Is heart size a factor in ventricular fibrillation? Or how close are rabbit and human hearts?

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Ventricular tachycardia (VT) and ventricular fibrillation (VF) account for several hundred thousand deaths annually in the United States. Although VF has been studied for well over a century, its mechanism remains largely unknown. The most important source of information on VF are clinical studies, which are subject to serious limitations. Therefore, various experimental approaches have been used to investigate VF. Historically, dog and pig open-chest preparations were considered the best experimental models for human VF because of the size similarity of dog and pig hearts compared with human heart. Several new animal models have been introduced, including the Langendorff-perfused rabbit heart and hearts of smaller animals, such as rat, guinea pig, and mouse. Although these hearts differ in size by more than an order of magnitude, VF can be induced in all of them. However, the question of how similar VF is in hearts of different size requires consideration. In this viewpoint, I present an argument that it is not the heart size *per se* but its *effective size,* which takes into account the wavelength of reentry, that determines the VF pattern.

Effective size of reentry

It is generally accepted that VT is driven by one source and VF by several reentrant sources. What determines the geometry of such a reentrant wave pattern? An important characteristic of wave circulation in the heart is its wavelength Λ, which is the product of its velocity v and its refractory period R: $\Lambda = vR$.[1] Functional reentry in cardiac tissue often is referred to as a spiral wave because in tissue of large size it has a characteristic spiral shape. The geometry of a spiral also is determined by the wavelength, which is defined in a slightly different manner. In particular, for isotropic tissue far from the core of the spiral wave, the shape (in polar coordinates r, ϕ) can be approximated as $r \sim \lambda\phi 2\pi$. Here wavelength $\lambda = v(T)T$, where T = period of spiral wave rotation, and $v(T)$ = velocity of wave propagation at this period. We see that the only parameter determining the shape of the spiral wave is λ. Therefore, the overall spatial pattern, that is, the number of turns of a spiral in a given tissue, will be determined by the ratio of the size of the tissue D to the wavelength λ, which we call the *effective size (L)* of the tissue: $L = D/\lambda$. Figure 1a shows two spiral waves in different models that have different wavelengths. The models nevertheless produce similar wave patterns, as the media have the same effective size $L = 2.5$.

Therefore, I suggest that in order to compare VT and VF from hearts of different species, one should compare effective size rather than physical size. But what is the effective size of the heart?

Effective size of the heart

The concept of effective size also can be applied to the complete ventricles of the hearts of different species. For that we need to define the size of the ventricles and the wavelength of spiral waves for different species. The size of the heart cannot be specified by a single number because of the heart's complex shape, but the relative size of different hearts can be readily compared. If we assume that the heart shapes and anisotropy ratios of two hearts are similar, then the relative sizes can be evaluated by comparing the cubic roots of their volumes and hence masses.[2] The mass of the heart can be measured directly or approximated as *0.6%* of the body weight. To find the wavelength of a spiral wave, we need to know both the period of the spiral wave (the period of the arrhythmia) and the velocity of the wave at this period. The period of arrhythmias can be found easily from ECG recordings. However, no reliable data on the velocity of wave propagation at the frequency of the arrhythmias for all species compared here are available. As a consequence, an exact computation of the wavelength is not possible. However, we can compare wavelengths of arrhythmias in two hearts by comparing their periods, assuming, as a first approximation, that conduction velocities are the same. Under this assumption, the relative effective size of the heart I of a particular species is given by the following equation:

$$I = \frac{\sqrt[3]{Heart\ weight}}{T} \qquad (1)$$

This equation is a rough approximation that neglects many details, but it allows us to perform an effective first-order comparison of VF in hearts of different animals and in the human heart. The limitations of this approach are discussed later.

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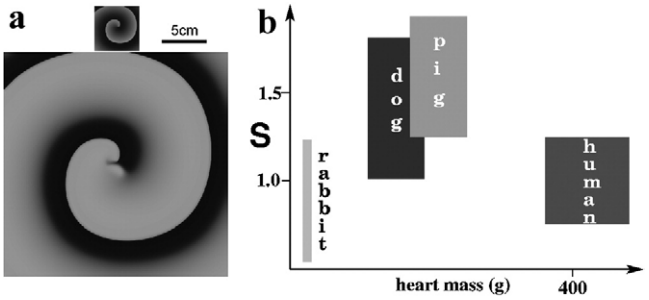

Figure 1 **a:** Spiral wave using the TNNP human ventricular cell model **(bottom panel)** and the Luo-Rudy phase 1 model for *gs* (conductance of the slow inward current) = 0 **(top panel).** The medium size is 25 × 25 cm and 5 × 5 cm. The effective size of both patterns is $L = 2.5$. **b:** The relative effective size of the heart S vs heart mass. Here $S = I/I_{human}$, where I is evaluated from Equation 1, and I_{human} is I for the human heart.

Effective size during VF

Using Equation 1, we estimate an effective size for rabbit, dog, pig, and human hearts. The weights of these hearts are well known, and experimental and clinical data on VF frequency in these hearts are available. The typical data ranges are as follows.

For the rabbit heart, we assign the frequency range 11.5 ± 3.5 Hz, based on studies in which the average VF frequency was approximately 15 Hz.[3] Recordings of VF induced during use of the excitation-contraction uncoupler DAM usually have a frequency of approximately 8 Hz.[4] The weight of rabbits used in these experiments was 3 to 5 kg, from which we derive a heart mass of approximately 18 to 30 g, and from Equation 1 the index $I = 33.2 \pm 12.9$.

For the dog heart, we assign the frequency range 10. ± 2 Hz, based on studies that reported frequencies of approximately 10.1 ± 2.1 Hz.[5] Huang et al[6] reported frequencies of approximately 8 Hz for stage I and II VF. In a study by Newton et al,[7] the mean frequency was 10.1 ± 0.87 Hz. We estimate a heart mass of 150 ± 40 g and derive the index $I = 53.1 \pm 15.3$.

For the pig heart, we assume the frequency range 10. ± 1.5 Hz, based on studies in which the average VF frequency in the left ventricle was 10 ± 1.3 Hz.[8] In a study by Newton et al,[7] the mean frequency was 9.3 ± 0.63 Hz. We estimate the weight of the pig heart is 210 ± 40 g and derive the index $I = 59.4 \pm 12.7$.

For the human heart, we assign the frequency range of 5. ± 1 Hz, based on studies in which a dominant frequency of 4.9 ± 0.17 Hz was reported[9] and a frequency of 5.8 ± 1.8 Hz was found.[10] Assuming an average adult human body weight of 60 to 80 kg, human heart mass should be 420 ± 60 g, and we obtain the index $I = 37.4 \pm 9.3$.

Figure 1b shows relative effective size for rabbit, dog, pig, and human hearts as a function of heart mass. From the figure we can see that despite large differences in heart weight, the effective sizes of these hearts are not so different. Interestingly, although the human heart has the largest weight, its effective size is relatively small and is closest to the effective size of the rabbit heart. The pig heart has the largest effective size, which is *1.6* times that of the human heart, and the effective size of the dog heart is *1.4* times that of the human heart.

Is it possible to estimate the number of sources during VF based on our estimates of the effective heart size? The number of sources during VF will depend on the mechanism of VF. However, in general it is reasonable to assume that the number of sources is proportional to the tissue size (half of the heart should contain half of all sources). This should be valid, for example, under the restitution hypothesis of VF,[11] where new sources are generated by the cardiac tissue itself. The proportionality of the number of sources to the tissue size means that in two-dimensional tissue, the number of sources will be proportional to the area of the tissue, and in large three-dimensional slabs it will be proportional to the tissue volume. However, the heart has a complex shape, with cavities enclosed by walls of different thickness at different regions. Therefore, one could expect that the number of sources will scale between the second and third power of the size of the heart. Indeed, in our early numerical study,[12] which involved dog heart anatomy and a simplified description of cardiac tissue excitability (using a two-variable model), we found that the number of sources scales with a 2.2. power of the heart size. If we estimate the number of sources assuming either a power 2 for the minimal value or a power 3 for maximal value, we find that the number of sources during VF in the rabbit heart should be 0.7 to 0.8 of the number of sources in the human heart. The number of sources in the dog heart should be 2 to 2.9 times and in the pig heart 2.5 to 4 times that in the human heart.

Based on these estimates, we suggest that wave patterns during VF in the human heart are similar to those in the rabbit heart, whereas VF in pig and dog hearts have a more complex organization.

Limitations and role of conduction velocity

We did not take into account the velocity of wave propagation in the evaluation of wavelength because finding velocity during VF is a complex problem, and no reliable data for the hearts of all species considered here are available. However, other studies have used the same method to measure conduction velocity during VF in both dog and human hearts.[6,10] The velocity for the dog heart was approximately 0.45 cm/s,[6] whereas the velocity in the human heart was almost 1.5 times faster at 0.67 cm/s.[10] If we take these data into consideration, then the difference in effective size between dog and human hearts becomes even larger, resulting in a relative effective dog heart size of 2.11. In general, it is reasonable to assume that species with smaller hearts also have smaller conduction velocities. This will move the effective size of the rabbit heart even closer to that of the human heart.

Our estimate for the number of sources during VF is based on the hypothesis that the number of sources is proportional to tissue size, which is not necessarily valid for all hypotheses of VF mechanisms. For example, the “mother rotor” hypothesis

assumes that a single fast source drives VF.[13] However, even in this case the spatial organization of VF (number of waves propagating through the heart) will depend on the ratio of heart size to wavelength. Therefore, we still can expect that the complexity of excitation patterns will be determined by the effective heart size.[3]

Finally, it should be noted that the approach presented here provides only a rough estimate that can serve as a guide for quantitative comparisons of VF patterns in the hearts of different species. Such studies should take into account various factors that are important for VF organization, such as differences in anatomy and fibrous structure.

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