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The Effects of Atrial Fibrillation on Myocardial Blood Flow and Energetics[1] (42135)

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Abstract: The changes produced by atrial fibrillation on myocardial blood flow and energetics are unclear. Accordingly, the effects of atrial fibrillation on myocardial blood flow and oxygen consumption were studied in 18 anesthetized dogs. With atrial fibrillation cardiac output and mean aortic pressure declined. Although average myocardial blood flow and oxygen consumption did not change, the alterations in these variables correlated strongly ($r = 0.95$, $P < 0.01$). Moreover, myocardial blood flow changes correlated with those of tension time index and peak dp/dt ($r = 0.64$, $P < 0.05$). Distribution of left ventricular regional flow remained uniform irrespective of the directional changes in blood flow. However, average left ventricular inner to outer wall flow ratio declined and myocardial oxygen extraction increased. Thus, with atrial fibrillation, myocardial blood flow does not change in a consistent fashion, although myocardial blood flow still reflects myocardial oxygen demand. Relative hypoperfusion of subendocardium and an increase in myocardial oxygen extraction suggest that with atrial fibrillation the myocardial blood flow response is abnormal.

Heart rate is a primary determinant of myocardial oxygen consumption and therefore myocardial blood flow (1). When heart rate increases, myocardial oxygen consumption and blood flow generally increase (2–5). For atrial fibrillation such a relationship might not apply. While early investigations found that coronary blood flow increases with a transient burst of atrial fibrillation (6, 7), more recent studies have actually found a decline (8, 9). Moreover, the effects of sustained atrial fibrillation on myocardial blood flow and the relationship of such changes to those of myocardial oxygen consumption have not been investigated. Accordingly, to clarify these relations, myocardial blood flow and oxygen consumption were measured in the dog with electrically induced and maintained atrial fibrillation.

Method. Eighteen mongrel dogs that weighed between 20 and 36 kg (average 24 kg) were anesthetized with α chloralose, 100 mg/kg, intravenously administered. No additional anesthesia was given during an experiment. All dogs were intubated and ventilated with a Harvard respirator. A left thoracotomy was performed and the heart was suspended in a pericardial cradle. Polyurethane catheters were positioned in the inferior vena cava and descending aorta. Cannulas were put in the left atrium and in seven dogs also in the left ventricle through the apex. A Millar catheter-tipped micromanometer was positioned in the left ventricle through the apical cannula. A size 7 Goodale catheter was passed to the coronary sinus through an incision in the right atrium. A bipole electrode was attached to the epicardial surface of the left atrial appendage for pacing. To maintain catheter patency, 6000 units of sodium heparin were administered. Pressures were measured with a Statham P 23dB strain gauge manometer with a zero reference taken at the mid-chest with the dog in the right lateral decubitus position. The first derivative of the left ventricular pressure pulse (dp/dt) was obtained with the catheter-tipped micromanometer. The tension time index of Sarnoff and co-workers (10) was calculated by planimetry of the left ventricular pressure curve in systole. Arterial and coronary sinus oxygen content was determined from oxygen saturation measured with an oximeter and the

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hematocrit; pH was measured with a Radiometer acid–base cart.

Blood flow measurements. Myocardial blood flow was measured with 15 μ microspheres using the method of Domenech and co-workers (11). Microspheres were labeled with strontium-85, cerium-141, iodine-125, or scandium-46. Microspheres that had been obtained in 10 ml of 10% dextran containing 0.5% of polysorbate were then suspended in 63% sucrose solution. These suspensions were agitated in an ultrasonic bath and then manually agitated until the moment of injection to ensure good separation of the microspheres. Between 1 and 2 million microspheres in 5 ml of the suspensions were rapidly injected into the left atrium and the cannulas flushed with 5% dextrose in water over 10 to 20 sec. Beginning 30 sec before and continuing for exactly $2\frac{1}{2}$ min a reference blood sample was withdrawn from the arterial catheter at 3.69 ml/min with a Harvard withdrawal pump. After the dog had been killed, the heart was removed and trisected transversely into apical, middle, and basal sections. These slices were then cut into quarters containing the septum, anterior wall, lateral wall, and posterior wall. Each of these tissue segments were divided into an inner and outer zone. For the purpose of analysis the right ventricular half of the septal segment was considered to be the outer wall. Tissue was counted for 5 min in a 3-in. well-type sodium iodide scintillation counter. Reference blood samples were divided into six aliquots. Appropriate energy windows and standard techniques were used for isotope separation (11). To reduce further any error that might be introduced by contaminant activity contributed by accompanying isotopes and background, the order of isotopes was randomized for each experiment. Flow to each area of the myocardium (ml/min/100 g) was calculated by using

$$Q_m = \frac{Q_r \times C_m \times 100}{C_r \times Wt}$$

Where Q_m = myocardial blood flow (ml/min/100 g), Q_r = reference blood flow (ml/min), C_m = total counts in the myocardial sample, C_r = total counts in the reference sample, and Wt = weight of the sample (in grams). Cardiac output (CO) (in liters/min) was calculated by using

$$CO = \frac{Q_r \times C_i \times 10}{C_r \times Wt}$$

Where C_i = total counts of isotopes injected. Calculations of flows were performed with an IBM Systems III computer.

Protocol. After the animals were prepared, control hemodynamic and myocardial blood flow determinations were made. Atrial fibrillation was induced by pacing the left atrium at a cycle length of 200 msec, at least at twice the diastolic threshold, and then delivering a second paired stimulus, 90–150 msec after the basic stimulus, until atrial fibrillation was induced. When paired atrial pacing failed to produce atrial fibrillation, a train of electrical stimuli, at least at twice the diastolic threshold, at cycle lengths sufficiently reduced to produce atrial fibrillation, was delivered. After induction of atrial fibrillation, pacing was stopped and electrocardiogram and atria were examined to ensure that atrial fibrillation persisted spontaneously for at least 5–10 sec (Fig. 1). To prevent spontaneous reversion to sinus rhythm, pacing was continued during the entire period that hemodynamic and myocardial blood flow determinations were made in atrial fibrillation. ECG was recorded concomitantly with all hemodynamic and myocardial blood flow determinations to ensure that rhythm had not reverted. The first measurements were made within 5 min of induction of atrial fibrillation and the second 15–20 min afterward. After the second determination, pacing was stopped and spontaneous sinus rhythm was allowed to return; this occurred generally within 10–20 sec after discontinuance of atrial pacing. However, in three dogs atrial fibrillation persisted for at least 15 min and postfibrillation data could not be obtained. Data were analyzed by one-way analysis of variance and Student t test for paired data, using Dunnett's tables (12). Bivariate and trivariate regression equations were calculated using least-squares method. Data are expressed as the means $\pm$ the standard error of the mean. $P < 0.05$ was considered statistically significant.

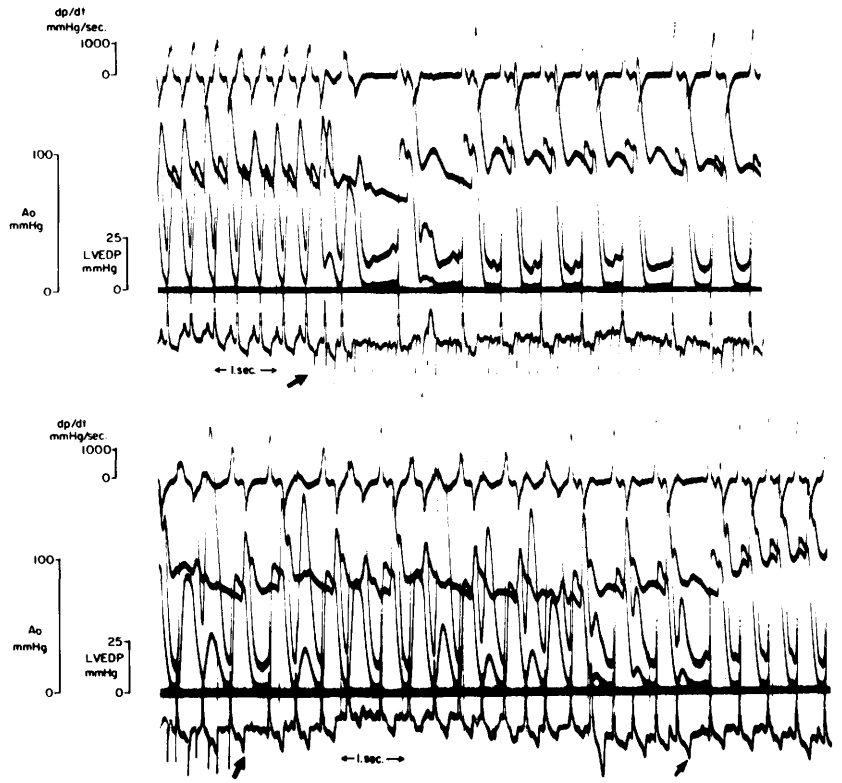

FIG. 1. Induction of atrial fibrillation with rapid atrial pacing and reversion to sinus rhythm with its discontinuance. Left ventricular pressures, aortic pressure (Ao), left ventricular *dp/dt*, and ECG are shown. Upper trace shows induction; lower trace reversion 7 sec (second arrow) after discontinuance (first arrow) of atrial pacing. LVEDP, left ventricular end-diastolic pressure.

Results. The hemodynamic data found in the intact dogs are shown in Table I; myocardial blood flow and myocardial oxygen data are shown in Table II.

Atrial fibrillation produced an increase in ventricular rate and left atrial pressure and a decline in mean aortic pressure and cardiac output. With reversion to sinus rhythm, ventricular rate, mean aortic pressure, and left atrial pressure returned to control values. However, cardiac output remained lower than control, even though arterial pH and oxygen saturation did not change significantly.

Although average myocardial blood flow and oxygen consumption did not change, in 11 dogs myocardial blood flow declined and in 7 it increased, whereas myocardial oxygen consumption paralleled these changes in all dogs. Myocardial oxygen extraction, however, increased with atrial fibrillation and the change was statistically significant 15 min after induction of atrial fibrillation (Table II). Table III shows the relationship of the changes of myocardial blood flow to those of myocardial oxygen consumption; a correlation coefficient of 0.96 was found.

To determine whether the changes of myocardial blood flow did, in fact, reflect, at least in part, those changes in myocardial demand that were produced by atrial fibrillation, in seven dogs the changes of peak positive *dp/dt* and tension time index were correlated both independently and conjointly with the changes in myocardial blood flow. A representative tracing of the ECG, *dp/dt*, left ventricular and aortic pressure is shown in Fig. 2. Myocardial blood flow correlated with tension time index (Table III). Although peak *dp/dt* by itself did not correlate significantly with myocardial blood flow, when both ten-

TABLE I. HEMODYNAMIC DATA

	C	AF	AF	POST
Ventricular rate (beat/min)	156 ± 7 (18)	240 ± 16* (18)	233 ± 14* (18)	159 ± 6 (15)
Mean aortic pressure (mm Hg)	106 ± 4 (18)	94 ± 5* (18)	92 ± 3* (18)	102 ± 3 (15)
Mean left atrial pressure (mm Hg)	10.8 ± 1.0 (18)	15.7 ± 1.0* (18)	14.7 ± 0.7* (18)	10.2 ± 0.6 (15)
Cardiac output (liters/min)	3.2 ± 0.2 (18)	2.3 ± 0.2* (18)	2.2 ± 0.1* (17)	2.1 ± 0.1* (15)
TTI (mm Hg·sec/min)	4609 ± 406 (7)	3299 ± 145 (7)	3239 ± 333 (7)	2822 ± 169 (6)
Maximum *dp/dt*	2457 ± 294 (7)	1820 ± 141 (7)	1968 ± 345 (7)	1969 ± 302 (6)
*p*Ha	7.39 ± 0.03 (18)	7.38 ± 0.03 (18)	7.37 ± 0.03 (18)	7.36 ± 0.03 (15)
Arterial oxyhemoglobin (%)	92 ± 2 (18)	92 ± 2 (18)	91 ± 2 (18)	93 ± 1 (15)

Note. Abbreviations: C, control; AF, atrial fibrillation; POST, after atrial fibrillation; TTI, tension time index; *p*Ha, arterial pH. Number of dogs in parentheses. Mean ± SEM.
* $p < 0.05$.

sion time index and *dp/dt* were correlated with myocardial blood flow the association with myocardial blood flow was stronger, producing a correlation coefficient greater than either alone (Table III).

Figure 3 displays myocardial blood flow and the inner–outer left ventricular wall flow ratios found in four regions of the heart. The regional blood flow changes were not different in these seven dogs, falling by between 11 and 16% (PNS). Although atrial fibrillation produced a reduction in the average left ventricular inner–outer wall flow ratio, this change was most marked in those regions where the ratio was highest and the decline became progressively less marked with lower control values.

Thus, while atrial fibrillation did not affect average myocardial oxygen consumption or average myocardial blood flow, an abnor-

TABLE II. MYOCARDIAL BLOOD FLOW AND OXYGEN CONSUMPTION

	C	AF	AF	POST
MBF (ml/min/100 g)	101 ± 10 (18)	99 ± 8 (18)	98 ± 7 (17)	97 ± 10 (15)
Oxygen extraction (ml/dl)	7.6 ± 0.4 (17)	8.0 ± 0.4 (17)	8.1 ± 0.3* (17)	7.9 ± 0.4 (14)
MVO_2 (ml/min/100 g)	7.7 ± 0.7 (17)	8.1 ± 0.7 (17)	7.7 ± 0.5 (17)	6.9 ± 0.8 (14)
I/O	1.05 ± 0.04 (18)	0.95 ± 0.04* (18)	0.93 ± 0.04* (16)	0.97 ± 0.04 (15)

Note. Abbreviations: MBF, myocardial blood flow; MVO_2, myocardial oxygen consumption; C, control; AF, atrial fibrillation; POST, after atrial fibrillation; I, inner wall; O, outer wall. Number of dogs in parentheses. Mean ± SEM.
* = < 0.05.

TABLE III. RELATIONS OF CHANGES IN MYOCARDIAL BLOOD FLOW TO CHANGES IN MYOCARDIAL OXYGEN CONSUMPTION AND OXYGEN DEMAND

(1)	$MBF = 13.8\ MVO_2 - 7.3$	
	$r = 0.96$	$p < 0.01$
(2)	$MBF = 0.028\ dp/dt - 10.5$	
	$r = 0.46$	PNS
(3)	$MBF = 0.017\ TTI + 3.19$	
	$r = 0.61$	$p < 0.05$
(4)	$MBF = 3.1 + 0.014\ TTI + 0.012\ dp/dt$	
	$r = 0.64$	$p < 0.05$

Note. Abbreviations: MBF, Δ myocardial blood flow (ml/min/100 g); MVO_2, Δ myocardial oxygen consumption (ml/min/100 g); TTI, Δ tension time index (mm Hg · sec/min); *dp/dt*, Δ peak *dp/dt* (mm Hg/sec).

mality of flow was, however, suggested by the findings of an increased myocardial oxygen extraction and a reversal of the left ventricular inner–outer wall flow ratios: Oxygen extraction increased by an average of 5 ± 2 to 6 ± 2% ($P < 0.01$); the left ventricular inner–outer wall ratio declined by an average of 0.10 ± 0.04 to 0.12 ± 0.04 ($P = 0.01$).

Discussion. Atrial fibrillation in the neurally intact dog produces a marked, but variable, alteration in cardiovascular hemodynamics. Unlike sinus or atrial tachycardia, which merely reduces the diastolic filling time, in atrial fibrillation there is a loss of atrial contractions and a variable occurrence of the time of ventricular activation. The loss of the "atrial booster" effect will exaggerate the impact of an abbreviated diastolic filling

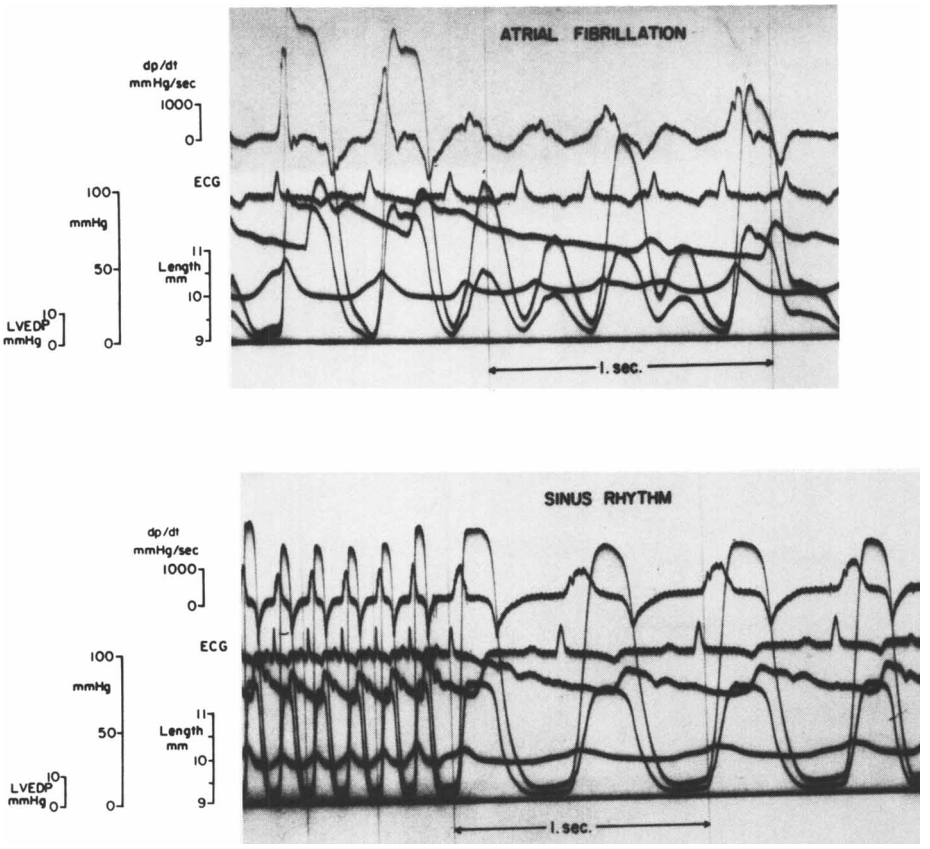

FIG. 2. Representative tracing of pressures of ECG before (lower trace) and during atrial fibrillation (upper trace). Abbreviations: see Fig. 1. Epicardial mercury-in-silastic length gauge changes are also shown.

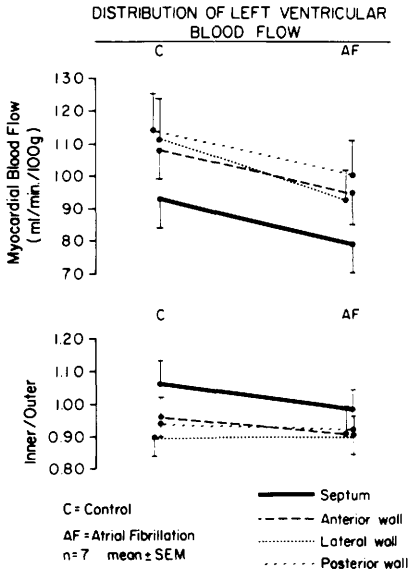

FIG. 3. Distribution of left ventricular blood flow in seven neurally intact dogs before (C) and with induction of atrial fibrillation (AF).

time, especially when ventricular rate is rapid (13). The greater the variability of ventricular activation time, the greater will be the beat-to-beat variability in the strength of ventricular contractions. Early occurring beats may produce weak and ineffectual contractions, whereas beats occurring after a long diastolic filling period may produce forceful contractions (14, 15). Moreover, the effects of abortive beats—those that generate insufficient pressure to open the aortic valve—may impact on subsequent beats through postextrasystolic potentiation or through the decline of aortic impedance resulting from the increased aortic run-off time (14, 15). Atrial fibrillation may also affect atrioventricular valve coaptation, thereby producing valvular regurgitation (16). Furthermore, the hemodynamic changes of atrial fibrillation itself would be expected to produce reflex effects on cardiac action (17). Thus, in atrial fibrillation, depending upon the ventricular response and the aforementioned factors, there can be considerable variability both in beat-to-beat and average cardiac dynamics and, accordingly, a variability in myocardial oxygen requirements.

The observation in atrial fibrillation of an increased myocardial blood flow in some studies (6, 7, 17) and a decline of blood flow in others (8, 9), therefore, should not be surprising. In our study we found considerable variability in myocardial blood flow so that the average response, when compared to control, was unchanged. However, the change in myocardial blood flow with atrial fibrillation still correlated strongly with the changes in myocardial oxygen consumption and these changes could be explained, at least in part, by the determinants of myocardial oxygen demand that were measured.

The hemodynamic alterations caused by atrial fibrillation not only alter myocardial oxygen requirements but also affect coronary perfusion. In atrial fibrillation the tachycardia itself—if the number of effective beats exceeds that of basal rate—will abbreviate diastolic filling time, the period in which most left ventricular perfusion occurs, especially in the subendocardium (18). The fall in aortic diastolic pressure and the rise of left ventricular diastolic and mean atrial pressure will reduce left ventricular perfusion pressure. Also, in response to the hemodynamic changes, reflexes will be activated that may cause coronary vasoconstriction (17). Thus, even if myocardial oxygen requirements are not altered, atrial fibrillation itself can adversely affect myocardial blood flow. The finding of a reversal in the normal pattern of left ventricular transmural blood flow and the increase in myocardial oxygen extraction could be explained by these hemodynamic alterations. In contrast to these findings, in experimental studies of other tachycardias, in which myocardial blood flow and oxygen consumption were also measured, a consistent rate-related increment in myocardial oxygen consumption (2–5) has been reported; however, no change or reduction in myocardial oxygen extraction (4, 5) and a more variable effect on the pattern of transmural blood flow have been observed (5, 19).

Thus, our study demonstrates that in the neurally intact, open-chest dog, atrial fibrillation does not produce a consistent change in myocardial blood flow. This variability of myocardial flow reflects the nonuniformity

of the hemodynamic changes in atrial fibrillation, since myocardial blood flow still reflects myocardial oxygen consumption and the hemodynamic determinants of myocardial oxygen demand. A primary disturbance of blood flow in atrial fibrillation is however suggested by the abnormal pattern of left ventricular wall flow and the increased myocardial oxygen extraction, although these findings might occur in other arrhythmias having equivalent ventricular rates.

Methodological considerations. Determination of blood flow with radionuclide tagged microspheres provides a measure of mean blood flow; immediate and instantaneous blood flow changes cannot therefore be determined with this technique. Since atrial fibrillation is characterized by substantial beat-to-beat variation in hemodynamics, this method might therefore not be reliable for measuring myocardial flow with this arrhythmia. The following observations argue against this theoretical objection: (9) although atrial fibrillation produces considerable beat-to-beat variation, an average reproducible hemodynamic response was observed over a 20- to 30-sec period, the time it would be expected to take for most of the microspheres to have been distributed (20). (b) Average myocardial blood flow responses were reproducible (Table II); moreover, the coefficient of variation—the ratio of the standard deviation to the mean—was actually lower during atrial fibrillation than with sinus rhythm. (c) In another study of regional blood flow with atrial fibrillation, flow determinations with radionuclide tagged microspheres were found to be at least directionally similar to those obtained with a Doppler velocity probe (21).

Also, hemodynamic findings in atrial fibrillation in an anesthetized, open-chest dog are different from those observed in an awake, healthy animal (22). The reduction in left ventricular dimensions produced by the thoracotomy and the neurohumoral effects from anesthesia and thoracotomy might be expected to exaggerate the hemodynamic findings of atrial fibrillation (23). Although this objection cannot be entirely dismissed, atrial fibrillation in the awake dog has been shown to produce no changes in average myocardial blood flow, despite a fall in cardiac output (24), the same findings observed in these experiments using chloralose anesthesia.

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