Dynamic regulation of atrial coronary blood flow in healthy adult pigs

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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

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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.

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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,

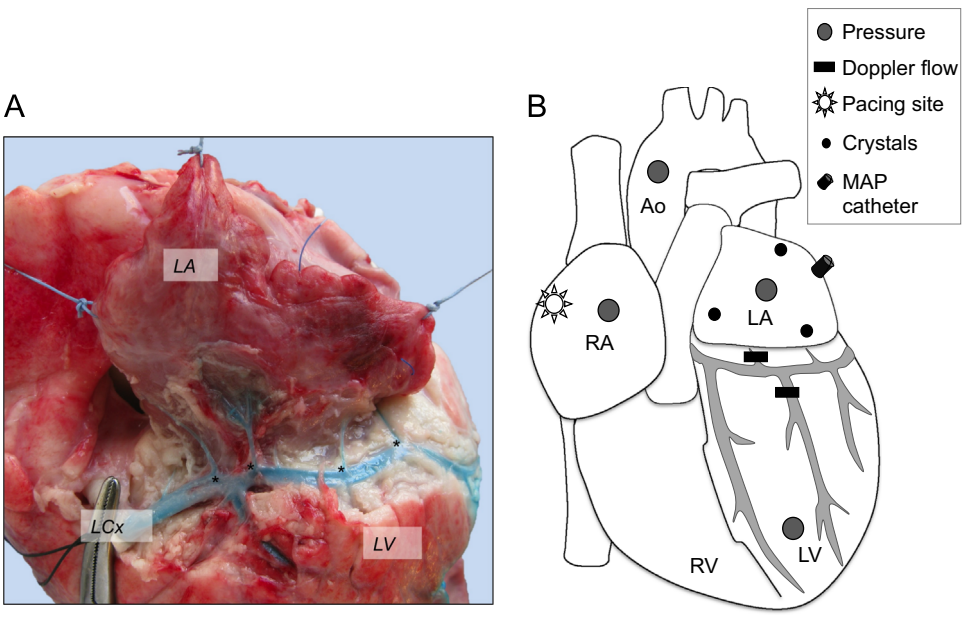

Figure 1 Instrumentation. **A:** Ink injection into the left circumflex artery (LCx). Atrial branches are indicated with *asterisks.* **B:** Instrumentation in the aorta (Ao), left ventricle (LV), left atrium (LA), and right atrium (RA). RV = right ventricle.

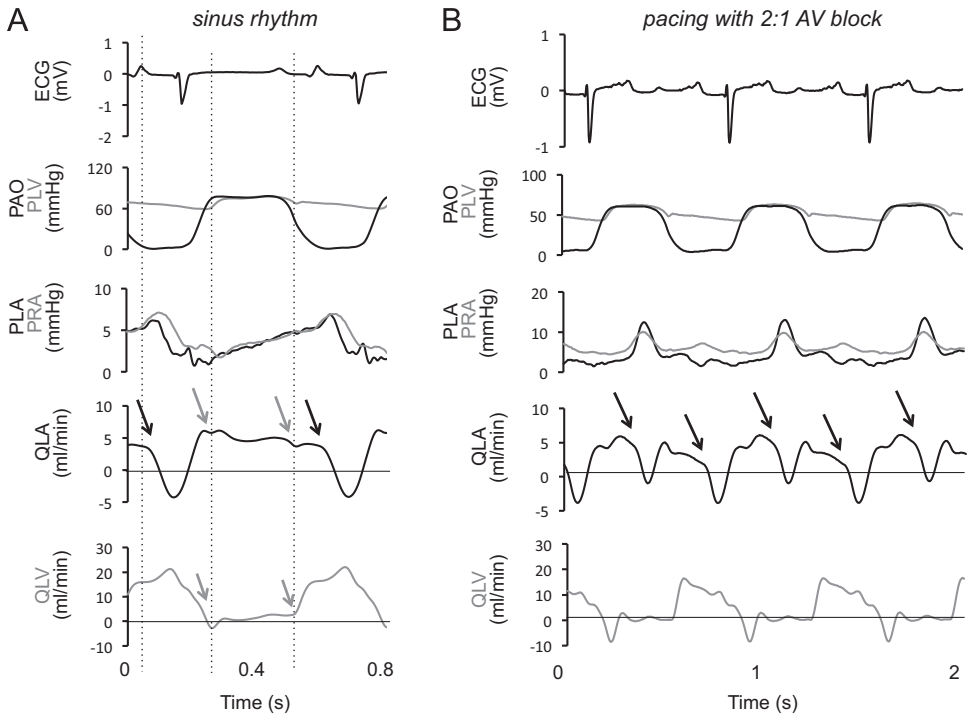

Figure 2 Phasic flow pattern during sinus rhythm **(A)** and 2:1 AV block **(B).** *Black arrows* indicate decrease in atrial flow during atrial systole. *Gray arrows* indicate timing of aortic valve opening and closure.

Holliston, MA). After 1 minute of pacing or steady-state ACh infusion, a 10-second period was analyzed to calculate the average atrial and ventricular conductance and work indices.

Calculation of diastolic and systolic fraction of flow

LV systolic flow was calculated as the flow occurring between the onset of ventricular contraction (ie, start of increase in LV pressure) and the onset of ventricular relaxation (ie, start of decrease in LV pressure; see Figure 3A). LA systolic flow was defined as the period between the start of atrial contraction (ie, increase in LA pressure after the start of the P wave on the ECG) and the start of atrial relaxation (ie, decrease in LA pressure; see Figure 3B). The time–flow integrals were calculated for 5 consecutive beats to determine the time–flow integral during systole (TFIs) and time–flow integral during diastole (TFId). The systolic fraction (SF, in %) of total flow per beat was calculated as SF = [TFIs/(TFIs + TFId)]*100.

Calculation of flow response kinetics

The response kinetics of the average flow signal over time was compared between LA and LV branches. The flow signal was filtered using a 10-level wavelet filter to eliminate the phasic pattern of the cardiac cycle, thereby deriving average flow. For 3 different pacing cycle lengths, the time to reach the half-maximal flow increase ($T_{1/2MAX}$) from baseline was calculated. In addition, the time to the half-maximal flow decrease ($T_{1/2bsln}$) from the maximum after the cessation of pacing was determined (see Figure 4A). To quantify the hyperemic phase after cessation of acute AF, the ratio between the time integral of the total conductance and the baseline over the same time period was calculated.

Calculation of work indices

Ventricular work indices were determined by integrating all completed LV pressure–volume loops during 10-second periods. Atrial work indices were assumed to be proportional to the integral of pressure–distance loops during atrial contraction.[18] Atrial pressure–distance loops result from both passive and active atrial emptying. Active atrial work starts at the moment of LA pressure rise and is followed by shortening of the atrial distance (indicated with star in Figure 5A). The atrial active work loop ends when the same atrial diameter is reached again. Three distances were recorded on the LA free wall, and the work index was calculated by the average value from the 3 pressure–distance loops. LAWI was normalized with respect to heart rate by multiplying the work per beat times the number of heartbeats per second and was expressed as mm*mmHg/s.

Statistical analysis

Results are expressed as mean ± SEM. Statistical analysis was performed using 1-way analysis of variance (ANOVA) to assess the effects of different interventions on work indices and conductance. Values were compared to baseline using a *post hoc* Dunnett multiple comparison test. LA and LV values were compared with 2-way ANOVA, followed by a *post hoc* Dunnett test. Correlation between work indices and conductance was tested using a linear mixed model analysis. We have applied 3 linear mixed models and chose

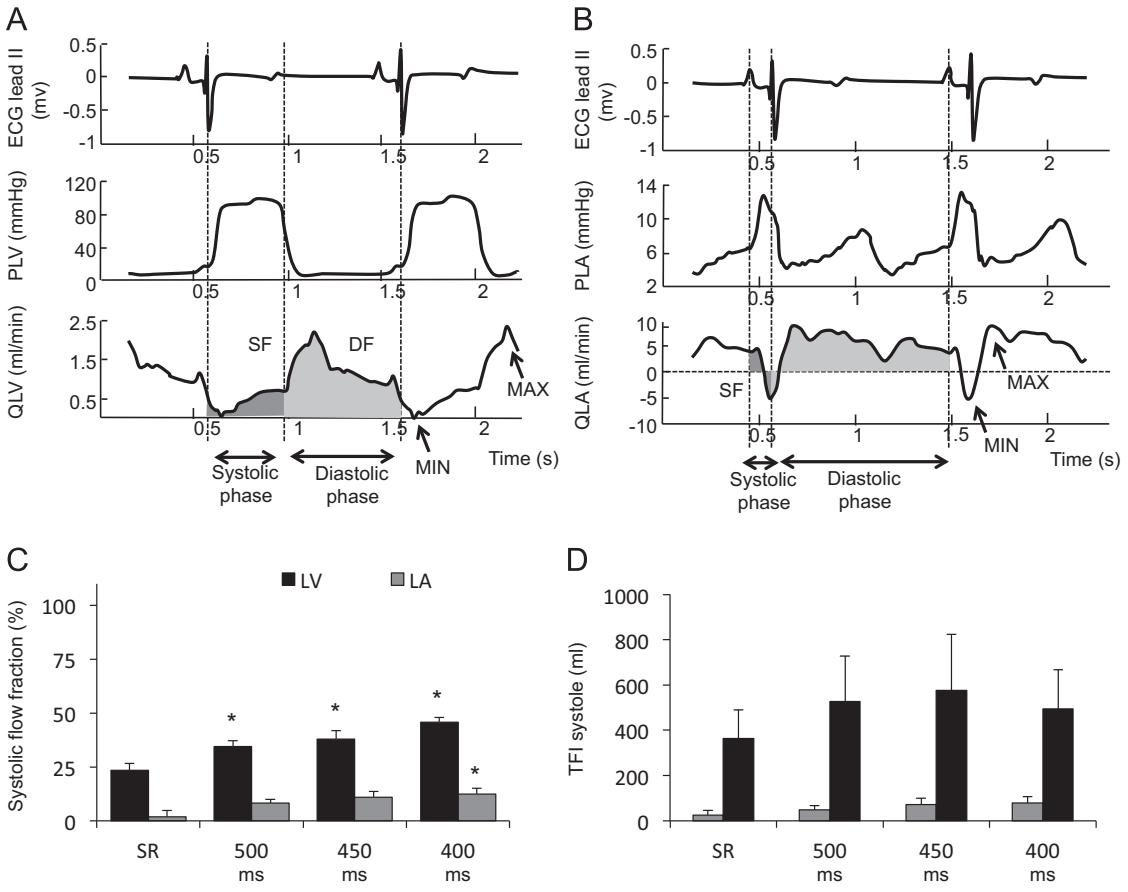

Figure 3 Calculation of systolic and diastolic fraction of flow. Systolic phase in indicated in *dark gray* and diastolic phase in *light gray* in left ventricular (LV; **A)** and left atrial (LA; **B)** phasic flow pattern. Minimum (MIN) and maximum (MAX) flow are indicated in the flow signal. From the flow signal of LV and LA, systolic flow fraction **(C)** and time–flow integral during systole (TFI) **(D)** were calculated. *$P \leq .05$ vs baseline.

the model with the lowest Akaike information criterion. $P < .05$ was considered significant.

Results

Phasic atrial flow pattern

The atrial flow signal showed a phasic pattern during every cardiac cycle. Both atrial and ventricular flow patterns consistently showed a small decrease during opening and closing of the aortic valve (Figure 2A, gray arrows). As expected, ventricular flow decreased during ventricular systole.[19,20] Similarly, a consistent decrease in atrial flow was observed during atrial activation (Figure 2A, black arrows). In principle, the decrease in atrial flow during atrial activation could be caused by either the increase in atrial pressure during the atrial contraction or the atrial contraction itself. When 2:1 AV block occurred during atrial pacing, the atrial pressure alternated between large increases, when the atria contracted against a closed mitral valve (isovolumetric contraction), and much smaller increases, when the atria contracted with an open mitral valve (Figure 2B). The decrease in atrial coronary flow was comparable for both types of contractions, indicating that the atrial contraction itself impedes atrial coronary blood flow (Figure 2B, black arrows). In 8 of 11 animals, atrial flow reversed during atrial contraction. The minimum in atrial flow (–0.76 ± 0.64 mL/min during SR) was reached at the end of atrial systole (Figure 3B). In the LV, flow reversed in 4 of 11 animals (minimum flow during SR –0.2 ± 0.9 mL/min). In both the LA and LV, maximal flow was reached in the early diastolic phase (Figures 3A and 3B). Atrial systole is short compared to ventricular systole. In the LA, 1.8% ± 2.9% of the total coronary flow occurred during atrial systole (Figure 3C) and 98.2% ± 2.9% during diastole. In the LV, 23.5% ± 3.3% of total ventricular flow occurs during ventricular systole and 76.5% ± 3.3% during diastole. The TFIs are shown in Figure 3D.

Response to atrial pacing

As heart rate increases, the diastolic period becomes significantly shorter in both LA and LV. LV diastolic time per heart beat was 52% ± 3% during SR, 41% ± 2% during 500-ms pacing, 37% ± 2% during 450-ms pacing, and 35% ± 2% during 400-ms pacing ($P < .01$ vs SR). The time–flow integral (TFI) was calculated during diastole and systole (Figure 3D) for both LA and LV. TFIs showed a trend toward an increase in both LA and LV with incremental pacing, but this was not statistically significant. The contribution of the systolic flow fraction gradually increased with pacing rate, both in the LA and in the LV (Figure 3C);

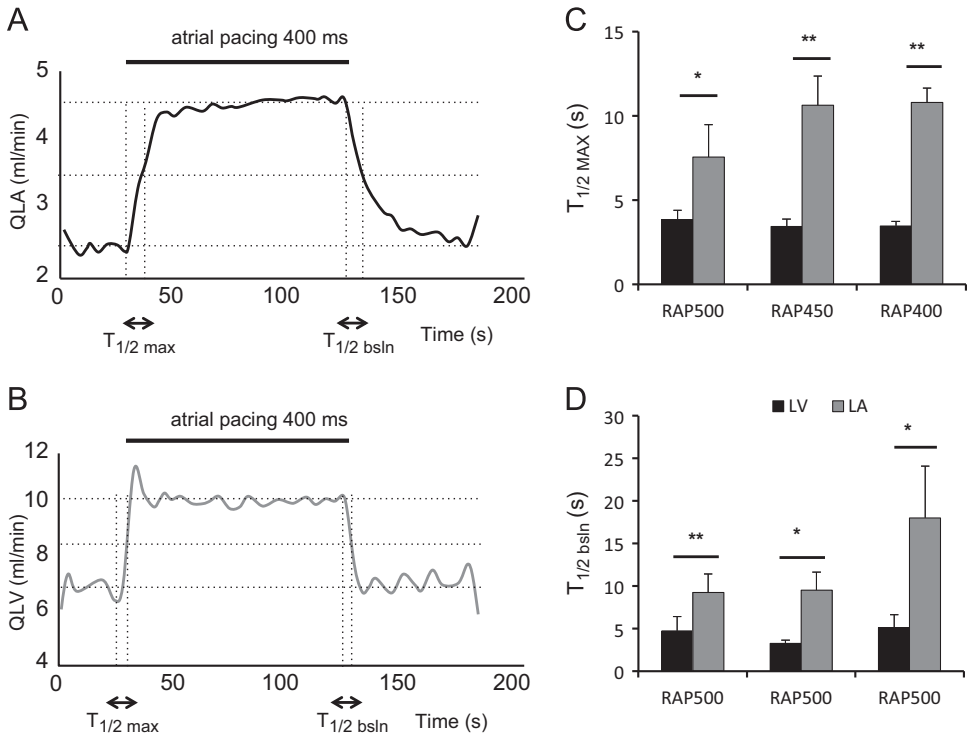

Figure 4 Kinetics of flow during pacing. **A:** Example of filtered flow signal in the left atrium (LA; **A**) and left ventricle (LV; **B**) with atrial pacing at 400 ms. The time to reach half-max ($T_{1/2MAX}$) and half-baseline ($T_{1/2bsln}$) of the flow signal are indicated in the signal. Calculation of $T_{1/2MAX}$ **(C)** and $T_{1/2bsln}$ **(D)** during pacing at cycle length of 500, 450, and 400 ms are shown. $*P \leq .05$; $**P \leq .01$ vs LA.

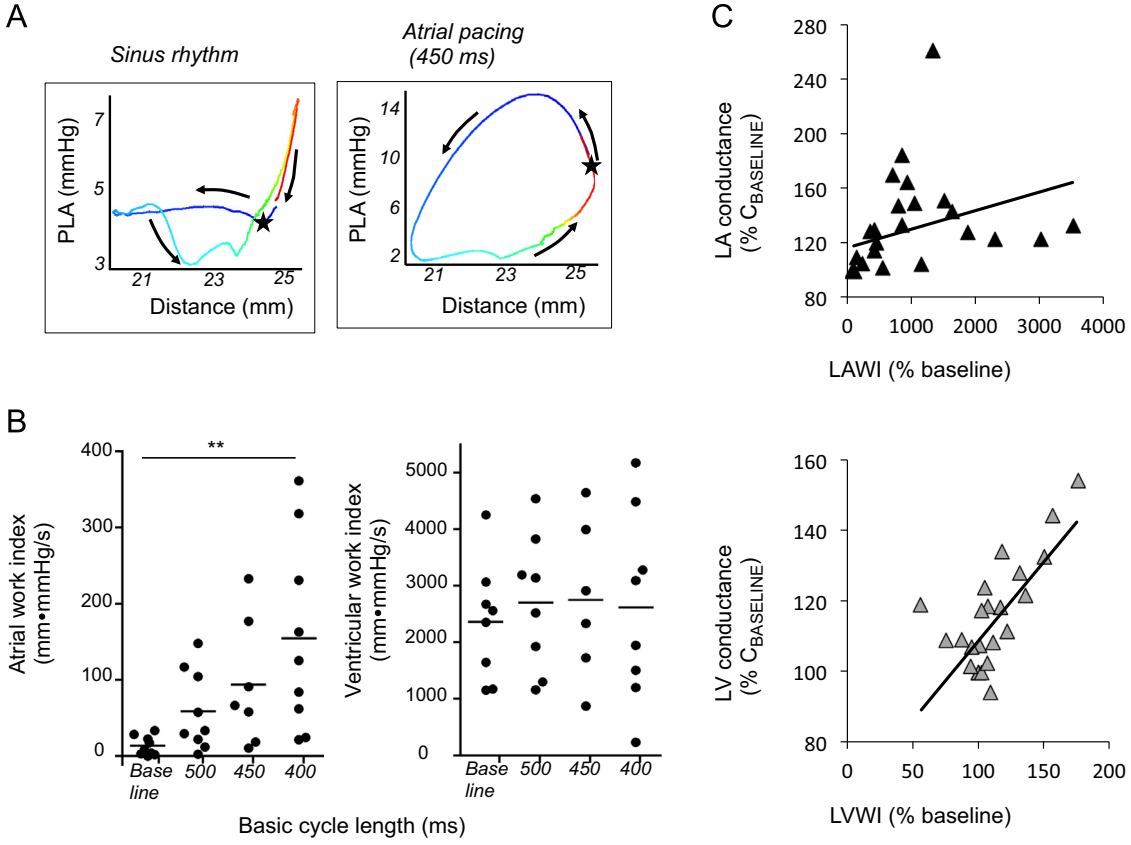

Figure 5 Work–conductance relationship during pacing. **A:** Example of atrial distance–pressure relationship. **B:** Atrial work index during baseline and atrial pacing at cycle length of 500, 450, and 400 ms. **C**: Correlation between left atrial work index (LAWI) and left atrial (LA) conductance expressed as percentage of baseline. **D:** Correlation between left atrial work index (LVWI) and left ventricular (LV) conductance expressed as percentage of baseline. $**P \leq .01$ vs baseline.

correspondingly, the contribution of diastolic flow decreased.

We previously showed that the average atrial and ventricular coronary flow increases with increasing pacing rate.[16] Figures 4A and 4B show the time course with which atrial and ventricular coronary flow respond to a period of pacing at a basic cycle length of 400 ms. LA flow reacted to pacing by increasing 120% ± 6%, 143% ± 16%, and 146% ± 21% of baseline flow at 500, 450, and 400 ms, respectively. LV flow increased 125% ± 10%, 125% ± 12%, and 121% ± 11% at the same respective cycle lengths. Both after the onset and cessation of pacing, the response of atrial flow appears to be slower than that of ventricular flow (Figure 4A vs 4B). At the start of pacing, the half-time was calculated to reach the steady-state coronary flow during pacing ($T_{1/2MAX}$; Figure 4A). After the cessation of pacing, the half-time to return to baseline coronary flow ($T_{1/2bsln}$; Figure 4A) was calculated. At all pacing cycle lengths investigated, the response time of flow to pacing was significantly slower in the LA than in the LV, both after the onset and after the cessation of pacing (Figures 4C and 4D).

Relationship between flow and work

To investigate the relationship between atrial work and atrial vascular tone, pressure–distance loops were measured simultaneously with coronary flow measurements. LAWI was 13 ± 4 mm*mmHg/s during SR and showed a cycle length dependent increase ($P = .0059$), with LAWI of 58 ± 16, 93 ± 29 and 154 ± 39 mm*mmHg/s at basic cycle length of 500, 450, and 400 ms, respectively (Figure 5B, left). LVWI was significantly higher during SR and at every pacing rate compared to LAWI ($P < .001$, Figure 5B, right). The average conductance was 0.042 ± 0.007 in the LA branch and 0.078 ± 0.011 in the LV branch. In agreement with the increase in LAWI, atrial pacing significantly increased LA conductance (data not shown, $P < .001$) from 100% at baseline to 112% ± 4% at 500 ms ($P > .05$, NS), 140% ± 9% at 450 ms ($P < .001$), and 156% ± 13% at 400 ms ($P < .001$). LV conductance also increased significantly with pacing ($P < .001$). A positive correlation was found during RA pacing between LAWI and the increase in LA conductance (Figure 5C, top). The slope 0.052 (95% confidence interval [CI] 0.016–0.088) is significantly different from zero ($P = .012$). As expected, LVWI and LV conductance also correlated significantly with a slope of 0.288 (95% CI 0.112–0.464; $P = .003$; Figure 5C, bottom).

Second, the relationship between atrial workload and coronary conductance was investigated by administration of ACh during atrial pacing at 450 ms. ACh-induced reduction in atrial contractility greatly reduced the phasic decrease in the atrial blood flow pattern (Figure 6A). During ACh infusion, atrial monophasic action potentials from the LA endocardial free wall were recorded. ACh administration resulted in shortening of the action potential (Figure 6B, inset), thereby reducing atrial contractility and active atrial work. The correlation between atrial work index and conductance had a slope of 1.01 (95% CI 0.83–1.20, $P < .001$; Figure 6B). At the same concentration of ACh, the ventricular action potential duration was not affected, as indicated by the lack of effect on QT time (236 ± 15 ms for baseline vs 230 ± 18 ms during ACh infusion, $P = .78$).

Atrial conductance was compared between baseline condition and the concentration of ACh that resulted in an approximately 50% reduction in LAWI (Figure 6B). A reduction in action potential duration at 80% repolarization (APD_{80}) to 33% ± 15% of baseline ($P = .02$) resulted in a reduction in LAWI to 47% ± 2% of baseline (Figure 6C). This was accompanied by a decrease in LA vascular conductance to 24% ± 8% of baseline (Figure 6D). P_{RA} and P_{Ao} did not change significantly, but P_{LA} increased significantly from 6.20 ± 1.01 mm Hg to 7.07 ± 1.11 mm Hg ($P = .03$). The effect of ACh on ventricular systolic function was evaluated by calculating the slope of the positive upstroke of the LV pressure curve (+dP/dt). The +dP/dt was unchanged, as was the LVWI (data not shown). Accordingly, LV conductance was not significantly influenced by ACh administration, as expected from the lack of effect on LV work.

Response to AF

During AF, the atrial flow pattern was irregular (Figure 7A). The average atrial conductance increased significantly during the first few minutes of AF. There was a trend toward an increase in LV conductance as well, but this was not statistically significant. The kinetics of the response in average conductance were measured for LA and LV flow after cessation of AF. LA vascular conductance was transiently elevated above baseline values (ie, period preceding the induced AF episode), reflecting a hyperemic phase (Figure 7B). In contrast, LV vascular conductance did not display a hyperemic phase. The ratio between the integrals of the area above and below baseline conductance was significantly higher for the LA compared to the LV (Figure 7C; P = .04).

Discussion

In this study, we investigated the dynamic regulation of atrial coronary blood flow in detail and compared it to that of the ventricle in normal adult pigs. The atrial coronary flow pattern was assessed during SR, atrial pacing, and acute AF.

Atrial flow pattern

A consistent decrease in atrial flow was observed during atrial contraction. This pattern is similar to the pattern found in other studies on LA branches in patients and dogs measured by a Doppler guidewire, Doppler crystals, and laser Doppler optical fibers.[6,21–23] In principle, this phasic decrease could be caused by the rise in atrial pressure or by the atrial contraction itself. However, when 2:1 AV block occurred during atrial pacing, every atrial contraction resulted in a similar decrease in atrial flow whereas atrial pressure alternated depending on whether the atrium contracted against an open or a closed mitral valve. In addition, we showed that

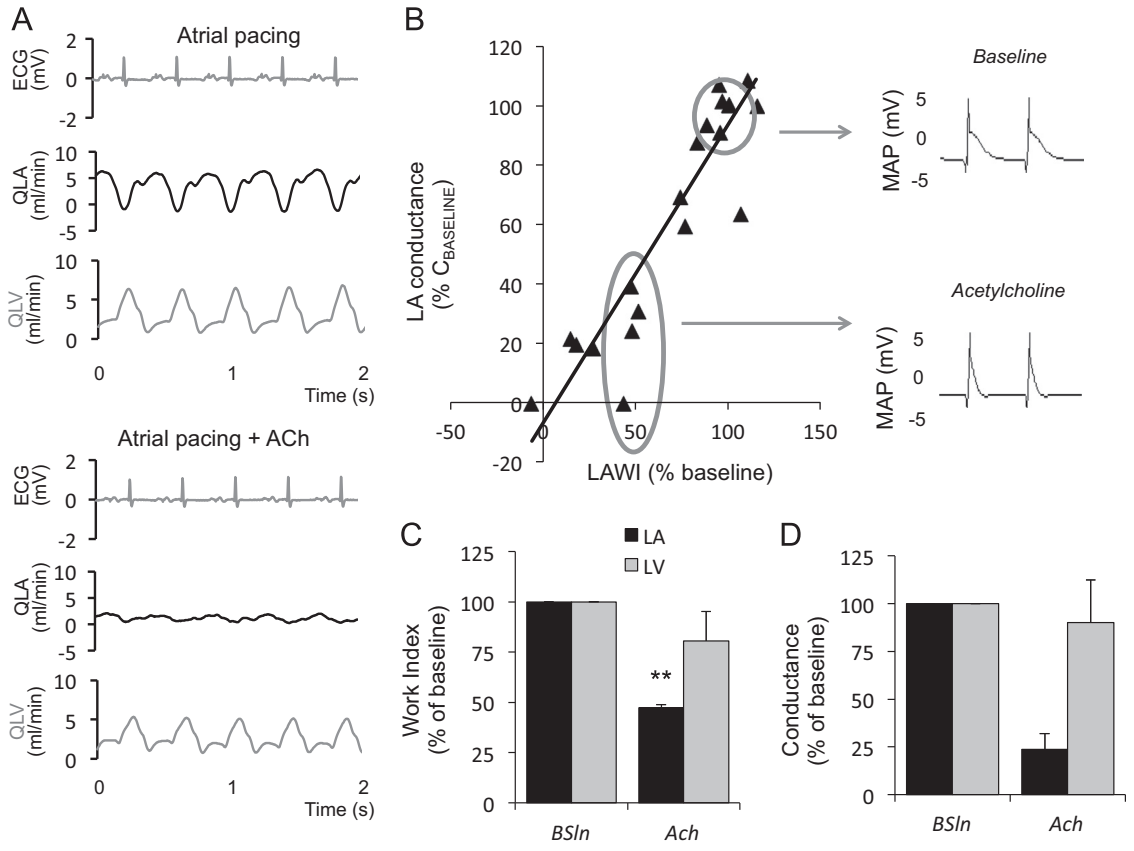

Figure 6 Work–conductance relationship during acetylcholine (ACh) infusion. **A:** Correlation between left atrial work index (LAWI) and conductance during ACh. Datapoints were divided into 2 groups: baseline and 50% reduction in LAWI. Examples of monophasic action potentials are shown for the 2 groups. Work index expressed as percentage of baseline **(B)** and conductance expressed as percentage of baseline and an example of atrial and ventricular flow **(C)** in the baseline and Ach groups are shown. $^{**}P \leq .01$ vs baseline. LA = left atrium; LV = left ventricle.

during ACh administration, the decrease in atrial contractility led to the disappearance of the decrease in atrial flow during atrial contraction. This is in agreement with studies of dogs in which premature ventricular stimulation caused a fluctuation in atrial pressure without affecting atrial coronary flow and increasing atrial contractility by administration of isoproterenol affected atrial flow but not atrial pressure.[23,24] In most pigs in our study, atrial flow reversed during atrial contraction. In an earlier study on dogs, reversal of atrial flow during atrial contraction was observed only during administration of isoproterenol and not under baseline conditions.[23]

In the LV, where the decrease of coronary flow during contraction has been investigated extensively, intramyocardial pump action is the major factor impeding systolic flow.[25,26] Our results are consistent with a similar mechanism affecting flow in the LA, which may have important consequences during AF. We recently reported that acute AF leads to a supply–demand mismatch, resulting in atrial lactate production. Although organized atrial contractility is absent during AF, the local contraction rate increases dramatically. Because atrial energy demand increases during AF, the negative effect of rapid local contractions on local flow may exacerbate the supply–demand mismatch.

The systolic contribution to total coronary flow was calculated for atrium and ventricle. The SF of total ventricular flow during ventricular contraction was 23.5% ± 3.3%, comparable to values of 25% to 35% reported in literature.[21,27] In the LA, flow during atrial systole contributes 1.8% ± 2.9% to total atrial flow. Our results on phasic atrial flow show that atrial systole is responsible for the transient decrease in atrial flow, often leading to a reversal of atrial flow; consequently, it constitutes only a small fraction of total atrial coronary flow.

Relationship between coronary flow and myocardial work

In the LA, the diastolic time was much longer than in the LV; as discussed earlier, flow was strongly diminished during atrial systole. As a consequence, the relative contribution of systolic flow to total flow was smaller in the LA, although it increased gradually with increased heart rate. During atrial pacing, the LAWI increased in a cycle length–dependent manner, in agreement with an earlier study on goats using distance–pressure loops for the RA that are similar to the LA loops in our study.[28] The increase in work index during pacing would be expected to increase atrial demand and thus lead to an increase in atrial coronary flow. Indeed, we observed a positive correlation between LA vascular conductance and work index.

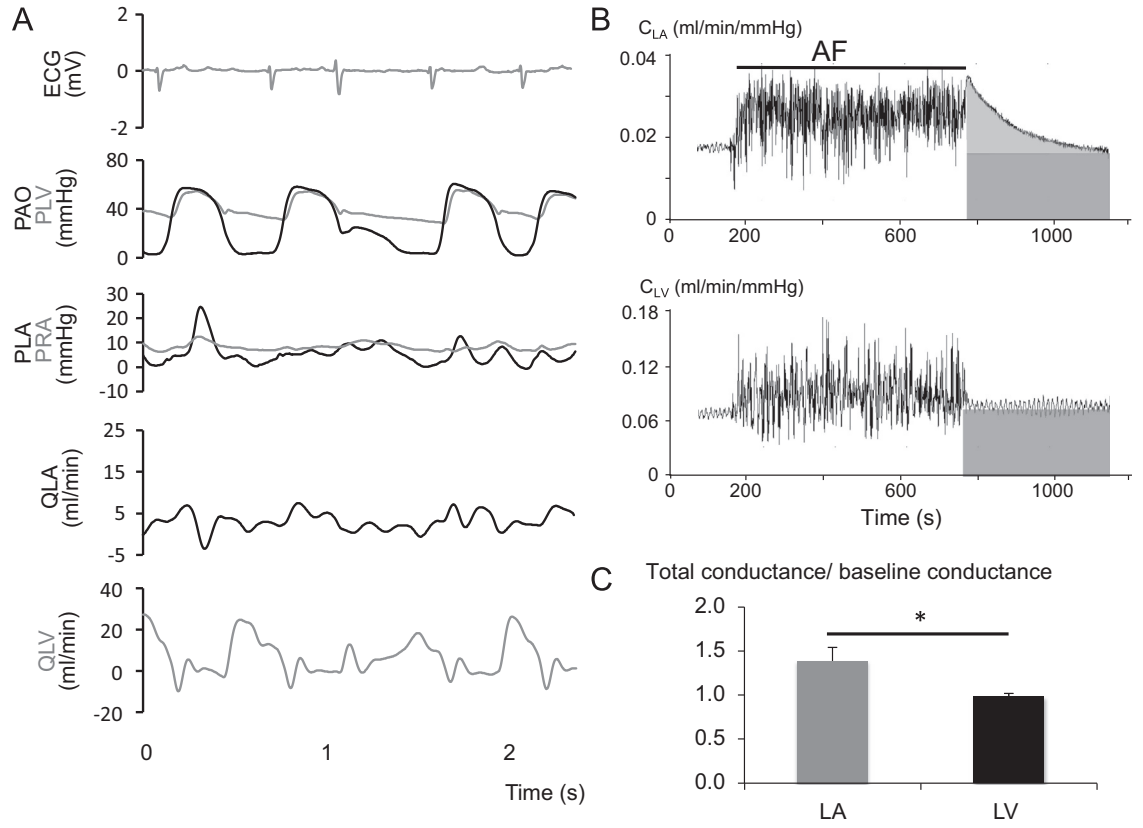

Figure 7 Atrial fibrillation (AF). **A:** Example of flow signals during AF. **B:** Conductance in left atrial (LA) and left ventricular (LV) artery before, during, and after an episode of acute AF. The hyperemic phase after cessation of AF was determined as the ratio of the time integral of total flow *(light gray + dark gray areas)* to baseline flow *(dark gray area).* **C:** Hyperemic phase was significantly larger in the LA than in the left ventricle (LV) $*P = .04$.

The total amount of myocardial work performed is the sum of external and internal work. External work reflects mechanical work during atrial or ventricular contraction to pump blood and is the calculated as the area within a pressure–volume loop. Internal work is used to elongate elastic and viscous elements in sarcomeres and connective tissue and therefore is proportional to wall stress. In addition to mechanical work, energy is used within cells to maintain ion homeostasis.

The response time of coronary flow to an increase in heart rate was significantly slower in the LA than in the LV. This may indicate either a difference in the rate of metabolic changes or a difference in the rate of response to a metabolic change. We recently showed that compared to the LV, the LA has a lower coronary flow reserve but a higher oxygen extraction reserve (due to lower atrial extraction under baseline conditions). Pacing led to an increase in both atrial coronary flow and oxygen extraction.[16] Although the time resolution of oxygen extraction measurements was low, it is conceivable that in response to an increase in atrial demand, atrial oxygen extraction increases more rapidly than atrial coronary flow.

During intracoronary infusion of ACh, ventricular vascular conductance, ventricular contractility, and QT time were not affected, whereas atrial action potential duration, contractility, and coronary flow were reduced. However, in the pig ventricle, ACh has a direct vasoconstrictor effect,[29] and we did observe a reduction in ventricular vascular conductance at much higher ACh concentrations. Therefore, our interpretation that the decrease in atrial work during ACh infusion causes the reduction in atrial flow would be incorrect if the atrial vasculature were more sensitive than the ventricular vasculature to ACh.

Atrial fibrillation

We recently showed that AF causes an increase in atrial coronary vascular conductance in pigs.[16] Interestingly, White et al[6] reported that increasing wall stress by volume expansion to the same level observed during AF caused significantly less increase in atrial myocardial blood flow compared to AF. This finding indicates that total energy expenditure, rather than wall stress *per se,* is the major determinant of atrial coronary blood flow during AF. The rapid and irregular contraction of atrial cardiomyocytes during AF likely contributes greatly to atrial energy expenditure while virtually no useful external work is delivered.

The time required for atrial coronary blood flow to return to baseline values after AF was significantly longer than after atrial pacing with a basic cycle length of 400 ms. After a short episode of AF, atrial vascular conductance remained elevated above the baseline level for a prolonged time. This finding reflects a hyperemic phase after an episode of AF. We previously showed that short-term AF causes a

supply–demand mismatch, marked by an increase in atrial lactate production.[16] During AF, active atrial pump function is abolished but atrial myocytes are contracting rapidly, increasing energy expenditure. We showed in the present study that atrial contraction in itself impedes atrial flow. It could be expected that local atrial contractions during AF impede atrial flow by local compression of the vessel wall. In addition, the diastolic phase, which normally provides most of atrial myocardial perfusion, is very short and irregular during AF. This resulting impediment of atrial flow may contribute to the occurrence of oxygen debt during AF and result in a hyperemic period after the return to normal SR. After the cessation of AF, the impediment of atrial flow is relieved immediately while the oxygen debt persists, resulting in a transient elevation of vascular conductance.

Study limitations

The experiments were performed in open-chest experiments under anesthesia. Opening of the pericardium may influence atrial wall stress and therefore atrial energy consumption and blood flow, as well as the mechanical interactions between the cardiac chambers.[30] Nevertheless, the waveform characteristics found in this study under open-chest conditions are very similar to those measured in humans using a Doppler guidewire in a closed-chest setting.

Conclusion

The atrial flow pattern showed a consistent decrease during atrial systole. This was caused by the atrial contraction itself rather than atrial pressure. Not only did atrial systole cause flow to decrease, it even reversed in most animals. The systolic phase contributes to only 2% of total atrial flow. However, the contribution of systolic flow fraction to total flow increased with increasing heart rate in both atrium and ventricle. Atrial vascular conductance is correlated with the performed external work. The flow response to acute changes in heart rate, however, was slower in the atrium compared to the ventricle. In addition, the occurrence of hyperemia after the cessation of short-term AF in healthy pigs supports our earlier findings of a supply–demand mismatch in AF.

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CLINICAL PERSPECTIVES

Regulation of the atrial blood supply is essential to maintaining the supply–demand balance, especially during periods of increased atrial demand such as atrial fibrillation. In this study, we investigated the dynamic regulation of atrial coronary blood flow in healthy pigs. Atrial coronary flow is positively correlated to atrial workload but responds more slowly to increased heart rate than ventricular flow. The atrial contraction itself strongly impedes atrial flow. After a period of acute atrial fibrillation, atrial flow shows a phase of reactive hyperemia, consistent with the occurrence of supply–demand ischemia. A fuller understanding of the conditions under which atrial supply falls short of demand may lead to novel strategies for preventing atrial remodeling and the progression of atrial fibrillation.

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