Renewal theory provides a universal quantitative framework to characterise the continuous regeneration of phase singularities in cardiac fibrillation and accurately predicts spontaneous AF termination

Dhani Dharmapraniti
Madeline Schopp
Pawel Kuklik
Darius Champan
Anandaroop Lahiri
Lukah Dykes
Feng Xiong
Martin Aguilar
Benjamin Strauss
Lewis Mitchell
Kenneth Pope
Christian Meyer
Stephan Willems
Fadi Akar
Stanley Nattel
Andrew McGavigan
Anand Ganesan

Introduction: Atrial and ventricular fibrillation (AF/VF) are postulated to be maintained by rotors, with pivoting regions called phase singularities (PS). Despite a century of research, no universal quantitative framework exists to describe the generation of PS in cardiac fibrillation, and the role of this in maintaining AF/VF. Here, we develop a Poisson renewal theory framework to quantify the continuous formation and destruction of PS in cardiac fibrillation, and demonstrate for the first time that this regeneration process is responsible for the perpetuation of AF/VF. Further, we demonstrate that this framework can accurately predict spontaneous AF termination.

Methods: PS formation/destruction was studied in 5 systems: i) human persistent AF (n=20), ii) tachypaced sheep AF (n=5), iii) rat AF (n=4), iv) rat VF (n=11) and v) computer simulated AF (SIM). PS survival data was fitted using maximum likelihood, and rates of PS formation and destruction ($\lambda_f/\lambda_d$) determined. A systematic review was conducted to cross-validate with source data from literature. The spatiotemporal stability of $\lambda_f/\lambda_d$ was assessed through bivariate correlation between: i) 5-min long vs. 30-sec short duration recordings and ii) local vs. global recordings of AF. The association between $\lambda_f/\lambda_d$ and AF termination was investigated in n=15 epochs of terminating human AF, and compared with n=43 control epochs of sustained human AF.

Result: PS lifetime and inter-formation times were consistent with underlying Poisson renewal processes (human: $\lambda_f$-4.5%/ms±1.1 (95%CI,4.3,5.0), $\lambda_d$-4.6%/ms±1.5 (95%CI,4.3,4.9); sheep: $\lambda_f$-4.4%/ms (95%CI,4.1,4.7), $\lambda_d$- 4.6%/ms±1.4 (95%CI,4.3,4.8); rat AF: $\lambda_f$- 33%/ms±8.8 (95%CI, 11, 55), $\lambda_d$- 38%/ms (95%CI,22,55); rat VF: $\lambda_f$- 38%/ms±24 (95%CI,22,55), $\lambda_d$- 46%/ms±21 (95%CI,31,60); SIM $\lambda_d$ 6.6-8.9%/ms (95%CI,4.1,6.7); R2≥0.90 in all cases). All PS distributions identified through systematic review were also consistent with an underlying Poisson renewal process. $\lambda_f/\lambda_d$ was


spatiotemporally stable (long vs. short duration \( \lambda_d \): R: 0.99; local vs global \( \lambda_d \): R : 0.74) and also accurately predicts spontaneous AF termination (\( \lambda_f \) non-term: 4.6\%/ms (95% CI, 4.3, 4.9); \( \lambda_f \) term: 12.7\%/ms (95% CI, 11.0, 14.3); \( \lambda_d \) non-term: 4.7\%/ms (95% CI, 4.5, 4.9); \( \lambda_d \) non-term: 11.8\%/ms (95% CI, 9.8, 13.8); \( P < 0.001 \)).

**Conclusion :** These data redefine AF/VF as continuous Poisson renewal processes that occur by repetitive formation and destruction of phase singularities. The rate constants of \( \lambda_f/\lambda_d \) are simple, robust, spatiotemporally stable metrics that accurately predict the likelihood of AF termination. The universality of this motif demonstrates that renewal processes are fundamental to understanding and quantifying fibrillatory dynamics with profound implications for mechanistic and clinical understanding of AF/VF.