Acute regional left atrial ischemia causes acceleration of atrial drivers during atrial fibrillation

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BACKGROUND The mechanisms by which acute left atrial ischemia (LAI) leads to atrial fibrillation (AF) initiation and perpetuation remain unclear.

OBJECTIVE To investigate the electrophysiological mechanisms of AF perpetuation in the presence of regional atrial ischemia.

METHODS LAI (90-minute ischemia) was obtained in isolated sheep hearts by selectively perfusing microspheres into the left anterior atrial artery. Two charge-coupled device cameras and several bipolar electrodes enabled recording from multiple atrial locations: with a dual-camera setup (protocol 1, n = 10, and protocol 1′, n = 4, for biatrial or atrioventricular camera setups, respectively), in the presence of propranolol/atropine (1 μM) added to the perfusate after LAI (protocol 2, n = 3) and after a pretreatment with glibenclamide (10 μM; protocol 3, n = 4).

RESULTS Spontaneous AF occurred in 41.2% (7 of 17) of the hearts that were in sinus rhythm before LAI. LAI caused action potential duration shortening in both the ischemic (IZ) and nonischemic (NIZ) zones by 21% ± 8% and 34% ± 13%, respectively (pacing, 5 Hz; $P < .05$ compared to baseline). Apparent impulse velocity was significantly reduced in the IZ but not in the NIZ (−65% ± 19% and 9% ± 18%; $P = .001$ and NS, respectively). During LAI-related AF, a significant NIZ maximal dominant frequency increase from 7.4 ± 2.5 to 14.0 ± 5.5 Hz ($P < .05$) was observed. Glibenclamide, an ATP-sensitive potassium current (IKATP) channel blocker, averted LAI-related maximal dominant frequency increase (NIZ: LAI vs glibenclamide 14.0 ± 5.5 Hz vs 5.9 ± 1.3 Hz; $P < .05$). An interplay between spontaneous focal discharges and rotors, locating at the IZ-NIZ border zone, maintained LAI-related AF.

CONCLUSIONS LAI leads to an IKATP conductance-dependent action potential duration shortening and spontaneous AF maintained by both spontaneous focal discharges and reentrant circuits locating at the IZ border zone.

KEYWORDS Atrial ischemia; Atrial fibrillation; Dominant frequency; IKATP

ABBREVIATIONS **AF** = atrial fibrillation; **AP** = action potential; **APD** = action potential duration; **BZ** = border zone; **CV** = conduction velocity; **DF** = dominant frequency; **DFmax** = maximal dominant frequency; **IKATP** = ATP-sensitive potassium current; **IZ** = ischemic zone; **LAA** = left atrial appendage; **LAAA** = left anterior atrial artery; **LAI** = left atrial ischemia; **LCX** = left circumflex artery; **NIZ** = nonischemic zone; **PLA** = posterior left atrium; **RAA** = right atrial appendage; **VF** = ventricular fibrillation

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia and affects more than 4 million Americans.[1] Furthermore, AF is a frequent complication of acute coronary syndromes, with a postmyocardial infarction incidence ranging between 5% to 18%.[2,3] Acute regional atrial ischemia/infarction has been observed after a *ventricular* myocardial infarction but also in isolation.[4–6] Atrial ischemia/infarction translates into PQ-segment depression or elevation on the electrocardiogram and often associates with atrial tachyarrhythmias.[4,5,7] In an experimental work, Sinno et al[8] indicated that right atrial coronary branch occlusion resulted in severe conduction slowing and in an increased duration of AF episodes. Also in a canine model, it was shown that the acute occlusion of the right coronary artery led to atrial effective refractory period shortening.[9]

Nishida et al[10] also demonstrated that the border zone (BZ) of an 8-day right atrial myocardial infarction region is an elective area for rotor anchoring and spontaneous focal discharges after an upregulation of the sodium-calcium exchanger current in cells from the BZ. Still, the electrophysiological mechanisms of short-term atrial ischemia-

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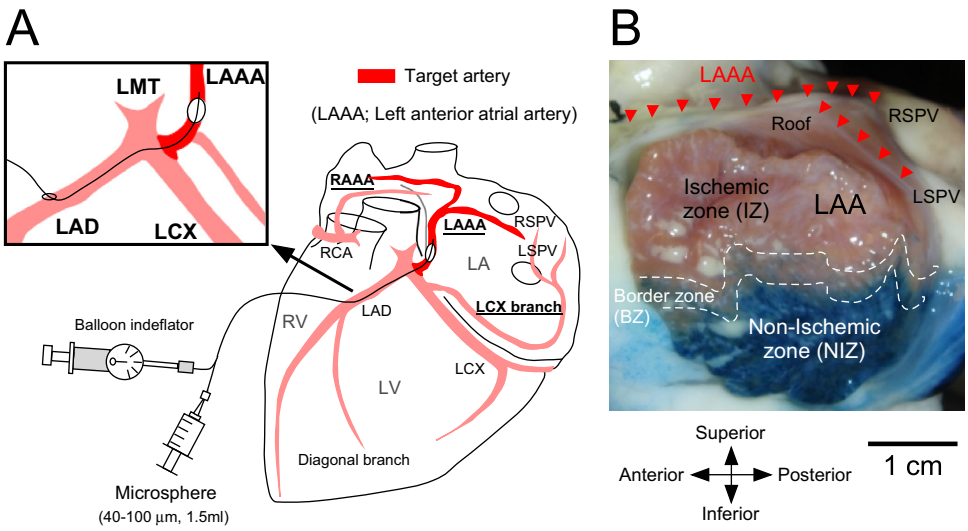

Figure 1 Regional atrial ischemia model. **A:** Schematic of the retrograde insertion of a guide wire into the LAAA (red) via the LAD artery. Then, an over-the-wire balloon catheter was introduced and the balloon inflated. Subsequently, microspheres were perfused into the LAAA. After removal of the balloon catheter, the LAAA was ligated. **B:** Photographic snapshot of the left atrial free wall after injection of Evans blue into the LCX, which perfuses the NIZ in this example. The BZ is defined as a 4-mm band peripheral around the IZ. Red triangles indicate the LAAA course. BZ = border zone; IZ = ischemic zone; LAAA = left anterior atrial artery; LAD = left anterior descending; LCX = left circumflex artery; LMT = left main trunk; LSPV = left superior pulmonary vein; LV = left ventricle; NIZ = nonischemic zone; RAAA = right anterior atrial artery; RCA = right coronary artery; RSPV = right superior pulmonary vein; RV = right ventricle.

induced AF remain unclear, especially when ischemia involves the left atrial muscle. Previous anatomical studies in humans and a study in sheep by our group have indicated that 3 main branches provide the coronary blood supply to the atria: the left anterior atrial artery (LAAA) that arises from the proximal segment of the left circumflex artery (LCX), the right anterior atrial artery (also known as right sinus node artery), and the branches of LCX.[11–13] Here, we implemented a newly developed model of acute left atrial ischemia (LAI) in isolated ovine hearts to demonstrate that regional impairment in atrial coronary perfusion is conducive to action potential duration (APD) shortening, AF initiation, as well as an acceleration and increased complexity of AF drivers.

Methods

Langendorff-perfused sheep heart and regional LAI model

All animal experiments were carried out according to the National Institutes of Health guidelines. Twenty-one sheep (45–50 kg) were anesthetized with propofol (0.4 mg/kg) and then heparinized (200 U/kg, intraperitoneal). After heart removal, the hearts were Langendorff-perfused with warm oxygenated Tyrode's solution (pH 7.4; 95% O_2, 5% CO_2, 36–38°C). During all experiments and to obtain a controlled and physiological level of intra-atrial pressure of 3–5 cm H_2O, we perforated the interatrial septum, sutured venous orifices, and connected the inferior vena cava to a cannula that enabled to maintain a constant level of intra-atrial hydrostatic pressure, as described previously.[13,14] We initiated ventricular fibrillation (VF) as soon as the heart was perfused and VF was maintained for the entirety of the experiment. After having identified the course of the main atrial coronary branches on the atrial epicardium, the left anterior descending artery was punctured with a 21-gage needle and a 0.36-mm angioplasty wire was retrogradely inserted into the LAAA. Then, we deployed an over-the-wire balloon catheter (1.5 × 9 mm; Ranger, Boston Scientific Corporation, Natick, Massachusetts, USA) or a metal needle (1.5 mm) into the LAAA through the left anterior descending artery (Figure 1A). To generate a regional impairment in atrial coronary perfusion and also avoid coronary collateral flow from other perfusion territories, we first inflated a balloon and then injected 40–100-μm microsphere (1.5 mL) into the LAAA. Finally, we ligated this artery. Thereafter, we waited 90 minutes before obtaining optical mapping and electrical recordings as described below. At the end of the experiment, to differentiate the ischemic zone (IZ) and nonischemic zone (NIZ), we delineated the boundaries of the IZ with an injection of Evans blue (1–5 mL, 2 mg/mL; Sigma, Inc) into the LCX and Congo red (1–5 mL, 4 mg/mL; Sigma, Inc) into the right coronary artery as previously reported.[13] The ischemic BZ was defined as a 4-mm band peripheral around the IZ. As an example, a representative snapshot is presented in Figure 1B. Evans blue was perfused into the LCX perfusion territory that corresponded to the lower left atrial appendage (LAA) region, while the ischemic region remained unstained.

Experimental setup and protocols

In 21 LAI sheep, we performed and analyzed optical mapping recordings as follows (Figure 2 and Online Supplement Table 1). In 14 sheep a right atrium-left atrium dual-camera setup (protocol 1) while in 4 sheep an atrial-left ventricle dual-camera setup was implemented (protocol 1′). In 3 sheep, propranolol (1 μM) and atropine (1 μM) were