Short-term hypertension is associated with the development of atrial fibrillation substrate: A study in an ovine hypertensive model

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BACKGROUND Hypertension is frequently complicated by the development of atrial fibrillation (AF). However, the mechanisms of this link remain poorly understood. In addition, whether short-term hypertension can result in a substrate for AF is not known.

OBJECTIVE The purpose of this study was to characterize the atrial substrate predisposing to AF due to short-duration hypertension.

METHODS Sixteen sheep were studied: 10 had induced hypertension for 7 ± 4 weeks via the "one-kidney, one-clip" model, and six were controls. Cardiac magnetic resonance imaging was used to assess functional changes. Open-chest electrophysiological study was performed using a custom-made 128-electrode epicardial plaque applied to both right (RA) and left atria (LA), including the Bachmann's bundle, to determine effective refractory periods (ERPs) and conduction velocity at four pacing cycle lengths from six sites. Tissue specimens were harvested for structural analysis.

RESULTS The hypertensive group demonstrated the following compared with controls: higher blood pressure ($P < .0001$), enlarged LA ($P < .05$), reduced LA ejection fraction ($P < .05$), uniformly higher mean ERP ($P < .001$), slower mean conduction velocity ($P < .001$), higher conduction heterogeneity index ($P < .0001$), greater AF inducibility ($P = .03$), and increased AF durations ($P = .04$). Picrosirius red staining of atrial tissues revealed increased interstitial fibrosis ($P < .0001$). There was also evidence of increased inflammatory cell infiltrates ($P < .0001$).

CONCLUSION Short-duration hypertension is associated with significant atrial remodeling characterized by atrial enlargement/dysfunction, interstitial fibrosis, inflammation, slowed/heterogeneous conduction, increased ERP, and greater propensity for AF.

KEYWORDS Hypertension; Arrhythmia; Atria; Remodeling; Magnetic resonance imaging

ABBREVIATIONS **1K1C** = one-kidney, one-clip; **ACE** = angiotensin-converting enzyme; **AF** = atrial fibrillation; **CMR** = cardiac magnetic resonance; **CRP** = C-reactive protein; **ECG** = electrocardiogram; **ERP** = effective refractory period; **LA** = left atrial; **LAA** = left atrial appendage; **LAFW** = left atrial free wall; **RA** = right atrial; **RAA** = right atrial appendage; **RAFW** = right atrial free wall

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Introduction

Because of its high prevalence in the population, hypertension accounts for more atrial fibrillation (AF) than any other risk factors.[1] With the increasing incidence of hypertension and the projected exponential rise in the number of persons with AF, this important synergistic association requires careful attention.[2,3] Clinical studies have identified a causal relationship between left atrial (LA) size and AF in hypertensive subjects.[1,4,5] In addition, the presence of hypertension in AF patients has been shown to result in higher cardiovascular morbidity and mortality.[6] Despite this known association, studies on atrial remodeling due to hy-

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pertension remain limited. In particular, whether short duration of hypertension can result in atrial remodeling is not known. By creating experimental hypertension using the "one-kidney, one-clip" (1K1C) model,[7] this study aimed to characterize atrial electrical, structural, and functional remodeling in an ovine model of short-term hypertension.

Methods

All procedures were conducted in accordance with the guidelines outlined in the "Position of the American Heart Association on Research Animal Use," adopted on November 11, 1984, by the American Heart Association. This study was approved by the University of Adelaide Animal Ethics Committee, Adelaide, Australia. A total of 16 Merino Cross sheep were studied: 10 with induced hypertension for 7 ± 4 weeks via the 1K1C model and six controls.

Animal preparation and care

All animals were acclimatized for ≥1week before study and fasted for 24 hours before anesthesia for the renal/carotid surgeries, cardiac magnetic resonance (CMR) scans, and euthanasia electrophysiological study. Intravenous sodium thiopentone (15–20 mg/kg) was used for induction before endotracheal intubation, while isoflurane (2%–4%) in 100% oxygen was used for maintenance. Invasive blood pressure, heart rate, pulse oximetry, end-tidal CO_2, and temperature were continuously monitored. Postoperative care included intramuscular administration of xylazine hydrochloride and penicillin for 3 days.

"One-kidney, one-clip" hypertension

There is no ideal animal model for hypertension given its complex multifactorial pathogenesis. The 1K1C hypertension has been well studied, whereby the primary mechanism for hypertension is due to volume expansion from sodium and water retention with no involvement of the autonomic or angiotensin system apart from brief initial renin activation during the first 1 or 2 weeks after renal clamping.[8–11] Moreover, given that renovascular hypertension is the most frequent secondary cause of hypertension in humans, the 1K1C model is more physiological than other endocrine, dietary, and nephron reduction models.

Unilateral nephrectomy was followed by renal artery clamping using a custom-made Goldblatt-type clamp 3 weeks later. The degree of induced renal artery stenosis was closely regulated to 50%–60% with a combination of perivascular flow (Transonic Flowmeter TS-401 with 6-mm precision flow probe, Transonic Systems Inc., Ithaca, NY) and Doppler velocity (Acuson XP-128, 7-MHz probe, Siemens Medical Solutions, Erlangen, Germany) estimations. The establishment and characterization of this model has been described elsewhere.[7] Blood pressure remained stable from baseline through post–unilateral nephrectomy but rose within the first week after renal clamping to reach a plateau by 4 weeks. Blood pressure was measured in the conscious state via cannulation of the exteriorized carotid artery.[12]

Cardiac functional assessment

CMR was performed 1 day before euthanasia to assess LA and left ventricular volumes and ejection fraction (Siemens Sonata 1.5 Tesla MR imaging system, Siemens Medical Solutions, Erlangen, Germany) with slice thickness of 6 mm through the atria and 10 mm through the ventricles without any interslice gap. Animals were placed and secured in the dorsal recumbent position for all CMR scans. Mechanical ventilation was maintained to facilitate ECG-gated image acquisition with adequate breath holding. All analyses were performed offline using Argus software (Leonardo workstation, Siemens Medical Solutions).

Electrophysiological study

Bilateral thoracotomy was performed to facilitate open-chest electrophysiological studies. Physiological arterial blood gases and body temperature were maintained throughout. Custom designed 128-electrode epicardial plaques with 5-mm interelectrode distance were then applied to the right atrium (RA) and LA and traversing the Bachmann's bundle before being attached to a computerized recording system (Figure 1; LabSystem Pro, Bard Electrophysiology, Lowell, MA). Surface ECG and overlapping bipolar electrograms were continuously monitored and stored for offline analysis. Electrograms were filtered from 30 to 500 Hz and measured with computer-assisted calipers at a sweep speed of 200 mm/s.

Atrial Refractoriness

Atrial effective refractory period (ERP) was measured at twice the diastolic threshold at cycle lengths (S1) of 500, 400, 300, and 200 ms from six sites (RA appendage [RAA], RA free wall [RAFW], RA Bachmann's Bundle [RABB], LAA, LAFW, and LABB). Eight basic (S1) stimuli were followed by a premature (S2) stimulus in 10-ms decrements. Atrial ERP was defined as the longest S1-S2 interval not

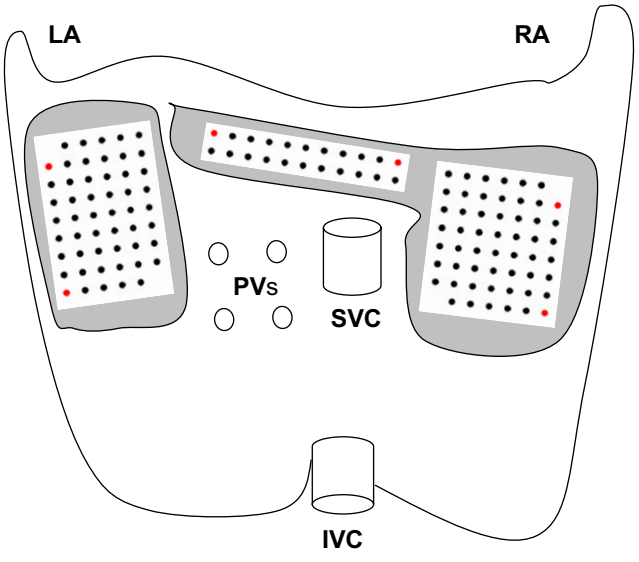

Figure 1 Epicardial plaque design. Illustration of plaque design showing a total of 128 electrodes covering the LA, RA, and Bachmann's bundle. *Red dots* represent prespecified pacing sites.