The effects of atrial fibrillation on coronary blood flow and performance of ischaemic myocardium in dogs with coronary artery stenosis

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SUMMARY

1. Atrial fibrillation may impair coronary blood flow by tachycardia and reflex vasoconstriction. It has not been documented, however, whether in the presence of coronary stenosis atrial fibrillation exceeds the effects of rhythmmic atrial tachycardia.

2. The effects of experimentally induced atrial fibrillation compared with atrial tachycardia, therefore, were tested in 22 anaesthetized dogs. Stenosis of the left anterior descending coronary artery was induced to reduce coronary blood flow by about 40%.

3. In the presence of coronary stenosis, atrial fibrillation (ventricular rate: 234 ± 21 beats/min) reduced coronary blood flow from 58 ± 7 to 44 ± 8 ml min⁻¹ 100 g⁻¹ (P < 0.001, mean ± SEM) and subendocardial segment shortening (ultrasonic crystals) from 12 ± 2 to 4 ± 2% (P < 0.0025), and resulted in a lactate production of 30 ± 1% (P < 0.005 vs sinus rhythm).

4. Atrial tachycardia (heart rate: 216 ± 21 beats/min, NS vs atrial fibrillation) did not significantly change coronary blood flow and reduced segment shortening to 7 ± 3% (P < 0.05 vs atrial fibrillation). Significant lactate production did not occur.

5. Since mean arterial pressure fell from 100 ± 4 mmHg at sinus rhythm to 89 ± 3 mmHg (P < 0.01) during atrial fibrillation but not during atrial tachycardia, it was held constant in 13 dogs by a pressurized blood reservoir. Coronary blood flow, however, fell from 43 ± 6 to 36 ± 5 ml min⁻¹ 100 g⁻¹ (P < 0.0025).

6. Thus atrial fibrillation may reduce coronary blood flow and induce myocardial ischaemia in the presence of coronary stenosis in excess of atrial tachycardia.

Key words: arrhythmia, atrial fibrillation, coronary blood flow, myocardial ischaemia.

Abbreviations: LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery.

INTRODUCTION

Atrial fibrillation is a common complication of acute myocardial infarction which frequently occurs intermittently and lasts in 50% of the cases for 30 min or less [1, 2]. The effect of atrial fibrillation on coronary blood flow is, therefore, of particular clinical importance. The most prominent manifestations of atrial fibrillation are tachyarrhythmia and deterioration of cardiac output [3, 4]. A fall of arterial pressure is prevented in part by a compensatory systemic vasoconstriction. Activation of the sympathetic nervous system [5, 6] and renin–angiotensin system [7] have been identified as mediators of this vasoconstriction. Thus the potential influences of atrial fibrillation on coronary circulation are complex. Most investigators report an increase in coronary blood flow during atrial fibrillation which is interpreted as a response to an augmented myocardial metabolic demand [4]. Two phenomena, however, indicate that metabolic coronary regulation is impaired during atrial fibrillation: (1) coronary oxygen extraction is increased, while (2) coronary blood flow rises less than expected considering the increase in heart rate [8]. In fact, atrial fibrillation reduces coronary blood flow when metabolic coronary regulation is blunted by drug-induced maximal coronary dilatation [8–10].

The effect of atrial fibrillation on coronary blood flow in the presence of coronary stenosis is not known. Tachycardia induces myocardial ischaemia in the presence of critically restricted coronary blood flow mainly due to an augmented myocardial metabolic demand [11, 12]. In addition, shortening of diastole may diminish coronary blood flow [12, 13]. Since basic differences exist between the haemodynamic sequelae of rhythmic atrial tachycardia and tachyarrhythmia due to atrial fibrillation, it is conceivable that both arrhythmias also differ in their
effects on coronary blood flow. The present study was designed to determine these differences. Since a fall of arterial pressure occurs during experimental atrial fibrillation, complementary experiments were performed with constant atrial pressure.

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**METHODS**

Experiments were performed on 22 mongrel dogs of either sex weighing 29±2 kg. Anaesthesia was initiated with ethyl-thiobarburate (10 mg/kg, intravenously), α-chloralose (40 mg/kg) and urethan (250 mg/kg). Additional α-chloralose and urethan were injected to suppress the medial ocular reflex. Dogs were intubated and ventilated with a Starling respirator at an end-expiratory pressure of 5 cmH₂O. Arterial blood gases, pH and packed cell volume were measured every half-hour, and ventilation was adjusted and sodium bicarbonate or saline was infused to provide values in a normal range. A Courand catheter (F8) was advanced from the left brachial artery to the ascending aorta and pressure was measured with a pressure transducer (Gould-Statham P23 Db). Left ventricular pressure was measured by a catheter tip micro-manometer (Millar PC-350) which was introduced through the right brachial artery. Left ventricular dP/dt was continuously calculated by electronic differentiation. A Courand catheter (F8) was placed via the left jugular vein into the distal great cardiac vein. The chest was opened in the 5th left intercostal space and the heart was suspended in a pericardial cradle.

A schematic diagram of instrumentation of the heart is presented in Fig. 1. The left anterior descending coronary artery (LAD) was dissected free from connective tissue 2–3 cm distal from its origin. A segment was prepared long enough to attach (from proximal to distal) an electromagnetic flow probe, mechanical occluder, and hydraulic balloon occluder. Coronary blood flow was measured by an electromagnetic flowmeter (Gould-Statham SP 2202). The mechanical occluder consisted of a wire (diameter 1.5 mm) which could be retracted into a PVC tube by a micrometer screw. Thus graded stenosis could exactly be adjusted. The balloon occluder served to set mechanical zero for the flowmeter and to determine reactive hyperaemia. An additional segment of the left circumflex coronary artery (LCX) was prepared and another flow-probe was attached to this.

A pair of ultrasonic crystals (1.8 mm × 1.8 mm × 1.2 mm in diameter) was implanted into the subendocardium approximately 1 cm apart, taking note of the precautions previously reported [14, 15]. The ischaemic region was defined by cyanosis during brief occlusions of the LAD and crystals were placed in the centre of this region. The characteristics of the sonomicrometer used in this study (UM3, Oswald, Düsseldorf, West Germany) have previously been reported in detail [16]. Subendocardial position of the crystals was verified by post-mortem examination. Myocardium supplied by the LAD and LCX, respectively, distal to the flow probes was delineated by dye injection, excised and weighed. All measured parameters were displayed on an eight-channel linear recorder (Linear Corder Mark V, Watanabe). Lactate was measured in samples from the aortic and coronary venous catheters, by an enzymatic microassay requiring 1 ml of blood [17].

In 13 dogs (group 2), both femoral arteries were cannulated with large bore polyethylene cannulas (3.5 mm × 3.5 mm × 6 mm) after anticoagulation with heparin (initially: 750 units/kg, followed by 425 units/kg every 2 h). One cannula was connected by tubing to a pressurized glass reservoir. The temperature of this reservoir was maintained at 37°C. Blood was returned via a roller pump (American Optical) to the other femoral artery. The reservoir (400 ml) was filled by blood previously obtained from a donor dog. Mean arterial blood pressure was thus continuously maintained constant by autotransfusion from the reservoir to the femoral artery throughout the experimental protocol.

**Experimental protocol**

After surgical preparation, a period of at least 30 min was observed for stabilization. Baseline haemodynamic measurements and arterial and coronary sinus blood samples were obtained for lactate determination. Coronary stenosis was induced which reduced reactive hyperaemia after a 30 s coronary occlusion to an 18±8% increase in coronary flow (P < 0.0005 vs pre-stenosis). Atrial fibrillation was induced as previously described [6, 8]. The left atrial appendage was electrically stimulated at a frequency of 50 Hz, an amplitude of 2–5 V and a stimulus duration of 2 ms (HSE stimulator P, Sachs Elektronik). This procedure has been shown to induce atrial fibrilla-
tion equivalent to local application of acetylcholine [6]. Recordings were obtained during sinus rhythm, atrial fibrillation and atrial pacing. Atrial pacing was adjusted to a rate similar to the average ventricular rate during atrial fibrillation. For clarity, we will refer to the rhythmic atrial pacing as 'atrial tachycardia' as distinguished from 'atrial fibrillation'. Between the atrial fibrillation and atrial tachycardia protocols, a period was allowed for haemodynamic parameters to return to baseline (15 min on average). Each rhythm was maintained for at least 10 min or until all values were stable (average 15 min). After termination of atrial fibrillation or atrial tachycardia, respectively, all parameters returned to pre-stimulation baseline, suggesting a reversible effect of the arrhythmias. In addition, four dogs showed the same changes during a repeated period of atrial fibrillation performed after completion of a first atrial fibrillation and tachycardia protocol. Occasionally, atrial fibrillation persisted for as long as 45 min after discontinuing atrial stimulation. As previously observed in a different model [6, 8] and by other investigators [18], all variables measured in this study remained unchanged when atrial fibrillation spontaneously persisted. Thus electrical stimulation alone did not affect our results. Group 1 consisted of nine dogs in which variation of atrial pressure was allowed. In group 2 (n = 13) arterial pressure was held constant after the application of coronary stenosis as described above.

Data analysis

Mean coronary blood flow was normalized to 100 g of myocardium supplied by the LAD or LCX, respectively, distal to the flow probes. Coronary conductance was calculated by dividing mean coronary blood flow by mean aortic blood pressure. All values are expressed as mean ± sem. A P value of less than 0.05 was considered significant. Wilcoxon's test for paired samples was used to compare data during atrial fibrillation vs sinus rhythm and atrial tachycardia vs sinus rhythm. Differences were calculated and compared by Wilcoxon's test for paired samples to analyse a potential difference between the effect of atrial fibrillation and atrial tachycardia. The changes from sinus rhythm to atrial fibrillation and sinus rhythm to atrial tachycardia in group 1 were compared with those in group 2 by Wilcoxon's test for unpaired samples.

RESULTS

Group 1

Fig. 2 presents an original recording from an experiment in group 1. The application of coronary stenosis resulted in a fall of left ventricular peak pressure and dP/dt max and arterial pressure. Left ventricular end-diastolic pressure increased from 3 to 6 mmHg. LAD coronary blood flow was reduced from 43.5 to 20.0 ml/min. Systolic and diastolic segment length rose without a major change of systolic segment shortening. With the onset of atrial fibrillation, heart rate rose in this experiment from 172 to 290 beats/min. On an average, left ventricular peak pressure and dP/dt max and arterial pressure fell, while left ventricular end-diastolic pressure rose to 8 mmHg. Mean LAD coronary blood flow fell from 20.0 to 16.8 ml/min and the systolic segment shortening decreased by 30%.

The coronary effects of atrial fibrillation are summarized in Fig. 3(a). LAD coronary blood flow was reduced by stenosis by about 40% of control while LCX coronary flow increased by about 10%. During atrial fibrillation, LAD coronary blood flow fell from 58 ± 7 to 44 ± 8 ml min⁻¹ 100 g⁻¹ (P < 0.001) while LCX coronary flow rose from 107 ± 16 to 118 ± 15 ml min⁻¹ 100 g⁻¹ (P < 0.05). Coronary conductance was reduced by coronary stenosis from 0.97 ± 0.09 to 0.60 ± 0.08 ml 100 g⁻¹ min⁻¹ mmHg⁻¹ (P < 0.002) and further decreased during atrial fibrillation to 0.50 ± 0.09 ml 100 g⁻¹ min⁻¹ mmHg⁻¹ (P < 0.01). A significant change in LAD coronary flow did not occur during atrial tachycardia (Fig. 3b). Coronary vascular conductance even increased during atrial tachycardia from 0.57 ± 0.10 to 0.63 ± 0.13 ml 100 g⁻¹ min⁻¹ mmHg⁻¹ (P < 0.025).

Systolic segment shortening fell both during atrial fibrillation and during atrial tachycardia (Fig. 4). The reduction of segment shortening was, however, consider-
Fig. 3. Effect of atrial fibrillation (AF) on coronary blood flow (a) and comparison of coronary blood flow changes during AF and atrial tachycardia (AT) (b). LCX blood flow increased during AF (a) somewhat less than during AT (two furthest left columns in b). LAD coronary blood flow was reduced by coronary stenosis and further by AF (a). LAD coronary flow did not change significantly during AT and the fall of LAD coronary flow during AF was significantly different from AT (*P < 0.005). Results shown are means ± SEM (n = 9).

Fig. 4. Effect of atrial fibrillation (AF) and atrial tachycardia (AT), respectively, on subendocardial segment shortening (a) and coronary lactate extraction (b). Segment shortening remained unchanged by coronary stenosis. AF depressed segment shortening significantly more than AT (*P < 0.025). Lactate production was significantly more pronounced during AF than during AT (**P < 0.05). Results are means ± SEM (n = 11). SR, Sinus rhythm. NS, Not significant.

ably more pronounced during atrial fibrillation than during atrial tachycardia (Fig. 4). A 30% lactate production occurred during atrial fibrillation, which was significantly different from atrial tachycardia (10%).

Table 1 summarizes the systemic haemodynamic data obtained with this protocol. Coronary stenosis induced a slight fall of mean arterial and left ventricular peak pressure. Left ventricular end-diastolic pressure rose from
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6.3 ± 1.3 to 8.3 ± 1.1 mmHg (P < 0.05) while the fall in left ventricular dP/dtmax did not achieve statistical significance. Heart rate slightly increased from 148 ± 11 to 160 ± 12 beats/min (P < 0.05), and further rose during atrial fibrillation to 234 ± 21 beats/min (P < 0.025). On average, left ventricular peak pressure and dP/dtmax and mean arterial pressure fell, while left ventricular end-diastolic pressure rose to 13.3 ± 1.2 mmHg (P < 0.025).

A significant difference was not found between baseline sinus rhythm before atrial fibrillation and baseline sinus rhythm before atrial tachycardia. Atrial tachycardia increased heart rate from 153 ± 13 to 216 ± 21 beats/min (P < 0.005), not significantly different from the increase in heart rate during atrial fibrillation. Mean arterial pressure and left ventricular peak and end-diastolic pressure remained stable during atrial tachycardia, while left ventricular dP/dtmax slightly increased. Significant differences were found between atrial tachycardia and atrial fibrillation in left ventricular peak pressure (105 ± 8 vs 74 ± 4, P < 0.005) and dP/dtmax (1625 ± 190 vs 1091 ± 87, P < 0.005).

**Group 2 (constant arterial pressure)**

The purpose of this protocol was to determine to what extent the fall of coronary blood flow during atrial fibrillation was due to hypotension. Arterial pressure was therefore, designedly maintained constant. As is shown in Table 2, the effects of atrial fibrillation and tachycardia were otherwise very similar to group 1. Fig. 5(a) shows that coronary blood flow was still reduced by atrial fibrillation. Fig. 5(b) compares the effects of atrial fibrillation and tachycardia on coronary flow in this group. The decrease in coronary blood flow during atrial tachycardia was not statistically significant, while during atrial fibrillation coronary blood flow fell by 15 ± 4% (P < 0.0025), significantly different (P < 0.05) from atrial tachycardia. The fall of coronary blood flow during atrial fibrillation in group 2 was not significantly different from that in group 1 (−25 ± 8).

**DISCUSSION**

Previous studies have documented that vasodilatation occurs during atrial fibrillation in the regulating coronary vascular system [4, 6, 8]. We have assumed, however, that coronary dilatation may not be adequate to compensate for the augmented myocardial metabolic demand [6, 8]. The reason for this assumption has been that coronary oxygen extraction increases during atrial fibrillation but not during rhythmic atrial tachycardia [6, 8]. Atrial fibrillation results in a considerably smaller increase in coronary blood flow than atrial tachycardia, although the increase in myocardial oxygen consumption is similar [6]. A coronary constrictive component appears to interfere with metabolic regulation of coronary blood flow. This coronary constrictive component becomes obvious when metabolic coronary regulation is blunted. During maximal

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**Table 1. Haemodynamic changes in group 1 (arterial pressure not constant)**

Results are means ± SEM (n = 9). Statistical significance: *P < 0.05 vs pre-stenosis; †P < 0.025 vs sinus rhythm; ‡P < 0.005 vs atrial fibrillation.

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<th>Pre-stenosis</th>
<th>Coronary stenosis</th>
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<td></td>
<td>Sinus rhythm</td>
<td>Sinus rhythm</td>
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<tr>
<td>Mean arterial pressure (mmHg)</td>
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<td>100 ± 4*</td>
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<tr>
<td>Left ventricular peak pressure (mmHg)</td>
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<td>Left ventricular end-diastolic pressure (mmHg)</td>
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<td>dP/dtmax (mmHg)</td>
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<td>1790 ± 150</td>
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<td>Heart rate (beats/min)</td>
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<td>160 ± 12†</td>
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<td>Arterial lactate concentration (µmol/l)</td>
<td>857 ± 145</td>
<td>786 ± 124</td>
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**Table 2. Haemodynamic changes in group 2 (arterial pressure constant)**

Results are means ± SEM (n = 13). Statistical significance: *P < 0.05 vs pre-stenosis; †P < 0.05 vs sinus rhythm; ‡P < 0.05 vs atrial fibrillation.

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<th>Pre-stenosis</th>
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<tr>
<td></td>
<td>Sinus rhythm</td>
<td>Sinus rhythm</td>
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<tr>
<td>Mean arterial pressure (mmHg)</td>
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<td>Heart rate (beats/min)</td>
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coronary dilatation by carboxyhemone or dipyridamole, atrial fibrillation reduces coronary blood flow [8].

The clinical relevance of these findings was limited since 'luxury coronary perfusion' was present during drug-induced maximal coronary dilatation. Patients with coronary heart disease, however, coronary metabolic regulation is exhausted as a consequence of critical coronary stenosis and coronary dilatation is the result of myocardial ischaemia. Myocardial ischaemia was generally assumed to be the most potent coronary vaso-dilatory stimulus. Data obtained during maximal pharmacological coronary dilatation, therefore, could not be extrapolated to a situation with coronary stenosis and it was questionable whether atrial fibrillation would reduce coronary blood flow in the presence of myocardial ischaemia. The present model was more adequate to the clinical situation since deterioration of segment shortening by 66% and lactate production of 30% indicated myocardial ischaemia during atrial fibrillation. The major finding of this study was that experimental atrial fibrillation depressed coronary blood flow in the presence of stenosis of the LAD while blood flow to the unrestrained LCX increased. Thus atrial fibrillation induced or aggravated myocardial ischaemia by tachycardia and a reduction of coronary flow.

The question is whether we observed a reduction of coronary blood flow by shortening of diastoles and/or deterioration of aortic pressure and thus coronary perfusion pressure since tachycardia and hypotension resulted from atrial fibrillation. Both hypotheses were tested by complementary protocols in this study. In presence of coronary stenosis, the effect of rhythmic atrial tachycardia with a heart rate similar to atrial fibrillation was compared with the effect of atrial fibrillation. Heart rate was slightly and statistically not significantly higher during atrial fibrillation than during atrial tachycardia in both groups (see Tables 1 and 2). Quantitative studies on the effect of heart rate on the non-regulating coronary vascular system have shown that coronary resistance increases by 14% when heart rate is raised by 100 beats/min [19]. Thus differences in heart rate of 9-18 beats/min between atrial fibrillation and atrial pacing may not explain the differences in coronary blood flow. In contrast to atrial fibrillation, no significant change of coronary flow occurred during atrial tachycardia. Thus the degree of stenosis was obviously severe enough to prevent an increase in coronary blood flow which was required by the augmented metabolic demand and met by the regulating LCX. These data indicate that atrial fibrillation exceeds rhythmic atrial tachycardia of similar ventricular rate in its inhibitory effect on coronary blood flow. It also exceeds atrial tachycardia in its capability to depress myocardial function. Deterioration of segment shortening was significantly more pronounced during atrial fibrillation than during atrial pacing. In addition, significant lactate production of 30% occurred during atrial fibrillation only. Thus atrial fibrillation appeared also to be more potent than atrial tachycardia in producing myocardial ischaemia in this model.

In the presence of critical coronary stenosis, coronary blood flow is highly pressure dependent [20]. The protocol in group 2 addressed the question to what extent hypotension determined the fall of coronary blood flow. Flow to the stenosed LAD fell, although significant changes in mean arterial pressure were prevented in this protocol. The fall of coronary blood flow during atrial
fibrillation in group 2 was not significantly less than in group 1 where mean arterial pressure was allowed to fall during atrial fibrillation. It is conceivable that hypotension was responsible in part for the reduction of coronary flow. However, the fall of coronary blood during atrial fibrillation was still considerably more pronounced than during atrial tachycardia where a significant reduction of coronary flow did not occur. These data suggest that tachycardia or hypotension alone or in combination do not conclusively explain the reduction of coronary blood flow by atrial fibrillation.

The mechanism by which atrial fibrillation reduces coronary blood flow in this model remains to be determined. Active coronary vasoconstriction might be involved. A number of studies has suggested that active coronary vasoconstriction may take place even in the presence of myocardial ischaemia. Some investigators have proposed this possibility for sympathetic coronary constriction [21, 22], others for the renin-angiotensin system [23, 24] or thromboxane [25]. Previous work from our group suggests a possible role of the sympathetic nervous system [6, 26]. Plasma catecholamines increase strikingly during experimental atrial fibrillation and an α-receptor blocking agent prevented the reduction of coronary blood flow in the regulating and maximally dilated coronary circulation [6, 26]. We have previously shown in anaesthetized dogs that plasma renin activity rises during atrial fibrillation from 10.8 ± 2.6 to 16.2 ± 3.0 ng of angiotensin 1 h⁻¹ ml⁻¹ [7]. In summary, it is most likely that coronary flow is influenced during atrial fibrillation by a number of factors which may reduce coronary blood flow in presence of coronary stenosis and aggravate or induce myocardial ischaemia.

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REFERENCES

