Dynamic regulation of atrial coronary blood flow in healthy adult pigs

Kelly A. van Bragt, MSc, Hussein M. Nasrallah, MSc, Marion Kuiper, BSc, Arne van Hunnik, BSc, Nico H.L. Kuijpers, PhD, Ulrich Schotten, MD, PhD, Sander Verheule, PhD

From the Department of Physiology, Faculty of Medicine, Maastricht University, The Netherlands.

BACKGROUND There are several indications for a mismatch between atrial oxygen supply and demand during atrial fibrillation (AF), but atrial coronary flow regulation has not been investigated extensively.

OBJECTIVE The purpose of this study was to characterize the dynamic regulation of atrial coronary flow in pigs.

METHODS In anesthetized open-chest pigs, Doppler flow probes were placed around left atrial (LA) and left ventricular (LV) branches of the circumflex artery. Pressures and work indices were measured simultaneously. Systolic and diastolic flow contribution, flow response kinetics, and relationship between pressures, work, and flow were investigated during sinus rhythm, atrial pacing, and acute AF.

RESULTS During atrial systole, LA flow decreased. Only 2% of total LA flow occurred during atrial systole. Pacing with 2:1 AV block and infusion of acetylcholine revealed that atrial contraction itself impeded atrial coronary flow. The response to sudden changes in heart rate was slower in LA compared to LV. Both LA and LV vascular conductance were positively correlated with work. After the cessation of acute AF, the LA showed a more pronounced phase of supranormal vascular conductance than the LV, indicating a period of atrial reactive hyperemia.

CONCLUSION In healthy adult pigs, atrial coronary flow is impeded by atrial contraction. Although atrial coronary blood flow is positively correlated with atrial external work, it reacts more slowly to changes in rate than ventricular flow. The occurrence of a pronounced hyperemic phase after acute AF supports the notion of a significant supply–demand mismatch during AF.

KEYWORDS Atrial coronary flow; Atrial fibrillation; Atrial contraction; Vascular function; Ischemia

ABBREVIATIONS **+dP/dt** = slope of the positive upstroke of the left ventricular pressure curve; **ACh** = acetylcholine; **APD_{80}** = action potential duration at 80% repolarization; **AF** = atrial fibrillation; **ANOVA** = analysis of variance; **CI** = confidence interval; **LA** = left atrium; **LAWI** = left atrial work index; **LV** = left ventricle; **LVWI** = left ventricular work index; **P_{Ao}** = aortic pressure; **P_{LA}** = left atrial pressure; **P_{RA}** = right atrial pressure; **RA** = right atrium; **SF** = systolic fraction; **SR** = sinus rhythm; **$T_{1/2bsln}$** = time to the half-maximal flow decrease; **$T_{1/2MAX}$** = time to reach the half-maximal flow increase; **TFI** = time–flow integral; **TFId** = time–flow integral during diastole; **TFIs** = time–flow integral during systole

(Heart Rhythm 2015;12:991–1000)

Introduction

Atrial fibrillation (AF), the most common tachyarrhythmia seen in clinical practice, is associated with increased morbidity and mortality.[1–3] The rapid and irregular rate of excitation and contraction during AF is likely to lead to increased atrial energy demand. Several studies using microspheres in healthy animals have shown that increased atrial demand, such as short-term atrial pacing, exercise, and AF resulted in increased atrial coronary blood flow.[4–11] However, if this increase in supply were insufficient to meet the increased demand, a state of supply–demand ischemia would ensue. In the goat model of AF, the occurrence of supply–demand ischemia over a longer period is supported by decreased phosphocreatine levels.[12] In addition, expression of hypoxia-inducible factor 1-alpha and vascular endothelial growth factor was increased in atrial biopsy samples of both goats in AF[13] and in AF patients.[14] Because their ventricular coronary anatomy and flow regulation are similar to those in humans,[15] we chose pigs to study atrial coronary flow regulation. We recently showed that, although atrial arteries dilate and atrial oxygen extraction increases in response to acute AF in healthy pigs, atrial lactate production increases, which is indicative of supply–demand ischemia.[16]

Understanding the dynamic regulation of atrial coronary flow will help in determining the role of ischemia in the onset and perpetuation of AF. In this study, we studied the dynamic regulation of atrial coronary blood flow in normal healthy pigs. The phasic coronary flow pattern was analyzed and the kinetics of flow regulation were investigated.

This work was supported by the Foundation Leducq (07 CVD 03) and the European Union (European Network for Translational Network in Atrial Fibrillation, EUTRAF, Grant 261057). **Address reprint requests and correspondence:** Dr. Sander Verheule, Department of Physiology, Universiteitssingel 50, 6229 ER Maastricht, The Netherlands. E-mail address: s.verheule@maastrichtuniversity.nl.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2015.01.016

Simultaneous measurements of atrial work and atrial flow were performed under different circumstances that influence atrial energy demand.

Methods

Animal preparation

Eleven healthy Dutch Landrace pigs (weight 66 ± 3 kg) were studied. Some aspects of the measurements in these animals have been reported previously.[17] For the present study, 3 additional animals were included, and additional analysis, interventions, and parameters are described.

All animal procedures were in accordance with national and institutional guidelines. Anesthesia was induced with Zoletil (5–8 mg/kg IM) and thiopental (5–15 mg/kg IV) and maintained with midazolam (0.8 mg/kg/h), sufentanil (6 μg/kg/h), and propofol (2.5–10 mg/kg/h). A left lateral incision was made, the 5th rib was removed, and the pericardium was opened to expose the left atrium (LA) and left ventricle (LV).

Instrumentation

Pigs were instrumented as shown in Figure 1B. To measure atrial and ventricular flow, Doppler flow probes (Transonic Systems Inc, Ithaca, NY) were placed around an LA and an LV branch of the left circumflex artery. Flow signals were recorded during sinus rhythm (SR), atrial pacing at different pacing cycle lengths (500, 450, and 400 ms), and AF. For this purpose, a pacemaker lead (5568, Medtronic Inc, Minneapolis, MN) was placed endocardially in the right atrium (RA) to pace and record local electrograms.

Because the stability of AF was low in healthy pigs, continuous rapid burst pacing at 20 Hz (4 × diastolic threshold) was used to artificially maintain the arrhythmia for recordings during AF. AF episodes had approximately the same duration in each animal because pigs spontaneously converted to SR within seconds of cessation of burst pacing.

To analyze the phasic flow pattern, the diastolic and systolic phases of the flow signal were defined (see section on Calculation of diastolic and systolic fraction of flow). To analyze the trends in the coronary flow pattern, the response kinetics of the flow signal were determined during atrial pacing (see section on Calculation of flow response kinetics).

LA and LV work indices were measured simultaneously with coronary flow signals. The left atrial work index (LAWI) was estimated using LA dimensions and pressure (see section on Calculation of work indices). Three piezoelectric crystals (Sonometrics, London, Ontario, Canada) were introduced through the LA free wall into the LA lumen in a triangular orientation (Figure 1B) in order to measure atrial dimensions. To measure LA pressures, a Millar microtip pressure sensor (Millar Instruments, Houston, TX) was inserted through the LA free wall into the LA lumen. The left ventricular work index (LVWI) was determined using a Sentron conductance catheter (Sentron Europe BV, Roden, The Netherlands) to measure LV volume and pressure. In order to calculate vascular conductance, aortic (Sentron Europe BV, Roden, The Netherlands) and RA (Millar Instruments) pressures were measured. Conductance was calculated by dividing coronary flow by the pressure difference over the coronary vascular bed ($P_{Ao} - P_{RA}$). Atrial work and flow were measured during atrial pacing at cycle lengths of 500, 450, and 400 ms and during short-term AF (10 minutes). The same parameters were measured during intracoronary infusion of acetylcholine (ACh) via a JR6 catheter (Cordis Corp, Bridgewater, NJ) in the left main coronary artery. Before and during ACh infusion, monophasic action potentials were recorded using a monophasic action potential catheter (7F MAP-4801, Harvard Apparatus,

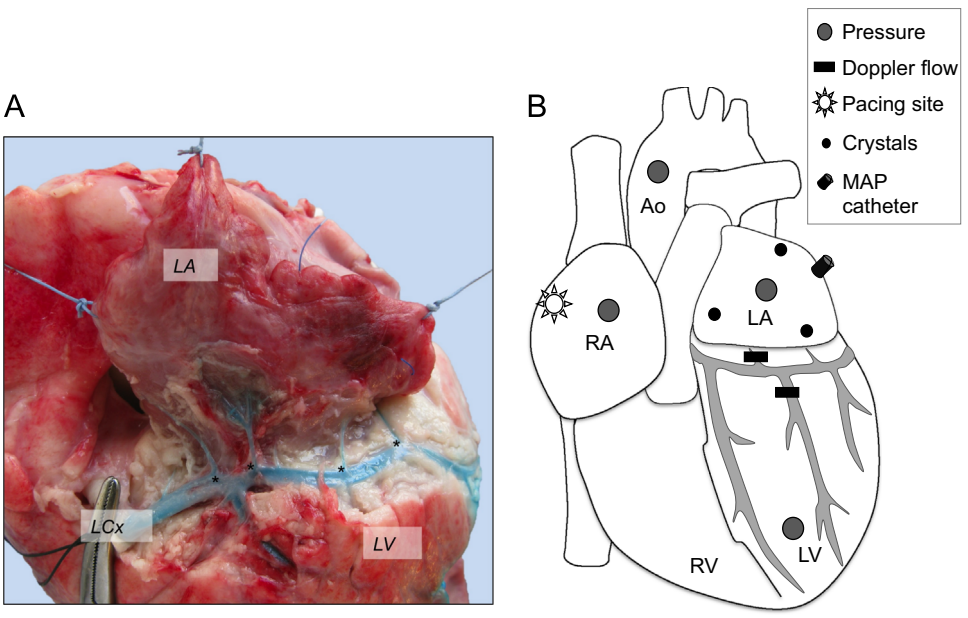

Figure 1 Instrumentation. **A:** Ink injection into the left circumflex artery (LCx). Atrial branches are indicated with *asterisks.* **B:** Instrumentation in the aorta (Ao), left ventricle (LV), left atrium (LA), and right atrium (RA). RV = right ventricle.