

Abstracts of the 2008th Encouragement Award's Memorial Lectures of the 76th Annual Meeting of the Medical Association of Nippon Medical School

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Heterogeneous Pulmonary Vein Myocardial Cell Repolarization and Heterogeneous Sympathetic Hyperinnervation as the Substrates for Atrial Fibrillation

Yasushi Miyauchi

Division of Cardiology, Hepatology, Geriatrics, and Integrative Medicine, Department of Internal Medicine, Nippon Medical School

Introduction

Atrial fibrillation (AF) is one of the frequent arrhythmias with a prevalence of up to 12% in the general population. AF may have significant effects on both the quality of life and morbidity due to cerebral thromboembolism and congestive heart failure. Studies in animal models have shown that shortening of the effective refractory period and the development of atrial fibrosis are the major components of the electrophysiological and anatomical substrates for AF. However, the mechanism of AF is not uniform. For example, although epidemiologic studies have shown that myocardial infarction is a risk factor for AF, the mechanism by which myocardial infarction induced AF was poorly determined. Second, although pulmonary veins (PVs) are thought to play a major role in the initiation and maintenance of AF, systematic evaluation from different regions in intact PV-atrial tissues are lacking. The present study was performed to address these issues.

Chronic Myocardial Infarction and AF

I and coworkers have elucidated the substrates for AF in hearts with myocardial infarction (MI)¹. We induced MI in 8 dogs by permanent occlusion of the left anterior descending (LAD) coronary artery. Seven dogs (3 undergoing thoracotomy) that had no LAD occlusion served as controls. Eight weeks after surgery, the incidence and duration of pacing-induced AF in the open chest anesthetized state were significantly ($P<0.05$) higher in MI dogs than in control dogs. Multisite biatrial monophasic action potential (MAP) recordings showed increased heterogeneity of MAP duration and MAP duration restitution slope. The AF in the MI group was preceded by significantly higher MAP duration ($P<0.01$) and MAP amplitude ($P<0.05$) alternans in both atria

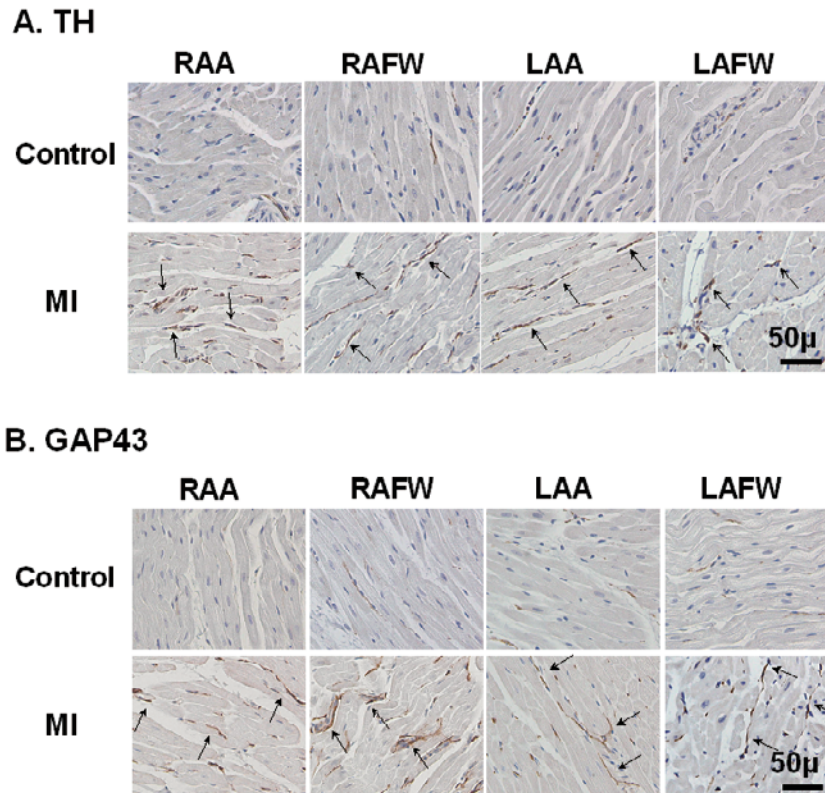


Fig. 1 Atrial immunostaining of TH-positive (A) and GAP43-positive nerves (B) at different atrial sites. Increased TH- and GAP43-positive nerves at the 4 atrial sites are evident in the dog with MI. RAA, right atrial appendage; RAFW, right atrial free wall; LAA, left atrial appendage; and LAFW, left atrial free wall.

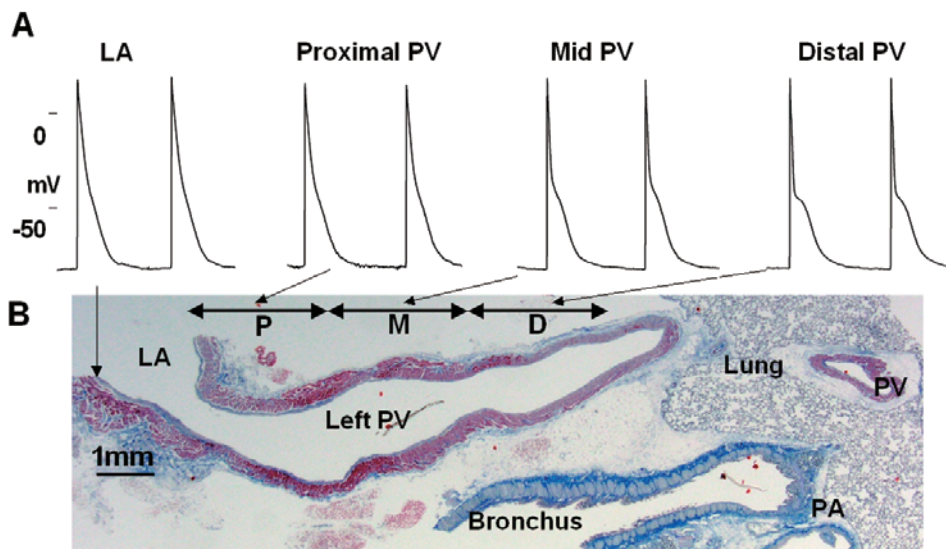


Fig. 2 Action potential recordings with glass microelectrodes from different regions of the PV and the LA. Panel A shows representative action potentials during pacing at a cycle length of 200 ms. Panel B show the anatomic locations of the LA, proximal (P), mid-(M), and distal (D) pulmonary recording sites as indicated by downward arrows. PA, pulmonary artery.

than in controls. Epicardial mapping using 1,792 bipolar electrodes (1-mm spatial resolution) showed multisite wavebreaks of the paced wavefronts leading to AF in MI dogs but not in control dogs. Multiple wavelets in MI dogs were associated with significantly higher incidence and longer duration of AF than in control dogs. The density of biatrial tyrosine hydroxylase (TH) and growth-associated protein43 (GAP43) nerves were 5- to 8-fold higher and were more heterogeneous in MI dogs than in control dogs (**Fig. 1**). On the basis of these findings, we concluded that chronic ventricular MI with no atrial involvement causes heterogeneous alteration of atrial electrical restitution and atrial sympathetic hyperinnervation that might provide important substrates for the observed increased AF vulnerability.

Electrophysiology of Myocardial Cells in PVs

It was demonstrated that the PVs and the left atrium (LA)-PV junctions provide a substrate for AF both in man and in animal models. I and coworkers determined the transmembrane action potential properties of myocardial cells in different regions of the PV and the LA and assessed their arrhythmogenic potential during perfusion with isoproterenol and rapid atrial pacing². Glass microelectrode recordings of action potentials were made from the left PV and the LA in Langendorff-perfused young male rats (n=9). Histologic examination of the PV and LA junction showed 5 to 10 cell layers of myocardial cells clearly visible in the PV that penetrates deep inside the lung (**Fig. 2**). Action potential recording exhibited a spike and dome configuration in the distal PV whereas triangular shape in the LA (**Fig. 2**). The action potential duration of atrial and PV cells was similar at a pacing cycle length of 200 ms. However, shortening of the pacing cycle length to 100 ms led to heterogeneous repolarization of PV cells. Mid-PV cells had a significantly higher maximum slope of action potential duration restitution than did atrial or other PV sites. Intra-PV conduction block developed at rates when LA and proximal PV cells manifested 1 : 1 capture. Perfusion of isoproterenol and rapid atrial pacing promoted the emergence of early afterdepolarization and triggered beats in 2 of 9 tissues, causing premature atrial activation. No difference in resting potential or action potential amplitude could be detected among the PV and LA cells. We concluded that PV myocardial cells develop marked heterogeneity in repolarization, and there is a slightly greater tendency for early afterdepolarization and triggered activity in response to rapid pacing and isoproterenol infusion.

References

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2. Miyauchi Y, Hayashi H, Miyauchi M, et al: Heterogeneous pulmonary vein myocardial cell repolarization implications for reentry and triggered activity. *Heart Rhythm* 2005; 2: 1339-1345.