New research could reduce the risk of sudden cardiac death

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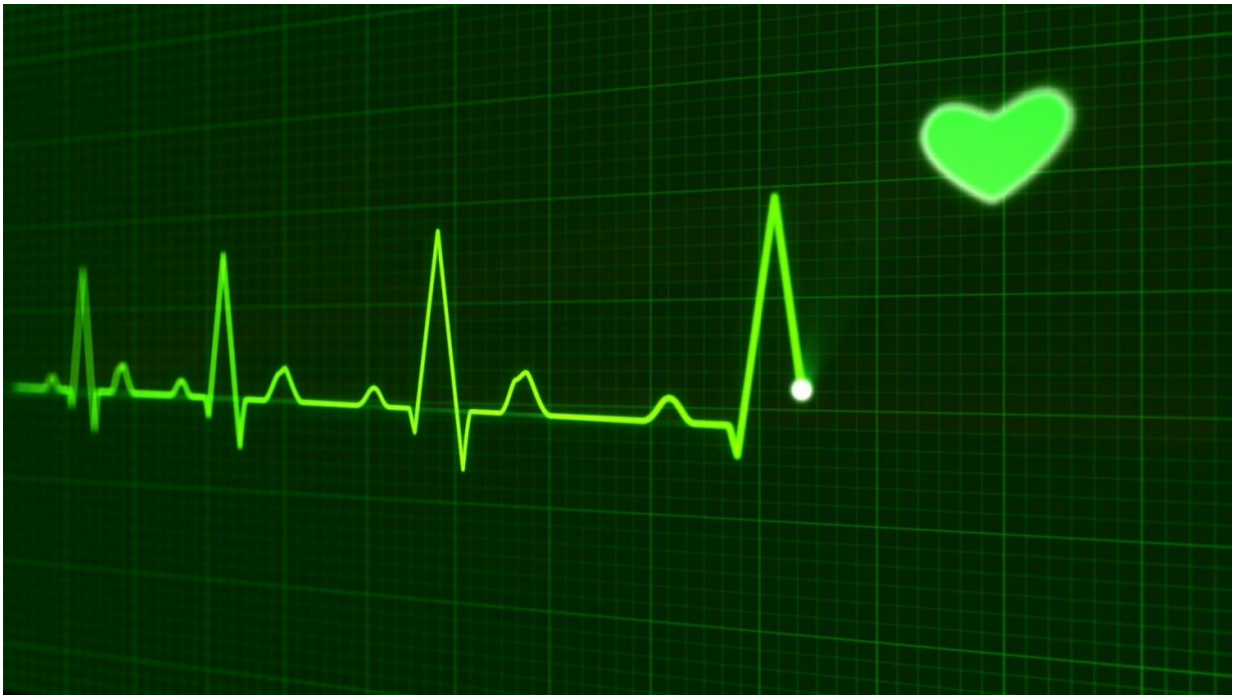

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Around 26 million people worldwide suffer from heart failure, with more than 50 per cent dying suddenly most likely due to the spontaneous onset of a heart rhythm problem, known as an arrhythmia. The link between the electrical signal that triggers the heart cell to contract (action potential) and consequent ability of the heart to pump blood has been known for nearly 40 years but understanding how and why the

heart's electrical rhythm becomes disturbed has remained a major research problem. New research has shown that by changing the time course of voltage change early in action potential it is possible to both withhold a potentially lethal electrical disturbance and improve the strength of cardiac contraction in heart failure at the same time.

The research led by the University of Bristol and funded by the Medical Research Council (MRC) is published today in the *Proceedings of the National Academy of Sciences* (*PNAS*).

At the cellular level, an identified initiator of cardiac arrhythmias are early after-depolarizations (EADs), but the cellular trigger for EADs in heart failure is unclear. EADs occur during the repolarization phase of the cardiac action potential (AP) where several ionic currents interact to control repolarization. EADs may be produced by reactivation of ionic currents during AP repolarization when the potassium currents forming the "repolarization reserve" are insufficient to maintain the repolarization trajectory of the AP, although why this should occur spontaneously within a steady train of APs is uncertain. Spontaneous calcium (Ca^{2+}) waves inside the cell have also been implicated in EAD generation, but it is unclear how such waves might be initiated.

The study has shown that the reduction in synchronous Ca^{2+} release early in the AP of failing heart muscle cells promotes the appearance of "late Ca^{2+} sparks" (microscopic Ca^{2+} release events) which can propagate, forming Ca^{2+} ripples and waves. These, in turn, produce an inward sodium-calcium exchange current which opposes AP repolarization. Restoration of AP phase 1 repolarization improved Ca^{2+} release synchrony and reduced late Ca^{2+} spark rate, suggesting an entirely new approach to reducing the risk of sudden death in heart failure.

Professor Mark Cannell, Chair in Cardiac Cell Biology in the University of Bristol's School of Physiology, Pharmacology and Neuroscience, who

led the research, said: "Our findings suggests that new therapies should be developed with the aim of improving early Ca^{2+} release by restoring AP phase 1 repolarization and/or restoring t-tubule regularity. This will reduce the risk for potentially lethal heart rhythm problems as well as mitigating the defective excitation-contraction coupling seen in heart failure. Our research proposes an entirely new approach to reducing the risk of sudden death in heart failure and the next step will be to move towards a clinical trial of new drugs."

'Arrhythmogenic late Ca^{2+} sparks in failing heart cells and their control by action potential configuration' by Ewan D. Fowler, Nan Wang, Melanie Hezzell, Guillaume Chanoit, Jules C. Hancox & Mark B. Cannell is published in the *Proceedings of the National Academy of Sciences* (*PNAS*).

More information: Ewan D. Fowler el al., "Arrhythmogenic late Ca^{2+} sparks in failing heart cells and their control by action potential configuration," *PNAS* (2020). www.pnas.org/cgi/doi/10.1073/pnas.1918649117

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