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計畫主持人：蔡青峰
共同主持人：葉宏一，翁國昌，林中生

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Greater Electrical Remodeling in Tissues Remote From the Infarction Area is Associated with Increased Risk for Ischemia-Dependent Ventricular Fibrillation After Canine Myocardial Infarction

Introduction

Ventricular tachyarrhythmias are life threatening cardiac arrhythmias and account for 75% of causes of sudden cardiac death (1, 2). Patients with ischemic heart diseases especially associated with post-myocardial infarction (MI) left ventricular (LV) remodeling and dysfunction are at increased risk of sudden cardiac death (3-9). However, the information about how the post-MI structural remodeling creates risk for lethal arrhythmias is lacking. LV remodeling after MI is characterized by progressive dilation, hypertrophy, distortion of cavity shape, and deterioration in contractile function (10, 11). The LV structural remodeling after MI involves the regions of necrosis and infarct scar, the central and border zone areas, as well as the non-infarcted myocardium remote from infarction sites. In many models, the non-infarcted myocardium shows gradual morphological changes indicative of hypertrophy as it adapts to the increased workload of the compromised heart during both the subacute (or healing at weeks) and chronic (or healed since 2 months) stages. Regional hypertrophy that accompanies ventricular remodeling is of interest since LV hypertrophy is a strong risk factor for ventricular arrhythmias (12-16). On the other hand, repolarization abnormalities are thought to be related to malignant tachyarrhythmias and sudden cardiac death in patients with various cardiac diseases. Arrhythmias responsible for post-MI sudden death also are associated

with enhanced regional heterogeneity of ventricular repolarization, which manifests as QT prolongation and greater QT dispersion on surface ECG (17-23). Thus, we hypothesize that the adverse LV structural remodeling at non-infarcted regions after MI also contributes to adverse electrophysiological remodeling and is closely related to cardiac electrical instability.

Methods

Animal Surgical Preparation

Mongrel dogs of either sex weighting 20-25 Kg were anesthetized with sodium pentobarbital (20 mg/Kg i.v.), and then intubated with a cuffed endotracheal tube with artificially ventilated with room air using a constant volume cycled respirator. The canine was anesthetized with 1.0-2.0% isoflurane. Cefazoline (20 mg/Kg IV) and continuous saline slow infusion were also administered. ECG monitoring was continuously used for rhythmic evaluation. Approval from the local institutional animal care and use committee was obtained after review of all protocols and prior to any experimentation.

The right groin was shaved to expose the femoral artery. One 7-Fr sheath was placed into femoral artery to connect a fluid filled cannula and a transducer for continuous monitoring femoral artery pressure. A 6-Fr angiographic catheter (JL 4 or AL 1) was advanced through femoral artery sheath into aortic root under fluoroscopy guidance, and was manipulated to engage the left main coronary artery. The position of the catheter was confirmed by contrast injection. We created an anterior MI by percutaneous transcatheter embolization of polyvinyl alcohol foam particles (Cook Inc., Bloomington, IN) (0.2-0.3 cc diluted in 10 cc of mixture of contrast material and normal saline) into the left anterior

descending coronary artery (just distal to the first septal branch). The angiographic catheter was withdrawn immediately after the embolization procedure. The dogs were continuously monitored 1-2 hours for arrhythmias development and hemodynamic status. The dogs were then allowed to recover and sent to its kennel after ligating femoral artery and closing groin incisions.

Risk for Ventricular Fibrillation (VF) after MI

Two months after MI, survived dogs were brought back to lab, and the left femoral artery and veins were accessed as previously described. Transient (2-4 minutes) myocardial ischemia was induced via balloon occlusion of the proximal left circumflex coronary artery. Cardiac rhythm was monitored for the occurrence of unstable arrhythmias during acute ischemia induction. If unstable ventricular tachyarrhythmias occurred, the balloon was deflated immediately and withdrawn, and the dog was electrically defibrillated. If no ventricular arrhythmia occurred during Lcx balloon occlusion, ventricular stimulation protocol was performed by using right ventricular S1S1, extrastimuli (up to S4). If ventricular arrhythmia was not induced from right ventricle, we would test left ventricular stimulation same as at right ventricle.

Dogs that developed ventricular tachyarrhythmias were labeled “susceptible” or at “high risk” for VF. The remaining dogs did not develop sustained ventricular arrhythmias and were labeled “resistant” or at “low risk” for VF.

QT Interval Measurements

Surface QT intervals were measured at baseline and 2 months after MI. One independent investigator read all QT intervals blinded to the dog condition. A second blinded readed also read QT interval assessments to provide

consistency. All QT intervals were obtained at fixed right atrial pacing cycle length 500 and 400msec to avoid potential confounding influences of heart rate correction algorithms.

Endocardial Regional Repolarization Mapping

The monophasic action potential (MAP) provides a faithful representation of the time course of the transmembrane potential, and is an established and widely used technique for investigating the in situ beating heart. We used a commercial pressure-contact MAP catheter (EP Technology) to get MAP data at different ventricular areas, and at fixed right atrial pacing cycle length 500 and 400 msec. We measured endocardial local repolarization time by calculating action potential duration made at 90% repolarization (APD_{90}). MAP recordings would be obtained at baseline (before MI creation) and 2 months after MI.

Local repolarization times were routinely recorded from right ventricular apex, right ventricular outflow tract, and four regions within the left ventricle, which were chosen based on the characteristics of regional remodeling following an anterior or anteroapical MI episode:

(1) ***Basal anterior wall*:** not directly involved with left anterior descending coronary artery embolization or acute circumflex ischemia

(2) ***Anteroapical wall*:** to examine repolarization characteristics of the chronic infarction

(3) ***Lateral or Posterior free wall*:** the previously noninfarcted areas will be exposed to acute ischemia event

(4) ***Anteroseptum or apicoseptum*:** a transition or border areas between the apical infarction and the basal anterior walls

After MAP study, all dogs were sacrificed for histopathological examination and further isolated tissue optimal mapping study. The heart was

excised to examine the chambers for gross structural abnormalities. The infarction size will be estimated 2-dimensional endocardially.

Optical Mapping Study in Isolated Non-infarcted Tissue

Optical mapping was performed in left ventricular wedge preparations isolated from the non-infarcted area that was perfused through the non-occluded circumflex artery (Lcx). After heart was rapidly excised and immersed in 4°C hyperkalemic cardioplegic solution. A section of the LV Lcx-perfused free wall was isolated and harvested. The Lcx was cannulated at most proximal end. The isolated tissue was perfused with a cardioplegic solution containing elevated KCl (20 mmol/l) at 4°C during surgical preparation to protect the cardiac tissue. Major arterial leaks in the tissue were ligated with 3-O silk surgical suture. After non-perfused excessive tissue is trimmed, the isolated tissue was mounted on a constant-flow perfusion apparatus and immersed in and perfused with 37°C Tyrode's solution (in mmol/L. NaCl 123.0, KCl 5.4, NaHCO3 22.0, NaH2PO4 0.65, MgCl2 0.50, Glucose 5.50, CaCl2 2.0, bubbled with a 95% O2 and 5% CO2 gas mixture) in a glass experimental chamber warmed by a water jacket with circulating 37°C water. Perfusate (37°C) was delivered to the tissue through the proximal cannula(s) by peristaltic pump at a diastolic perfusion pressure between 40-50 mm-Hg continuously monitored with arterial pressure transducer. The tissue was paced at 1 Hz for at least one hour of heating and temperature equilibration before one of the data of the cording protocols. Three Ag/AgCl wire-electrodes were placed in the bath to record the ECG. The healthiness of the tissue preparation and its suitability of the optical mapping studies was examined. Then membrane-potential-sensitive dye, di-4-ANEPPS (100 μg, dissolved in 100 μl dimethyl sulfoxide), was added to the perfusate at a concentration of ~2 μmol/L to stain the membrane of myocytes. The evenness of

dye staining was tested and when necessary, a second dose of di-4-ANEPPS was added to the perfusate. To eliminate the motion artifacts in the optically recorded action potentials, 10 μmol/L cytochalasin D (dissolved in one ml of DMSO for every 2 mg of cytochalasin D) was added to the perfusate after the initial tissue immobilization with 25 μmol/L of cytochalasin D in the perfusate for 10 minutes. At the end of the experiment, the tissue was preserved in 10% buffered formalin phosphate solution. The fluorescent-optical mapping system (CardioCCD-SM, CCS 256, RedShirtImaging LLC, USA) consisting of a light source and an observation and recording unit, was used to record the optical action potential by converting the fluorescent emission from the tissue with high spatial (80 x 80 pixels) and temporal (2 Hz) resolution. The depolarization time (1^{st} derivative), repolarization time (2^{nd} derivative), electrical movement were analyzed automatically and further examined manually if necessary.

All the isolated tissues were underwent routine stimulation protocol: S1S1 700, 600, 500, 400 msec, and S1S2 with basic pacing cycle length 600 msec and coupling interval 400, 300, then at 10 msec decrement till tissue refractoriness. In addition, extrastimulus test (up to three extrastimuli) was performed to evaluate the ventricular vulnerability. We assessed the electrophysiological characteristics of the isolated non-infarcted tissues, including conduction velocity, repolarization time (longest, shortest, average, and dispersion) and any tachyarrhythmic episodes available for electrical movement analysis.

Statistical Analysis

Data are presented as mean ± SD unless otherwise noted. Differences between groups (regional endocardial repolarization, regional wall thickness, surface QT intervals) were evaluated with Student's t-test. Repolarization differences between regions was evaluated using one-way analysis of variance

with Neuman-Keuls multiple pairs comparison post test. An alpha level of $P < 0.05$ is considered statistically significant.

Results

Risk for Post-MI VF

Two dogs (20%) died within 2 months after MI creation. A total of eight dogs underwent acute myocardial ischemia test eight weeks after MI. Four dogs (50%) were susceptible to VF and were successfully defibrillated. The other four dogs had no sustained ventricular arrhythmias (resistant group) during acute myocardial ischemia and ventricular electrical stimulation protocol. Risk status was confirmed in all dogs at least test twice after regional repolarization mapping with MAP recordings. Additionally, compared to dogs without VF (n=4), susceptible dogs with inducible VF (n=4) had relatively larger infarction scar (5.4±1.2 vs. 2.1±1.0 cm2, $p<0.05$).

Surface QT Measurements

Surface QT intervals were obtained at fixed right atiral pacing cycle length 500 msec to avoid the need of correction algorithms. Surface QT intervals were longer in susceptible dogs (242.8±16 msec) compared to resistant dogs (219.3±5.3 msec, $p<0.05$).

Endocardial Regional Repolarization Mapping

Endocardial repolarization maps with MAP recordings were obtained at fixed right atiral pacing cycle length 500 msec. The mean endocardial repolarization times at all LV regions were significantly longer in susceptible (226±30 msec) compared to resistant dogs (201±18 msec, $p<0.05$), but no

significant repolarization difference at right ventricle (202±14 msec vs. 199±13 msec) between two groups. In comparison with different LV regions of the susceptible dogs, a significant longer endocardial repoalrization time in the lateral/posterior free wall (258±13 msec) than other areas of the susceptible ventricle (basal anterior 233±20 msec, $p<0.05$; anteroapical scar 207±24 msec, $p<0.001$; anteroseptum 217±15 msec, $p<0.05$). In addition, the basal anterior and posterolateral walls repolarization times in resistant dogs were also shorter compared to susceptible dogs (basal anterior 207±24 msec vs. 233±20 msec, $p<0.05$; posterolateral 211±32 msec vs. 258±13 msc, $p<0.01$). No significant regional repoalrization differences of both groups were found in anteroapical scar and anteroseptum border zones.

Optical Mapping Data

Optical mapping was performed in left ventricular wedge preparations isolated from the non-infarction area that was perfused through non-occluded circumflex artery. As compared to dogs without inducible VF (resistant group), VF dogs (susceptible group) had longer optical action potential duration (APD_{90} 239.6±14.3 msec vs. 214.8±15.8 msec, $p<0.05$), increased repolarization dispersion between the longest and shortest APD_{90} (24.4±6.1 msec vs. 6.0±1.4 msec; $p<0.05$), and reduced conduction velocity (329.9±34.5 vs. 475±26.6 mm/sec; $p<0.05$). Despite the fact that the tissue preparations were isolated remote from the infarction region, sustained VF was still inducible in 3 of 4 isolated wedge preparations by programmed stimulation in dogs with inducible VF in vivo. In contrast, VF was not induced in all 4 preparations obtained form dogs without inducible VF in vivo.

Discussion

The main finding in this study is that adverse structural and electrophysiological remodeling in non-infarcted regions after myocardial infarction contributes to heterogeneous regional endocardial repolarization and also to a vulnerable myocardial substrates conductive to lethal reentrant arrhythmias. Post-MI VF is associated with greater electrical remodeling in tissues remote from the infarction area, including prolongation of action potential duration, increase of repolarization dispersion and decrease of conduction velocity. The present data provides a direct link between post-MI adverse remodeling and the electrical consequences on ventricular repolarization and conduction associated with high risk for sudden death.

Spatial Repolarization Heterogeneity as the Arrhythmogenic Substrate

Lethal ventricular arrhythmias responsible for post-MI sudden death has been shown to be associated with enhanced regional dispersion of ventricular repolarization, which manifests on surface ECG QT interval prolongation or greater QT dispersion (17-23). Our study shown that susceptible dogs had prolonged surface QT intervals. However, QT interval yields a limited view of the complex electrogenesis of the ventricular endocardial repolarization. QT dispersion also addresses macroscopic rather than microscopic inhomogenenity. Thus, in this study, the extent of repolarization heterogenenity could not be delineated by the QT interval prolongation observed. The monophasic action potential (MAP) recordings by a contact electrode technique in this study is a simple and established technique to provide a faithful representation of the time course of the transmembrane action potential (24).

Regional dispersion of repolarization are arrhythmogenic perturbations that are closely associated with reentry. The induced ventricular arrhythmia observed in this experimental tissue for optical maps was most consistent with a reentrant mechanism. Spatial heterogeneities of repolarization found in susceptible dogs provide the potential for unidirectional block, because the posteroalteral hypertrophic area, which had the longest repolarization duration, was located in close proximity to the apicoanterior scar region, which had the shortest repolarization duration. This refractory gradient (average repolarization discrepancy of 50 msec) in susceptible dogs possibly increased the likelihood of unidirectional block leading to reentry. This study using intact sedated canine allows the opportunity to characterize the substrate directly associated with high arrhythmia risk. We also performed electrical mapping of life-threatening arrhythmias in isolated heart preparations, and demonstrated that prolonged and heterogeneous repolarization at non-infarcted area provides a substrate for arrhythmia occurrence. Previous studies showed that heterogeneity of ventricular sympathetic innervation could be a basis. Spatial heterogeneity in expression and catecholamine responsiveness of potassium currents may result in heterogeneous LV repolarization and contribute importantly to the arrhythmogenic substrate (21-22, 25).

Adverse Post-MI Remodeling and Ventricular Arrhythmias

Patients with more extensive post-MI LV structural remodeling are at greater risk for cardiovascular fatalities, including sudden death attributable to arrhythmias (3-9). Sutton et al. recently demonstrated that altered LV architecture and function during post-MI LV remodeling could predict the occurrence of ventricular arrhythmias, and thus provide an important substrate for triggering high-grade ventricular arrhythmias (8). Our study showed

susceptible dogs had larger infarction areas and more hypertrophic mass in non-infarcted region. Prior study also showed that large infarcts tend to show greater increases in cell size in the non-infarcted remote areas, compared to smaller infarcts (26). The mechanism for ventricular arrhythmias associated with increased LV mass is complex, but important etiologic factors include the combination of patchy subendocardial fibrosis, increased calcium-dependent slow inward current, altered kinetics of the outward potassium current, and altered repolarization time of hypertrophied myocardium (12-14, 16, 27, 28). Previous intracellular microelectrode recordings had shown that action potential duration is typically prolonged in remote areas from infarction sites, and appears to be increased to a greater extent than in the infarct zone. The extent of action potential prolongation appears to depend on the age of the infarct (27). In addition, post-MI ventricular tachycardia is thought to be due to anisotropic reentry, consequent on slowed impulse propagation velocities through myocardium partially replaced by fibrosis, which typifies postinfarction remodeling myocardium (29, 30). The interplay between spatial heterogeneities of repolarization and tissue structure can further form a vulnerable substrate for unidirectional block and reentry (31).

Our study clearly showed that post-MI VF is associated with greater electrical remodeling in hypertrophied tissues remote from the infarction area. Chen et al. recently propose the nerve sprouting hypothesis of ventricular arrhythmia. Post-MI regional heterogeneous myocardial sympathetic hyperinnervation may couple with adverse structural (histologic or architectural) changes over time and electrically remodeled myocardium, resulting in ventricular tachyarrhythmias and sudden death (25, 32, 33). Swann et al. recently showed that susceptible animals responded to perturbations with sympathetic activation as demonstrated by post-MI depression of baroreflex

sensitivity and tachycardia response to acute ischemia. Thus, the differences in repolarization heterogeneity between susceptible and resistant dogs are possibly caused by different tissue responses to autonomic changes associated with the MI, and/or the development of myocardial hypertrophy. Augmentation of sympathetic input to the heart can result in hypertrophy and prolongation of repoalrization. Furthermore, development of LV hypertrophy causes down-regulation of repolarizing K+ currents, leading to repolarization heterogeneity (28). Clinical benefit obtained from beta-blocker and angiotensin-converting enzyme inhibitor therapy after MI probably not only reduce adverse remodeling of the ventricle and progression of ischemic heart disease but also reduce sudden death.

Conclusion

The present study documented that significant electrophysiological remodeling including repolarization and conduction abnormalities at the non-infarct areas may play an important role in the genesis of post-MI lethal ventricular arrhythmias. Greater electrical and structural remodeling in tissues remote from the infarction area draws our more attention to apparently “normal” non-infarction regions to further understanding of post-MI VF and sudden death.

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