Reentry and Fibrillation in the Mouse Heart
A Challenge to the Critical Mass Hypothesis

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Abstract—The idea that fibrillation is only possible in hearts exceeding a critical size was introduced by W. Garrey >80 years ago and has since been generally accepted. In ventricular tissue, this critical size was originally estimated to be 400 mm$^2$. Recent estimates suggest that the critical size required for sustained reentry is $\approx 100 \text{ to } 200 \text{ mm}^2$, whereas 6 times this area is required for ventricular fibrillation. According to these estimates, fibrillation is not possible in the mouse heart, where the ventricular surface area is $\approx 100 \text{ mm}^2$. To test whether sustained ventricular fibrillation could be induced in such an area, we used a high-speed video imaging system and a voltage-sensitive dye to quantify electrical activity on the epicardial surface of the Langendorff-perfused adult mouse heart. In 6 hearts, measurements during ventricular pacing at a basic cycle length (BCL) of 120 ms yielded maximum and minimum conduction velocities (CV$_{\text{max}}$ and CV$_{\text{min}}$) of 0.63±0.04 and 0.38±0.02 mm/ms, respectively. At a BCL of 80 ms, CV$_{\text{max}}$ and CV$_{\text{min}}$ changed to 0.55±0.03 and 0.34±0.02 mm/ms. Action potential durations (APDs), measured at 70% repolarization at those pacing frequencies were found to be 44.5±2.9 and 40.4±2.6 ms, respectively. The wavelengths (CV×APD) were calculated to be 28.6±3.4 mm in the CV$_{\text{max}}$ direction and 16.8±1.5 mm in the CV$_{\text{min}}$ direction at BCL 120 ms. Wavelengths were significantly reduced ($P<0.05$) at BCL 80 ms (CV$_{\text{max}}$, 22.2±1.8 mm; CV$_{\text{min}}$, 13.7±0.9 mm). In 5 hearts, stationary vortex-like reentry organized by single rotors (4 of 5 hearts) or by pairs of rotors (1 of 5 hearts) was induced by burst pacing. In the ECG, the activity manifested as sustained monomorphic tachycardia. Detailed analysis showed that the local CVs were reduced in the vicinity of the rotor center, which allowed the reentry to take place within a smaller area than was calculated from wavelength measurements during pacing. In 4 of 7 hearts, burst pacing resulted in a polymorphic ECG pattern indistinguishable from ventricular fibrillation. These data challenge the critical mass hypothesis by demonstrating that ventricular tissue with an area as small as 100 mm$^2$ is capable of undergoing sustained fibrillatory activity. (Circ Res. 1999;85:174-181.)

Key Words: rotor ■ vortex-like reentry ■ curvature ■ wavelength ■ conduction velocity

The concept that reentry and fibrillation are only possible in hearts exceeding a “critical mass” was introduced >80 years ago and is presently widely accepted. Garrey originally observed a direct relationship between the size of a piece of cardiac tissue and its ability to sustain fibrillatory activity. He noted that if he cut the tissue into progressively smaller pieces he could achieve a size at which fibrillation would stop. On the basis of his results, he concluded that the minimum size of cardiac tissue required for fibrillation was $\approx 400 \text{ mm}^2$.

More recent studies support Garrey’s findings. For example, Winfree calculated the critical size required for sustained reentry to be $\approx 100 \text{ to } 200 \text{ mm}^2$. Such an estimate was based on the assumption that the mechanism of ventricular fibrillation (VF) involves rotors (vortex-like reentry). Winfree also predicted that VF requires substantially more tissue. His estimates suggested that the minimum size required for sustained fibrillation was $\approx 6$ times the diameter of a rotor. This approximation was based on the ability of the center of rotation of a vortex wave to drift at high speed throughout the ventricles. On the basis of such estimates, VF requires a volume of $\approx 6 \times 6 \times 1 \text{ cm}$, which corresponds to $\approx 12 \text{ g}$ of cardiac tissue. Accordingly, sustained fibrillation should not be possible in the mouse heart of which the ventricular area is $\approx 100 \text{ mm}^2$ and the total mass is $\approx 200 \text{ mg}$.

Theoretical and experimental studies have suggested that meandering or drifting rotors should result in complex electrocardiographic (ECG) patterns. Recently, video imaging experiments by Gray et al have shown that polymorphic ventricular tachycardia may result from a single rotor that drifts throughout the ventricles, as recorded from the epicardial surface of the rabbit heart. When the drift speed was $>30\%$ of the wavefront speed, the ECG was indistinguishable from VF. These data suggest that the critical size required for fibrillation may not be significantly larger than that required for reentry. Other data have also suggested that reentry may be possible in much smaller pieces of cardiac...
tissue than those predicted by the critical mass hypothesis.

Our aim here was to carefully examine the predictions of the critical mass hypothesis and the basis for those predictions. In this regard, our first objective was to determine whether arrhythmias are possible in the ventricles of the adult mouse heart of which the ventricular surface area is less than 100 mm². According to the critical mass hypothesis, the wavelength is relevant for predicting the ability to initiate and maintain reentry in cardiac tissue. Using high-speed video imaging and voltage-sensitive dyes, we have characterized the electrophysiology of the normal adult mouse heart. This included measurements of epicardial longitudinal and transverse conduction velocities (CVs), mean action potential duration (APD), APD frequency dependence, and wavelength of the tissue. Our second objective was to use these measurements to determine whether there is indeed a predictive relationship between the wavelength during regular epicardial pacing and the ability to sustain arrhythmias. Our data demonstrate for the first time that the normal Langendorff-perfused mouse heart is capable of sustaining rotors and VF.

Materials and Methods

Langendorff-Perfused Mouse Heart

All animal care protocols conformed to institutional and NIH guidelines. Adult C57 mice were heparinized (0.5 U/g IP) and then anesthetized with a mixture of ketamine (100 μg/g) and acepromazine (0.5 μg/g). The hearts were quickly removed through a thoracotomy and rinsed in a Tyrode’s solution containing (in mmol/L) NaCl 130, NaHCO₃ 24, NaH₂PO₄ 1.2, MgCl₂ 1.0, glucose 5.6, KCl 4.0, and CaCl₂ 1.8, equilibrated with a 95% O₂, 5% CO₂ gas mixture. Hearts were then rapidly cannulated and perfused in a retrograde fashion via an aortic cannula with warm (37°C to 39°C) oxygenated Tyrode’s solution (2 to 3 mL/min). Once connected to the Langendorff perfusion system, hearts were placed in a custom-built perfusion chamber. Warm oxygenated Tyrode’s solution was also superfused; this ensured that no temperature gradients were present between the endocardium and the epicardium. The solution in the chamber was used as a volume conductor for the tissue bath and flanking the heart.10 –12 Signals were amplified and filtered with a differential amplifier (World Precision Instruments, Inc, Sarasota, FL).

To increase the temporal resolution of the video recordings, we implemented a synchronous acquisition system, whereby the first frame acquired by the camera was synchronized with each stimulus delivered to the tissue; ie, each stimulus occurred precisely when the camera started acquiring a frame. Later, offline, 6 to 10 of these activations were ensemble averaged to reveal a sequence of frames that the camera recorded at 0 ms, 4 ms, etc, from the instant of stimulus delivery. Immediately after the above acquisition, the camera was again synchronized with a delay of 1 ms from the time of stimulus. An ensemble average of these activations revealed a sequence of frames that the camera recorded at 1 ms, 5 ms, etc, from the instant of stimulus delivery. Thus, each frame of this sequence is offset from the corresponding frame of the previous sequence by 1 ms. Similarly, sequences were obtained with the camera delayed 2 and 3 ms from the time of the stimulus. All 4 sequences were obtained within a single episode of steady-state pacing, and the total acquisition procedure lasted 4 seconds. The frames from all 4 sequences were then interleaved (0, 1, 2, 3, 4, 5 ms, etc), to reveal an activation sequence with a 1-ms resolution. Acquisition with this system was limited to signals that were regular. The electronics were tested using the camera to record defined sweeps of an oscilloscope beam. In another study, we have carefully evaluated the CVs (see below) measured with this technique and have determined that this approach yields measurements that are statistically indistinguishable from those obtained with a faster camera (DALSA, CA-D1 1484 frames per second) running in a nontriggered acquisition mode.16 CV measurements were obtained by averaging local conduction vectors as described by Morley et al. Briefly, an activation time (defined as the time a given pixel reached 50% of the maximal fluorescent amplitude) was determined for each pixel. Local conduction vectors were calculated for each pixel on the basis of the activation times of the surrounding pixels. The conduction vectors were used to establish both the direction and speed of conduction for every point on the heart and to determine maximum and minimum CVs (CV max and CV min).

Stimulation Protocol

Bipolar pacing electrodes were placed on the epicardium near the center of the anterior left ventricle. Preparations were paced at basic cycle lengths (BCLs) of 80 and 120 ms. The left ventricle was paced using pulses equivalent to 1.5× threshold amplitude at each BCL with a duration of 2 ms. The BCLs were set at random, and 1.5 minutes was allowed at each BCL before changing to a new BCL. Arrhythmias were induced using a burst-pacing stimulation protocol. Short bursts (~20 stimuli) were applied at critical pacing frequencies, which were determined by scanning a range of cycle lengths shorter than the 1:1 capture cycle length. It was our experience that induction of arrhythmias in the mouse heart was variable and dependent on many factors, including the electrode position, stimulus strength, and pacing frequency. In all cases, this pacing protocol was repeated many times while the above variables were changed before an arrhythmia was successfully induced. Typically, the source of any sustained arrhythmia was located outside the field of view of the camera. Thus, the camera was repositioned to record the source of the arrhythmia.

Pseudo-ECGs

The fluorescent signals from pixels in the left and right halves of each frame were summed, and the difference between the 2 halves was calculated. The pseudo-ECG, ie, the time series of these differences, was used to summarize the optical data from a recording.

Electrocardiograms

ECG leads I, II, and III were recorded sequentially from lightly anesthetized animals (avertin, 0.015 to 0.017 mL/g body weight, IP). Horizontal ECG recordings were obtained continuously from the Langendorff-perfused heart using electrode leads immersed in the tissue bath and flanking the heart. Signals were amplified and filtered with a differential amplifier (World Precision Instruments, Inc).
Fig 1. ECG recordings from the normal mouse. A, Three-lead ECG obtained from an anesthetized mouse during sinus rhythm. B, Horizontal volume–conducted ECG recorded from the Langendorff-perfused heart of the same mouse after isolation.

Inc) and displayed on an oscilloscope. Signals were digitized at 2471 Hz and stored for offline analysis.

Signal Processing
Standard signal processing techniques were used to study the spectral content of VF. Spectral analysis was performed using the fast Fourier transform (FFT).

Determination of Stability of Reentrant Activity During Monomorphic Tachycardias
Optical records that were obtained during arrhythmias associated with monomorphic volume–conducted ECGs were signal averaged to confirm the stability of reentrant processes. Fluorescent signals were averaged at the peak frequency obtained from the FFT of the volume-conducted electrogram. Enhancement of the signal-to-noise ratio in these movies indicated the stability of the activation pattern during the total acquisition period.

Statistical Analysis
When appropriate, statistical analysis was carried out with the Excel software package. Values are reported as mean±SEM for a given measurement. ANOVA (with post hoc Student’s t test) was performed on the wavelength data, and regression and correlation analysis were used to determine the relation between CV and radial distance. Differences were considered significant when P<0.05.

Results
ECG of the Normal Mouse Heart
A 3-lead ECG from an anesthetized mouse in sinus rhythm is presented in Fig 1A. The spontaneous cycle length was ~113 ms, corresponding to a heart rate of 531 bpm. In Fig 1B, the horizontal ECG of the Langendorff-perfused heart (same animal as in Fig 1A) shows a similar but somewhat slower rhythm (~390 bpm) than that obtained from the surface ECG. Surface ECG data obtained from 10 lightly anesthetized male mice are summarized in the Table. Surface ECG intervals and heart rates measured here are similar to those previously reported for the normal anesthetized mouse.

Sequence of Activation During Epicardial Pacing
Color isochrone maps obtained during point bipolar stimulation near the base of the anterior left ventricle at BCLs of 120 and 80 ms are shown in Fig 1B. In each case, the pattern of optical action potentials recorded from any position of the stained preparation (not shown) was nearly identical, confirming a high signal-to-noise ratio. Figure 2A shows data at a BCL of 120 ms. The color map reveals an anisotropic excitation wavefront moving away from the stimulating electrode (black shadow) toward the apex and base, to excite the entire anterior epicardial wall in <13 ms. In Fig 2B, stimulation at a BCL of 80 ms yielded a similar but somewhat slower activation sequence. The respective vector maps are shown in Fig 1C and 1D. The vertical arrow in the lower left corner of Fig 1D marks a magnitude of 1.0 mm/ms. For clarity, only a few of the calculated vectors are drawn. Note the vectors emanating from the site of stimulation in an anisotropic fashion, permitting identification and quantitative analysis of CV max and CV min.

CV, APD, and Wavelength
Measurements of CV max, CV min, and mean APD at 70% repolarization (APD 70 ) were made to estimate the wavelength in the longitudinal and transverse direction of the fibers. As in other species, CV in the normal mouse heart was dependent on stimulation cycle length, as well as fiber orientation. At a BCL of 120 ms, CV max was 0.63±0.04 mm/ms, and CV min was 0.38±0.02 mm/ms (n=6). At a BCL of 80 ms, CV max decreased to 0.55±0.03 mm/ms, whereas CV min went down to 0.34±0.02 mm/ms (n=6).

Optical measurements of APD are presented in Fig 3. In Fig 3A, the fluorescent image of a heart is shown together with action potentials (inset) recorded by all pixels in a demarcated 1.1×1.1-mm square on the anterior epicardial surface. The heart was paced at a constant BCL of 120 ms. In Fig 3B, we present mean values of APD 70 (n=6) at constant BCLs of 120 ms (APD 70, 44.5±2.9 ms) and 80 ms (APD 70, 40.4±2.6 ms). The bar graph in Fig 3C shows the calculated wavelengths (CV max ×APD 70 and CV min ×APD 70) at these BCLs. It is clear that, regardless of the BCL or epicardial fiber direction, the wavelength was much larger than the long axis of the heart (~7 mm).

Arrhythmias in the Normal Mouse Heart
In 7 of 7 separate hearts (5 perfused with DAM and mapped, and 2 not perfused with DAM and not mapped), burst pacing near the apex of the left ventricle induced sustained monomorphic tachycardias. We defined a sustained arrhythmic episode as one that lasted >30 seconds. In 4 of the 5 hearts
that were mapped, sustained vortex-like reentry occurring around a single organizing center (core) was observed. In Figure 4A, we present the color isochrone map of a single counterclockwise rotation of a stationary vortex induced by burst pacing. The wavefront rotated with a period of 72 ms. In Figure 4B we show the pseudoelectrogram obtained from the optical data (upper trace) and the horizontal volume-conducted ECG (lower trace); the FFTs of these records are in Figure 4C. The FFTs of both the electrogram and the pseudoelectrogram show single narrow peaks at nearly identical frequencies that are consistent with the observed rotation period. This suggests that the rotor that gives rise to the periodicity in the pseudoelectrogram is also responsible for the periodic frequency of the volume-conducted electrogram. In one heart, 2 counterrotating vortices (figure-of-8 reentry) were recorded during sustained monomorphic tachycardia. Figure 5 shows an isochrone map of this episode. The black areas indicate pixel locations near the centers of rotation, where activation times could not be clearly identified. These data demonstrate that the mouse heart is capable of sustaining at least 2 stable reentrant sources.

In Figure 6, we present the analysis of the velocity vector field obtained from the clockwise rotation (arrow) of a stationary vortex with a period of 68 ms. In the pseudo-ECG, vortex-like activity manifested as a stable episode of monomorphic ventricular tachycardia. In Figure 6B, the vector map shows the spatial variation of the CV vectors displayed over the entire cycle. The direction of the propagation vectors was normal to the rotating wavefront, and the speed of propagation increased radially from the core. This is displayed quantitatively in Figure 6C. A sector was identified in the vector map, the tip of which was located at the center of the core. The local velocities within this sector are plotted against the radial distance. The regression line shows a significant positive correlation ($r^2=0.342$, $P<0.05$). As a control, Figure 6D shows an isochrone map obtained from the same heart during stimulation at a constant BCL of 120 ms, soon after the termination of the tachycardia. As shown also in the vector map (Figure 6E), the excitation wavefront moved...
downward at a faster velocity than during reentry. The vectors within the same sector as that in Figure 6B show conduction in approximately the same direction. As shown in Figure 6F, in this case, there was no correlation ($r^2=0.0007$, NS) between the velocity within the sector and the distance from the center of the anterior ventricular surface, which suggests that the spatial distribution of CVs observed during reentry (Figure 6A through 6C) was associated with the reentrant process itself. Overall, the results are in agreement with the theory of wave propagation in excitable media, which suggests that during vortex-like reentry, the local curvature of the wavefront increases toward the core and imposes a slowing of CV.

In 4 of 7 experiments, including both hearts in which DAM was not perfused, burst pacing of the left ventricle induced more complex arrhythmias. Simultaneously recorded electrograms of these episodes resembled VF. Figure 7A shows color isochrone maps of activity recorded during an episode of VF. The 2 maps show a wavefront on the epicardial surface that changes origin and direction. This aperiodic activity continued throughout the optical record. In Figure 7B, the horizontal ECG recorded during this episode shows complex ventricular activity indistinguishable from VF. In Figure 7C, the FFT of the horizontal ECG shows a narrow-banded spectrum consistent with VF.

**Discussion**

The results presented in this study demonstrate for the first time that ventricular tissue with an area as small as 100 mm$^2$ is capable of undergoing sustained reentrant activity and VF. The results are unexpected in the sense that it is difficult to conceive the occurrence of fibrillation or even sustained reentry in an excitable medium of which the wavelength ($\approx$10 to 30 mm) is larger than the length of the medium,
particularly a medium in which APD shows little or no frequency dependence. One possible explanation for this phenomenon may be found in recent computer simulations that indicate that the core around which a vortex rotates may exert a strong repolarizing influence on the surrounding tissues. Under such conditions, APDs of the cells near the core are shorter than APDs of cells in the periphery of the vortex. Such a repolarizing influence of the core is evident in the fact that the average APD of the whole preparation was shorter during reentrant activity than during external stimulation at a rate identical to that generated by the reentry. Thus, the results further demonstrate that the wavelength during periodic stimulation is a poor predictor of the conditions needed for maintenance of reentry in the mouse heart.

Electrophysiological Characteristics
We have measured the ECG parameters during sinus rhythm in the anesthetized mouse. Our results are in good agreement with those previously reported by other authors. In this study, we have used a technique for optically measuring conduction and repolarization characteristics in the Langendorff-perfused mouse heart at 37°C. Parameters of ventricular conduction, including CV and APD, have been described in several small mammals. The ratio of longitudinal to transverse CVs in murine myocardium is similar to those reported for other species.

Critical Mass
For >80 years since Garrey’s experiments, there has been a general belief that cardiac tissue smaller than a certain critical mass cannot support fibrillatory activity. This concept has been applied not only to comparisons between heart tissue of different sizes from the same species, but also to hearts of different species. In ventricular tissue, this critical size was originally estimated by Garrey to be 4 cm². By contrast, recent data have suggested that reentry is possible in smaller pieces of cardiac tissue. West and Landa reported in 1962 that sustained arrhythmic activity was detected in

Figure 6. Velocity profile during sustained reentry. A and D, Averaged isochrone maps obtained from the same heart during a stable episode of monomorphic ventricular tachycardia induced by burst pacing (A) and during constant pacing (BCL = 120 ms) soon after the termination of the tachycardia (D). Beneath panel A is a pseudoelectrogram derived from the unprocessed optical movie (bar = 100 ms). A color scale (red = 0 ms, purple = 68 ms) and a 1-mm bar appear under panel D. A stable reentrant process is seen in panel A (shown by the white arrow). B and E, Respective vector maps. Each black arrow represents an average of many adjacent vectors. Vertical arrow (E, lower right) represents 1.0 mm/ms. A sector was identified in which the vectors in both maps indicated conduction in approximately the same direction (marked in both panels). The tip of this sector was located in the center of the rotor in panels A and B. C and F, Local velocities within this sector are plotted against the distance from the center of rotation. Regression lines show a significant positive correlation for the rotor ($r^2 = 0.342, P < 0.05$) but none for the paced case ($r^2 = 0.0007, NS$), which suggests that the presence of the rotor is responsible for a slowing of local CVs near the center of rotation.
fragments of rabbit atrial tissue larger than 30 mg in size, with an estimated area >30 mm². However, they did not map a reentrant circuit.

In their paper supporting the leading circle hypothesis, Allessie et al.32 were able to induce a rotor in the rabbit atrium (≈1000 mm² in area). The diameter of the leading circle was estimated at 6 to 8 mm, suggesting that an area of 30 to 50 mm² (which we now term the core) is not sufficient to sustain a rotor. As Allessie et al.32 note, the leading circle must not only supply centrifugal wavefronts, but it must also provide current to nonsustained centripetal waves. Thus, from the calculations of Allessie et al.32 it is not easy to determine the minimum tissue area that is required to sustain a rotor.

Although the concept of Allessie et al.32 was a vast improvement over Mines’33 original idea of anatomical reentry, it has required radical reworking into the spiral wave paradigm to account for an excitable gap and the effects of wavefront curvature. It is therefore a pleasant surprise that the calculations of Allessie et al.32 which are based on a different model using data from heterogeneous atrial tissue, are not in conflict with our observations. This is the first demonstration and mapping of sustained reentry in an area of tissue that is ≈100 mm². Spach et al.34 and Spach and Josephson35 demonstrated nonsustained microscopic reentry in highly anisotropic tissue with an area <10 mm². This required very slow propagation velocities (0.028 m/s), which were similar to the velocities measured near the center of the rotor in our study (Figure 6). However, in the case of the data of Spach et al.,34 a fully regenerative wavefront must have been present very close to the rotor center, and hence, the distance dependence of velocity demonstrated in this study (Figure 6) cannot be derived from their interpretation. A circuit so anchored would also not be expected to drift or give rise to the polymorphic activity we saw in some hearts.

An estimate of the critical mass required for fibrillation has recently been made by Winfree5–7 who used a “rule of thumb” to suggest that the rotor size in two dimensions is equal to the diffusion distance during 1 rotor period, and the diameter d of the rotor can be given by $d = (2Dt)^{1/2}$, where D is the diffusion coefficient and t is the rotor period. Average estimates of D found in the literature range from 0.5 to 2.0 cm²/s. Using these values and the rotation period of the reentrant activity found in the mouse heart (≈70 ms), we come to a range for $d$ of 0.53 to 1.0 cm. This estimate falls within the long axis of the mouse ventricle of 0.6 cm. As such, it is not entirely unexpected to find a stable rotor in a mouse heart with a ventricular surface area of ≈1 cm².

VF has been defined as turbulent cardiac excitation. In this regard, Winfree5 gives the thickness threshold as 1 rotor diameter corrected for anisotropy, and an adequate area to allow for the “slithering” of the rotor as at least 6 times the size of the rotor in each surface dimension. With these assumptions and some general approximations, he arrives at a ventricular critical volume of 12 cm³ (mass of ≈12 g) for fibrillation. The caveat is that if rotor size is species dependent, the critical mass must be calculated for that respective species. This leads to a paradox, as our observations demonstrate that fibrillation is possible in the mouse heart. We were unable to directly identify the source of fibrillatory activity; thus, we cannot exclude multiple reentrant sources. However, given that we observed only a single wavefront in any frame during the fibrillatory episodes, our observations are consistent with previous results10–12 showing that a single drifting rotor can give rise to a polymorphic ECG compatible with VF. On the basis of these results, it is reasonable to postulate that an area just larger than that required for reentry could support fibrillation.

**Limitations of the Study**

In this study, we have addressed two questions regarding the induction and maintenance of arrhythmias. First, are arrhythmias possible in the adult mouse heart of which the ventricular surface area is <100 mm²? Second, what is the relation-
ship between wavelength during regular epicardial pacing and the ability to sustain arrhythmias? The observation of ventricular arrhythmias in Langendorff-perfused mouse hearts, both in the absence and in the presence of the electromechanical uncoupler DAM, answers the first question conclusively. However, because the measurements of APD and CVs were done only in the presence of DAM, which has been shown to affect APD in other species, we cannot be certain whether this agent altered wavelength in these mouse experiments. Therefore, the quantitative accuracy of the estimate of the relationship between wavelength and heart size remains somewhat uncertain. Nevertheless, in the presence of DAM, we have shown that the size of cardiac tissue that is required to sustain rotors and fibrillation need not exceed the wavelength measured during regular pacing. Clearly, the critical mass hypothesis needs revision.

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