of atrial contraction in the cardiac cycle can be predicted from the RR interval. Despite the limited number of observations (10) in only one species (human), this striking observation has important implications in light of the fact that, in all vertebrates, the PR interval relates proportionally to the duration of the RR interval that is, the duration of the cardiac cycle.[33,34] This finding deserves further study because changes of AV delay affect LV filling and cardiac functional capacity.[35,36] The findings presented here suggest that, in patients requiring sequential dual-chamber pacing, particularly patients with heart failure, AV delay should be adjusted to the duration of the chosen cardiac cycle.

Physical models

Both physical models yield a theoretical scaling factor of 1/3 power (third root) of heart mass for the duration of blood transport by atrial contraction into the ventricle. A study[6] using allometric equations and an earlier publication[37] supports a 1/4 power scaling factor for PR interval (AV delay) versus heart mass. This discrepancy may reflect the difference between standard Euclidian and fractal biologic approaches.[38,39] In both studies, the difference between 1/3 power and the 1/4 power may be negligible, particularly in the context of biologic variability (see Appendix for details).

Evolution

When considering evolution as the driving force of shape, size, and function of all mammals,[40] three fundamental principles must be considered. (1) Form prevails over function.[41] (2) Similar organs and structures are found in mammalian species of widely different sizes.[42] (3) All mammals have cells that are approximately the same size.[43–45] In the eon during which evolution shaped a similar blueprint for all mammalian hearts,[46] the energy demands[2,3] of varying body masses had to be obeyed. The ultimate result was the adaptation and thus the scaling of late LV filling time by the LA and, as a necessary consequence of AV conduction times, of the mammalian heart. Therefore, we can conclude that, during the evolution of mammalian species, scaling of AV conduction time is necessitated by the heart size–dependent filling time of the LV by the LA. The question of how these physical properties of LV hemodynamics became linked to, and in command of, the electrical properties of the AV conduction system remains unresolved. In a previous study,[4] we concluded that *"evolution may be represented by changes in form and structure of the mammalian heart, but survival of the species depends on proper adaptation of the function of the heart in health and disease."* Almost 20 years later, the problem of the relationship between hemodynamic and electrical AV scaling remains a challenge for the 21st century.[47] A solution to this problem may shed light on the true nature of AV nodal function in conducting the atrial impulse.

Study limitations

An increase or decrease in LV size is, for physical reasons, accompanied by a longer (or shorter) late LV filling time. Our measurements were limited to the left side, but these principles reasonably are assumed to apply to the right side of the heart as well. Right and left heart output ought to remain identical in the short term. Another limitation comes from the mammalian heart's lack of a well-defined geometric shape. Depending on its habitat, each mammalian species has a differently shaped heart, which may have an effect on actual hemodynamic data in different species. Nevertheless, the scaling principle for late diastolic LV filling can simply apply. At a given similar velocity of late diastolic blood flow, LV filling time depends on the distance the bulk of LA blood must cover to enter the LV. The distance is directly related to the third root of heart mass. A further limitation comes from the fact that diameters of the mitral orifice were obtained at room temperature and at varying postmortem times, although never longer than 24 hours. In addition, we were not able to obtain data from very small or very big hearts, such as those from cattle, horses, and other larger species. Another untested assumption in the present study is that the viscoelastic properties of myocardial tissue during diastole are equal in all mammalian species.[48,49] This assumption is compatible with the similarity in cell shape, size, and arrangements across mammalian species but remains to be proved. Finally, MRI data were obtained from human hearts only, and we consider the human heart representative of mammalian hearts. These limitations and the difficulties in obtaining objective data in this field clearly call for further studies if we are to better understand the scaling of AV conduction in the mammalian heart. The present study must be considered a first step toward connecting hemodynamic and electrical scaling in mammalian hearts.

Conclusion

The mitral orifice does not appear to impose any hindrance to diastolic LV filling. During evolution, mammals have changed in shape and size and so have their hearts. Scaling of AV conduction time in mammals has been necessitated by the varying atrial filling time of the LV. The physical properties of late (left) ventricular filling in mammalian species had to be translated into varying AV conduction times. We assume the same holds true for the right side of the heart. As can be appreciated from observed mammalian species, LV filling time by LA contraction scales with 1/3

power of heart mass and AV conduction time with 1/4 power of heart mass.[6] The apparent mismatch of PR interval variations with body size may be explained by the fact that distance (one-dimensional) has been compared to mass (three-dimensional), so in reality no mismatch exists. Finally, at least in humans, atrial contraction starts at a fixed moment in the normalized cardiac cycle length, a finding that may help in the treatment of patients with heart failure.

In 1953, King, Jenks, and White[50] in their paper "The electrocardiogram of a Beluga whale" wrote: *"The relationship of heart size to the time intervals of the electrocardiogram, in particular of the P-R interval and the QRS duration, plays an important role in the interpretation of normal and abnormal tracings."* To this quotation we add that in all individual vertebrates, *"electricity rules the heart"*. In evolution, hemodynamics seems to rule the electricity of the heart.

Appendix

(1) A first approach to estimate the filling time of the (left) ventricle by the (left) atrium is as follows. Assume the work required for this process is produced completely by the atrial myocardium. The force F that a muscle can produce is proportional to its cross-section, so $F \sim L^2$, where we assume that all muscle cross-sections (including the heart muscle) scale with the "size" (nominal length = third root of body mass) L of the animal. Thus, the stress F/L^2 is independent of the "size" of the animal. By analogy, the same holds for the pressures in atria and ventricles. The work performed by the atrial myocardium is primarily used to transport the blood from the atrium to the ventricle. Thus, the following relation is approximately valid (Bernoulli): $\Delta p \sim \rho v^2/2$, where Δp is the pressure difference over the mitralis ostium, and ρ is the density of the blood (equal for all animals). This reasoning leads to the result that the velocity of blood in the heart v is independent of the "size" of the mammal. If we now assume for the filling time $T \sim V/(v \cdot Area)$, where V is the volume of the heart and $Area$ is the area of the ostium, and we also assume that both V and $Area$ relate linearly again with the "size" of the animal, we find that $T \sim L$ or the filling time scales with the "size" of the animal and thus with the third root of its body mass.

(2) For a second approach to estimate the filling time T of the left ventricle, we introduce an inertia *(L)*–compliance *(C)* model. For this model, one has $T \sim \sqrt{(L \cdot C)}$. Modeling the LV as a cylinder with height h and radius r, we deduce from Newton's law $(F = m \cdot a)$ that $P \cdot \pi \cdot r^2 = \rho \cdot \pi \cdot r^2 \cdot h$. For a simple (flat) profile, the flow Q reads as $Q = v \cdot \pi \cdot r^2$, and thus $a = dv/dt = d/dt(Q/[\rho \cdot r^2])$. Combining the different expressions, we get $P = \rho \cdot h/(\pi \cdot r^2) \cdot dQ/dt$. For the inertia I, we have $I = \rho \cdot h/(\pi \cdot r^2)$. Blood fills the elastic container LV, and its pressure–volume relationship is described by its compliance C.[49] For containers with a wall $<<r$, we have $C = 3 \cdot \pi \cdot r^2 \cdot h/(2 \cdot E)$, where E is Young's modulus. From $T \sim \sqrt{(L \cdot C)}$, we see by this approach that T is linearly related to the "size" (nominal length) of the cylinder (third root of body/heart mass).

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