A runaway pacemaker is a malfunctioning pacemaker that paces the heart at rapid rates. A report from Australia 30 years ago described a patient with a runaway pacemaker that paced the ventricles at 280 bpm. The patient survived only because one of the coauthors alertly cut the pacemaker wires to disconnect the high-frequency focal source from the myocardium. In this issue of Circulation, Thomas et al report that they occasionally detected sustained high-frequency sources during ventricular fibrillation (VF) in sheep with myocardial infarction (MI). Specifically, in 3 of 12 hearts, they detected periodic high-frequency activations at 1.3% of the intramural electrodes sampled. The authors propose that these findings support the hypothesis that a relatively stable periodic source ("mother rotor"), with bidirectional conduction block occurring in the remainder of the ventricle, may be the mechanism of VF in this model. This mother rotor mechanism of fibrillation contrasts with the multiple wavelet mechanism, in which all rotors are unstable and wavebreak is the engine driving fibrillation. Both mechanisms of fibrillation have been documented in various settings, but controversy exists over which is the most common in and clinically relevant to diseased human hearts. This issue has therapeutic implications because it has been suggested that ablation of the mother rotor may be a strategy to abolish VF. At the same time, ablation of the mother rotor may just allow the next-fastest daughter rotor to take its place because fibrillatory wavebreaks act as niduses for new rotors. In any case, however, to even test this intriguing therapeutic strategy, it is first necessary to identify the location of the mother rotor, which has been elusive to date, especially in large animals. The findings of the present study, in a large-animal diseased heart model, are therefore significant. They also raise important questions. For example, were mother rotors also present in the remaining 75% of hearts but undetected because of the limited area accessible to mapping? Or was the mechanism of fibrillation different in these hearts? Were the high-frequency focal sources that the authors detected really rotors that activate the ventricles in the form of scroll waves, or some other mechanism such as automatic foci or triggered activity?

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Division of Cardiology, Department of Medicine, Cedars-Sinai Medical Center and the David Geffen School of Medicine, University of California--Los Angeles, Los Angeles, Calif.

Correspondence to Peng-Sheng Chen, MD, Room 5342, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048. E-mail chenp@cshs.org

(Circulation. 2005;112:148-150.)
© 2005 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.105.548669

Editorial

Runaway Pacemakers in Ventricular Fibrillation

Peng-Sheng Chen, MD; James N. Weiss, MD

Winfree coined the term "rotor" to describe a source of rapid activation that creates a spiral wave in 2 dimensions and a scroll wave in 3 dimensions. Although a spiral or scroll wave has a large rotating waveform, the actual source of activation is the rotor in the center. For a scroll wave to behave as a high-frequency focal source, it must stay in one place and have a long lifespan. A rotor is relatively stable in thin tissues, but electrically induced rotors usually have a short life span in normal canine ventricles in situ. In an attempt to detect sustained rotors in large animals, Rogers et al performed transmural mapping in 6 healthy anesthetized pigs using plunge electrodes inserted into the left ventricle. They found only sporadic and short-lived intramural reentry, although more sustained reentry (more than a few seconds) was seen on the epicardium in 3 of the 6 animals. The absence of sustained intramural rotors in large animals in situ seems to be inconsistent with the hypothesis that a relatively stable periodic source underlies the mechanisms of VF.

The thickness of the tissue is not the only factor that can affect rotor stability. Gray et al showed that a single rapidly meandering rotor in isolated rabbit ventricles could cause fibrillation through the Doppler effect. In their experiment, the rotor itself was stable and did not break up; however, because it was constantly meandering, the cycle length of activation in the remaining myocardium became variable, and hence the overall ECG resembled fibrillation rather than tachycardia. This meandering rotor scenario cannot be used to explain the results of the study by Thomas et al because the high-frequency focal source remained at the same site. Other factors that are important in maintaining rotor stability must be considered to explain the results of this study.

One possible explanation is that the electrophysiological and structural remodeling in chronic MI played a role in maintaining the rotor stability. Recent studies showed that the rotor stability is critically dependent on electrophysiological characteristics such as the excitability and the slope of action potential duration (APD) restitution and the preexisting structural heterogeneity of the ventricular tissues. Interaction between these dynamic factors and the preexisting structural heterogeneity determines the scroll wave phenotype. Wu et al showed that it is possible to convert multiple-wavelet (type 1) VF to sustained ventricular tachycardia (VT) by flattening the APD restitution without changing the excitability. Adding sodium channel blockage to reduce the excitability can convert VT to slow (type 2), VF with a stationary tachycardia. This meandering rotor scenario cannot be used to explain the results of the study by Thomas et al because the high-frequency focal source remained at the same site. Other factors that are important in maintaining rotor stability must be considered to explain the results of this study.

See p 157

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
flatten APD restitution and reduce excitability, converting type 1 VF into type 2 VF, with a mother rotor anchored to the papillary muscle. Ablation of the papillary muscle may terminate VF in that model. It is possible that electrophysiological and structural remodeling associated with chronic MI might have stabilized the rotors and created the periodic sources in the study by Thomas et al. Without these changes (eg, in normal swine ventricles), a stable rotor cannot survive for long periods of time; however, the location of the high-frequency sources in the Thomas et al study was distributed at multiple different locations in the ventricles. Because the authors did not perform histological examinations, it is unclear whether specific anatomic structure or heterogeneity is present at these high-frequency sites.

Although a mother rotor mechanism and sustained scroll waves are an attractive interpretation of the results of the present study, nonreentrant mechanisms such as a rapid automatic focus or triggered activity cannot be excluded. A number of studies have demonstrated that high-frequency nonreentrant focal sources can be causally related to the initiation of VF. For example, local injection of aconitine into the ventricle can induce rapid focal activation, with focal wavefronts originating from the site of injection in rapid succession.14 If the APD restitution is flat, then this focal activation continues as a source of monomorphic VT; however, if the restitution is steep, then VT-to-VF transition occurs. In the latter condition, the excision of the site of aconitine injection does not guarantee the termination of VF. Focal activations are also present in ventricular tachyarrhythmia in human patients. Pogwizd et al15 performed 3-dimensional intraoperative mapping in patients with healed MI and refractory VT. In addition to documenting intramural reentrant wavefronts, the authors also documented that focal (and presumably nonreentrant) activation may be responsible for the induction of VT. These findings suggest that nonreentrant mechanisms are present in diseased human ventricles and may serve as the initiating event in ventricular arrhythmias. Whether or not the focal activation triggers VT or VF depends on the electrophysiological and anatomic properties of the ventricles. The presence of a rapidly activating focus does not necessarily mean that this focus is essential for VF maintenance.

The coexistence of rapid focal discharges in the presence of disorganized activity in other parts of the myocardium also points to the possibility that reentrant mechanisms (rotors) and the nonreentrant mechanism may work together to maintain VF. The nonreentrant mechanisms (automaticity or triggered activity) depend critically on intracellular Ca\(^{\text{2+}}\) (\(C_{\text{ai}}\)) dynamics. In cardiac muscle, depolarization triggers entry of extracellular Ca through voltage-gated Ca channels, which in turn triggers the release of stored Ca in the sarcoplasmic reticulum. Relaxation occurs when Ca is taken up by the sarcoplasmic reticulum and extruded by the Na-Ca exchanger. Although Ca channel opening and Ca-induced Ca release are normally triggered by the action potential, Ca\(^{\text{2+}}\) cycling can also exhibit its own dynamics. It is possible that the rapid activation rate during VF induces Ca\(^{\text{2+}}\) overload and facilitates spontaneous Ca release,16 which in turn causes afterdepolarizations and triggered activity.17 The triggered activity may manifest as high-frequency periodic focal activity recorded by extracellular electrodes. This high-frequency focal activity in turn increases the number of activation wavefronts through fibrillatory conduction and helps to maintain a high rate of activation, which in turn exacerbates Ca\(^{\text{2+}}\) overload. In this scenario, the reentrant and nonreentrant mechanisms work together to promote VF.

The development of both reentrant and nonreentrant mechanisms may be facilitated by sympathetic stimulation. Hearts with more sympathetic nerve terminals may respond more vigorously to the sympathetic discharges than do normal hearts. Although the sympathetic nerve terminals were not examined in the present study, it is reasonable to hypothesize that significant neural remodeling has occurred in these infarcted hearts.18 After division, crushing, interference of blood supply, or other means of injury to a nerve, peripheral nerves undergo degeneration, which may be followed by neurilemma cell proliferation and axonal regeneration. The regeneration effort is triggered by the reexpression of nerve growth factor or other neurotrophic factor genes in the non-neuronal cells around the site of injury. Because nerves in the heart may be injured during myocardial ischemia, nerve growth factor overexpression also occurs after MI, resulting in nerve sprouting and sympathetic hyperinnervation.19 A potential benefit of the increased sympathetic innervation is the improved hemodynamic performance that compensates for the myocardium lost during infarction; however, the increased sympathetic innervation also allows the nerve terminals to release more catecholamines during sympathetic discharges. VF induces hypotension, which is a potent trigger of sympathetic activation. An increased catecholamine release into the myocardium enhances automaticity and increases the propensity for triggered activity, more so in hearts with MI and nerve sprouting than in normal hearts. This mechanism may partially explain the different observations made in chronic infarcted ventricles and in normal swine hearts.

In summary, Thomas et al have detected regions of high-frequency activations during VF in dogs with chronic MI. These high-frequency periodic discharges may act as runaway biological pacemakers that underlie the mechanisms of VF. If a runaway biological pacemaker underlies VF, it is possible that cutting the pacemaker wires and/or removing the pacemaker itself could both terminate VF and prevent its recurrence, or would a marginally slower ancillary pacemaker replace it? There is already clinical and experimental evidence showing that some types of VF can be cured by radiofrequency ablation of a focal source of rapid activation.13,20 Whether this is generally true for VF in the setting of common forms of heart disease remains to be investigated. The study by Thomas et al takes an important step toward testing this hypothesis in a clinically relevant model of ischemic heart disease. Even though a putative mother rotor was identified only in a minority of the hearts studied, its maternal influence on VF can now be tested.

Acknowledgments
This work was supported in part by NIH grants P50 HL52319, R01 HL78932, R01 HL66389, and R01 HL71140, and by Laubisch, Kawata, and Pauline and Harold Price Endowments.
Disclosure

Dr Chen has received equipment from pacemaker companies (including Medtronic, Guidant, and St. Jude) to support research in animals.

References


Key Words: Editorials ▪ pacemakers ▪ arrhythmia ▪ death, sudden ▪ fibrillation
Runaway Pacemakers in Ventricular Fibrillation
Peng-Sheng Chen and James N. Weiss

Circulation. 2005;112:148-150
doi: 10.1161/CIRCULATIONAHA.105.548669
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/2/148

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/