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The Effects of an Intracoronary Infusion of Adenosine on Cardiac Performance, Blood Supply and on Myocardial Metabolism in Dogs

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Summary. The effects of 10-min intracoronary infusion of 10 μg/kg/min adenosine on coronary and systemic haemodynamics, cardiac performance, myocardial CO_2 and H^+ balance and myocardial substrate metabolism were investigated in 7 anaesthetized dogs. The following results were obtained.

1. During the adenosine infusion coronary blood flow rose 3- to 4-fold above the preinfusion value whereas the coronary AVD-O_2 and coronary resistance fell. Cardiac oxygen consumption fell significantly during the first 5 min of infusion but rose thereafter to values exceeding the starting value. The aerobic efficiency of the heart was significantly increased during the first 7 min of the adenosine infusion.

2. The myocardial release of total CO_2 was significantly diminished within the second minute and increased at the end of the adenosine infusion. Myocardial H^+ release showed a tendency to increase during the first 7 min of infusion becoming significant if a correction was applied for the concomitant decrease in myocardial CO_2 production.

3. Myocardial balance and OER values for FFA indicated a FFA release whereas glucose and pyruvate uptake were significantly increased during the whole infusion period. The myocardial lactate uptake and OER were significantly decreased between the 5th and 10th min of the infusion.

4. The temporal course of the decrease in myocardial lactate uptake and of the increase in myocardial flow was nearly identical. Myocardial glucose uptake showed a similar course but with a 2-min lag period. 5 min after the commencement of the adenosine infusion 34 μmoles/100 g more of glucose and 63 μmoles/100 g less of lactate (mean values) were taken up by the heart.

5. The results were interpreted on the basis of a glycolytic and lipolytic action of adenosine on the myocardium brought about by a stimulation of myocardial 3,5-AMP production. A connexion between the observed metabolic effects and the effects of adenosine on coronary resistance and flow is discussed and the myocardial metabolic acidosis as mediator in positive feedback control over myocardial metabolic processes and cardiac blood supply is stressed.

Key-Words: Adenosine i.c. — Coronary Blood Flow — Mycocardial Metabolism — Cardiac Performance.

Schlüsselwörter: Adenosin i. c. — Koronardurchblutung — Herzstoffwechsel — Herzleistung.

It was propounded in recent theories on the molecular mechanism of cardiac hypoxic reactive hyperaemia [28,51,52] and of pharmacogenic coronary dilatation (dipyridamol, hexobendine) [7,13,17,19,30,31,37, 45,54,56] that adenosine acts as a mediator within a feed-back system between cardiac metabolic processes and myocardial oxygen supply. The hypothesis was put forward that the changes in coronary haemodynamic resistance occurring in myocardial hypoxia and following the administration of long-acting coronary dilators result from an increase in the adenosine concentration at the receptors of resistance vessels by a changed steady-state equilibrium between adenosine formation and re-uptake by the myocardial cell [48,31,52]. Changes in myocardial substrate metabolism were found to occur in myocardial hypoxia and in pharmacogenic coronary dilatation simultaneously with the observed changes in coronary blood flow. Myocardial glucose uptake was found to be increased in both myocardial hypoxia [60,53,57] and following the administration of hexobendine [35,36] and of dipyridamol [38]. Moreover, changes in the level and metabolism of FFA in the heart were found to be typical of the hypoxic state in this organ [18] and following the administration of hexobendine were reflected by changes in the coronary arteriovenous differences and myocardial oxygen extraction values for FFA [35,36]. Furthermore, a release of H^+ and CO_2 from the heart [32,15] and the brain [33] was observed after the systemic administration of hexobendine in dogs. On the basis of these findings a theory of pharmacogenic coronary dilatation was proposed [32,33,31] involving a primary effect on cardiac substrate metabolism with subsequent formation of H^+ and, hence, an increase in myocardial pCO_2 and a positive feed-back effect on the coronary blood flow. It seemed now of interest to prove whether the "adenosine" and the "metabolic" theories of pharmacogenic coronary vasodilatation were compatible with one another or might even reflect two partial mechanisms of a general feed-back system involving the energy requirement of metabolic events in, and oxygen and substrate supply to the heart. For this purpose investigations were carried out in order to find out whether the well-known coronary dilatory effects of adenosine are accompanied by metabolic changes similar to those obtained in myocardial hypoxia or following the i.v. administration of coronary dilators, especially hexobendine.

Methods

Experimental Procedure. The investigations were carried out on 7 male mongrel dogs weighing between 24 and 32 kg, which were starved for 24 h. The dogs were pretreated with morphine (3 mg/kg) and then anaesthesia was induced with 3.5 ml/kg Urethane-Chloralose [Urethane 25%, Chloralose 2% (w/v)]. Following intubation the animals were artificially respirated with a mixture of N_2O and O_2 (3 : 1) using an Engström respirator, and the end tidal CO_2 concentration (URAS 4, Hartman

and Braun) was maintained constant at 4.5 vol-% by varying the respiration volume. The blood pressure was recorded electromanometrically in the femoral artery by means of Statham transducer Hewlett-Packard bridges and Hewlett-Packard 8-channel recorder, the heart rate simultaneously through electrical integration from the EGG II with a Hewlett-Packard cardio tach unit. The cardiac output was determined by the thermodilution method, using a Hewlett-Packard Cardiac Output computer. Cardiac arteriovenous differences (AVD) in O_2 and CO_2 content, pCO_2, pH and substrate levels were obtained by simultaneous sampling of blood from the femoral artery and the coronary sinus before, during and at various time intervals following the intracoronary infusion of 10 µg/kg/min adenosine (Boehringer & Soehne, GmbH, Mannheim).

Catheterization of the Coronary Sinus and Left Coronary Artery. The coronary sinus was catheterized under X-ray control from the left jugular vein according to Goodale *et al.* [20]. By using an electromagnetic flow tip catheter [40], coronary flow measurements and blood sampling could be done at the same time. After placing the animals in the supine position a special catheter (developed for coronary angiography by Cordis Co, Miami) was introduced under X-ray control from the right femoral artery into the left coronary artery. A control injection of Endografin® showed the correct position of the catheter not only by distribution of the radio-opaque fluid in the left coronary artery under X-ray control, but also by a significant increase in the coronary sinus outflow.

Determinations. The oxygen and CO_2 content of the blood was obtained by volumetric analysis (van Slyke), the pH and pCO_2 values electrometrically (both Radiometer Kopenhagen). The blood samples were treated as described in Kraupp *et al.* [35] for the determination of substrates: glucose was determined according to Slein [55], lactate according to Hohorst [26], pyruvate according to Bücher *et al.* [10], FFA according to Dole and Meinertz [14].

Calculations. Coronary vascular resistance (dyn × sec × cm^{-5}/100 g) = mean art. RR (mm Hg)/coronary flow (ml/min/100 g) × 0.0800496. Total vascular resistance (dyn × sec × cm^{-5}) = mean art. RR (mm Hg)/cardiac output (l/min) × 80.0496. Left ventricular work (kg × m/min) = mean art. RR (mm Hg) × cardiac output (l/min) × 0.0136. Oxygen consumption (ml/min/100 g) = AVD-O_2 (ml/100) × coronary flow (ml/min/100 g)/100. Efficiency (%) = left ventricular work (kg × m/min)/O_2 consumption (ml/min) × 46.8384. Cardiac oxygen extraction ratios (OER-%) = $AVD_{substr.}$ (µmoles/ml) × K/AVD-O_2 (where K for glucose = 1344, for pyruvate = 560 and for lactate = 672). OER_{FFA} (%) = AVD_{FFA} (µmoles/l) × 0.057 × (100 − hematocrit)/AVD-O_2.

Substrate balance were found by the $AVD_{substr.}$ × flow values. The statistical significance of changes in respect to preinfusion values at various intervals during and following the adenosine infusion were assessed by means of the Student's *t*-test.

Results

Average curves for the values of mean arterial blood pressure, coronary blood flow, coronary vascular resistance, cardiac output, total vascular resistance, heart rate, left ventricular work, cardiac oxygen consumption, aerobic efficiency of the heart, coronary AVD-O_2, AVD-pCO_2, AVD-H^+ and net changes in H^+ before, at different time intervals during and following a 10 min intracoronary infusion of 10 µg/kg/min adenosine are given in Figs. 1a, 1b, 2a. In 5 of the 7 dogs volumetric determinations of arterial and coronary venous O_2 and CO_2 content were

carried out and the average curves of left ventricular oxygen consumption and CO_2 release, H^+ release and of the respiratory quotient of the heart before, during and following the intracoronary adenosine infusion are presented in Fig. 2b. Arterial levels, oxygen extraction ratios and cardiac balances (AVD $\times$ flow) of glucose, free fatty acids, lactate and pyruvate were estimated in all 7 dogs and given as average curves in Figs. 3 and 4.

Within 3 min of the commencement of the adenosine infusion the *mean arterial blood pressure* dropped significantly from a mean starting value of 125 mm Hg to 114 mm Hg and remained at this level until the end of the infusion. A few minutes after the end of the infusion the starting value was reached again (Fig. 1a). The decrease in mean arterial blood pressure was accompanied by a slight increase in *cardiac output* and the *total vascular resistance* was significantly decreased by about 25% during the whole period of infusion (Fig. 1a).

The *coronary sinus outflow* rose immediately after the onset of the adenosine infusion from a mean value of 74 ml/100 g/min to a maximum mean value of 279 ml/100 g/min at the end of the infusion (Fig. 1a). This approximately 4-fold increase in coronary outflow represents a mobilization of the entire coronary reserve in the dog [5, 6, 8, 46] and is considerably higher than the rise in coronary outflow observed by Hirche [24] on infusion of a similar dose of adenosine (11.4 μg/kg/min), into one of the main branches of the left coronary artery in dogs. *Coronary vascular resistance* fell immediately after the onset of the infusion the minimum mean level (26% of the preinfusion value) being reached within 5 min (Fig. 1a).

Both coronary flow and coronary resistance returned to the preinfusion level between the 5th and the 10th min after the end of the infusion.

Heart rate and *left ventricular work* were slightly increased during the adenosine infusion (Fig. 1b). These insignificant changes in both parameters may be interpreted as occurring secondarily to slight alterations in the systemic circulation probably caused by small amounts of adenosine being swept back into the aortic and hence the peripheral circulation during systole. In spite of the observed increase in left ventricular work, *myocardial oxygen consumption* was significantly decreased during the initial period (0—5 min) of the adenosine infusion (Fig. 1b). As a consequence, *aerobic efficiency of the heart* was increased significantly up to the 7th min following the onset of infusion (Fig. 1b). Later on the myocardial oxygen consumption returned to preinfusion levels or even exceeded them in some experiments (Fig. 1b). An increase in cardiac oxygen consumption during an i.c. infusion of adenosine was reported by Hirche (1966) but unfortunately without any data on the time inter-

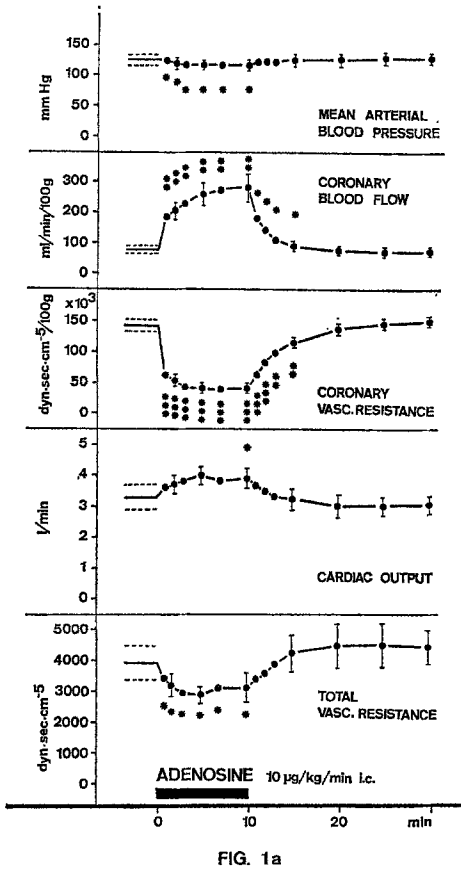


FIG. 1a

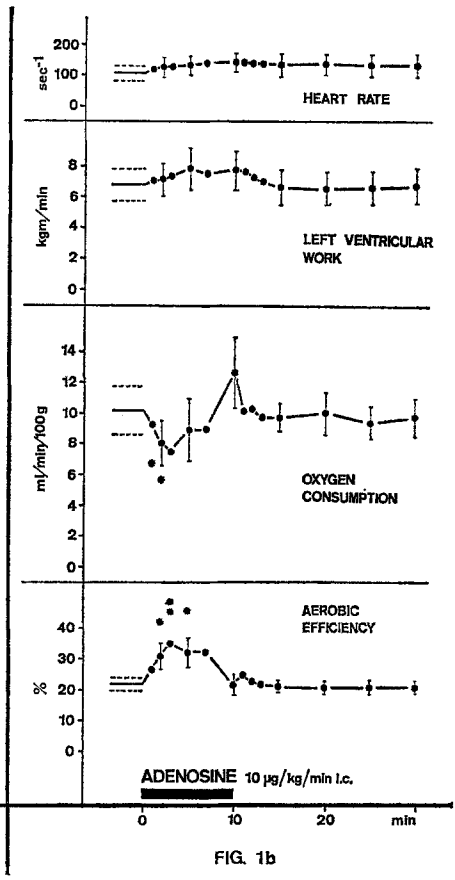


FIG. 1b

Fig. 1a. Experiments on 7 dogs (Urethane/Chloralose/N_2O). Average curves and standard error of mean of: mean arterial blood pressure, coronary blood flow, coronary vascular resistance, cardiac output, and total vascular resistance prior to, during and following an intracoronary infusion of 10 µg/kg/min adenosine. Significance of changes (compared to the pre-infusion value): * $0.05 > P > 0.01$, ** $0.01 > P > 0.001$, *** $P < 0.001$

Fig. 1b. Experiments on 7 dogs (Urethane/Chloralose/N_2O). Average curves and standard error of mean of: heart rate, left ventricular work, oxygen consumption and aerobic efficiency prior to, during and following an intracoronary infusion of 10 µg/kg/min adenosine. For significance symbols see Fig. 1a

val between start of the infusion and sampling. The *stroke volume* remained constant throughout the whole experiment within a range of 34 to 38 ml.

The pre-infusion *coronary* $AVD\text{-}pCO_2$ and $AVD\text{-}H^+$ were negative, indicating a steady release of H^+ from the heart [32]. Immediately after

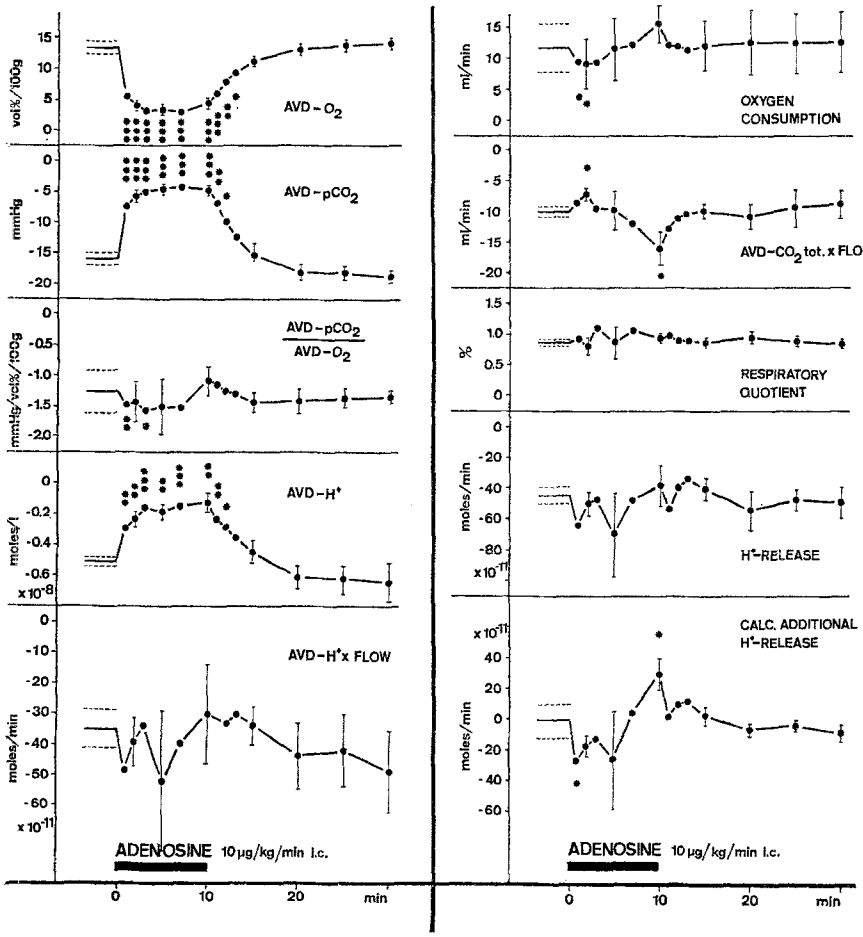


Fig. 2a. Experiments on 7 dogs (Urethane/Chloralose/N_2O). Average curves and standard error of mean of: AVD-O_2, AVD-pCO_2, AVD-pCO_2/AVD-O_2, AVD-H^+ and AVD-H^+ × flow prior to, during and following an intracoronary infusion of 10 µg/kg/min adenosine. For significance symbols see Fig. 1a

Fig. 2b. Experiments on 5 dogs (Urethane/Chloralose/N_2O). Average curves and standard error of mean of: oxygen consumption, AVD-CO_2 tot. × flow, respiratory quotient, H^+-release and calculated additional H^+-release prior to, during and following an intracoronary infusion of 10 µg/kg/min adenosine. For significance symbols see Fig. 1a

the onset of the adenosine infusion both AVDs became significantly less negative on account of the increase in flow (Fig. 2a). The changes reached a maximum within 5 min and regressed promptly following the end of the infusion (Fig. 2a). On calculating cardiac net balances for H^+ (AVD.

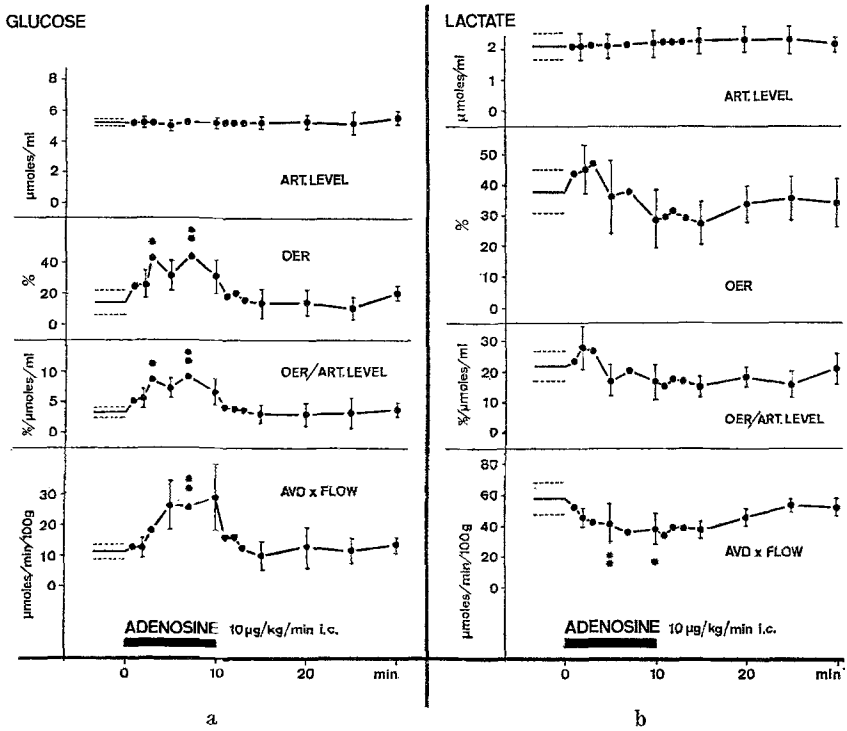
flow values, Fig. 2a) a tendency to a increase in myocardial H^+ release became apparent during the adenosine infusion. Moreover, on correlating coronary AVD-pCO_2 to the corresponding AVD-O_2 values by calculation of the quotients AVD-pCO_2/AVD-O_2 a significant change to more negative values was obtained within the early infusion period, indicating an increase in the ratio of myocardial release of free CO_2 to myocardial oxygen consumption (Fig. 2a).

True cardiac net balances of *total* CO_2 were only obtained in those 5 dogs in which volumetric determinations of O_2 and CO_2 content of arterial and coronary venous blood had been carried out. The left ventricular oxygen consumption, myocardial release of total CO_2, *respiratory quotient* and left ventricular H^+ release obtained with these 5 dogs before, during and following the i.c. adenosine infusion are presented in Fig. 2b. It can be seen that the initial significant decrease in myocardial oxygen consumption (obtained also with all 7 dogs) was accompanied by a significant, transient decrease in the formation and release of CO_2 from the heart (Fig. 2b). At the same time the myocardial respiratory quotient rose insignificantly from the 3rd min and twice reached values above unity (Fig. 2b). A decrease in myocardial CO_2 formation should be accompanied by a corresponding decrease in the myocardial release of H^+. However, exactly the opposite effect [an increase in myocardial H^+ release (Fig. 2b)] was observed. The estimated H^+ release arising from the hydration of metabolically-formed CO_2 "H^+ equivalent of CO_2" was calculated from the changes in the coronary AVD of total CO_2 according to this formula: AVD-H_0^+/AVD-CO_{2_0} × AVD-CO_{2_t} × Flow.

A measure of the H^+ release from other metabolic processes (*extra* H^+) was obtained by subtracting the H^+ equivalent of CO_2 from the measured net cardiac balance of H^+ (Fig. 2b) and a significant increase in this entity was found during the initial period of the i.c. adenosine infusion.

Myocardial glucose metabolism underwent significant changes during the i.c. adenosine infusion: In spite of a constant mean arterial level (Fig. 3a) the myocardial oxygen extraction ratio and the myocardial net uptake of glucose both increased significantly following the onset of the infusion. The maximum levels being two or threefold higher than the pre-infusion values (Fig. 3a). After the end of the adenosine infusion, the OER and balance values declined to the pre-infusion values within 5 min.

The changes in *myocardial lactate metabolism* brought about by i.c. adenosine infusion contrast with those of myocardial glucose metabolism. Although arterial lactate levels remained practically constant throughout the experiment, the net myocardial uptake of lactate fell significantly and continuously during the adenosine infusion (Fig. 3b).



a b

Fig. 3a. Experiments on 7 dogs (Urethane/Chloralose/N_2O). Average curves and standard error of mean of: glucose arterial level and myocardial oxygen extraction ratio (OER), OER/art. level and AVD×flow prior to, during and following an intracoronary infusion of 10 µg/kg/min adenosine. For significance symbols see Fig. 1a

Fig. 3b. Experiments on 7 dogs (Urethane/Chloralose/N_2O). Average curves and standard error of mean of: lactate arterial level and OER, OER/art. level and AVD×flow prior to, during and following an intracoronary infusion of 10 µg/kg/min adenosine. For significance symbols see Fig. 1a

OER lactate values rose initially up to the 3rd min after the commencement of the adenosine infusion at a time when myocardial oxygen consumption was significantly diminished. In the later course of the perfusion myocardial OER lactate values decreased in accordance with the simultaneous reduction in myocardial lactate uptake and were found to be lower than the starting value at the end of the infusion period. Both the myocardial uptake and the OER values of lactate returned only gradually to the pre-infusion value (Fig. 3b).

The arterial *pyruvate* level decreased significantly during the first 7 min of the i.c. adenosine infusion (Fig. 4a) and returned gradually to the pre-infusion level within 20 min of its discontinuation. Myocardial

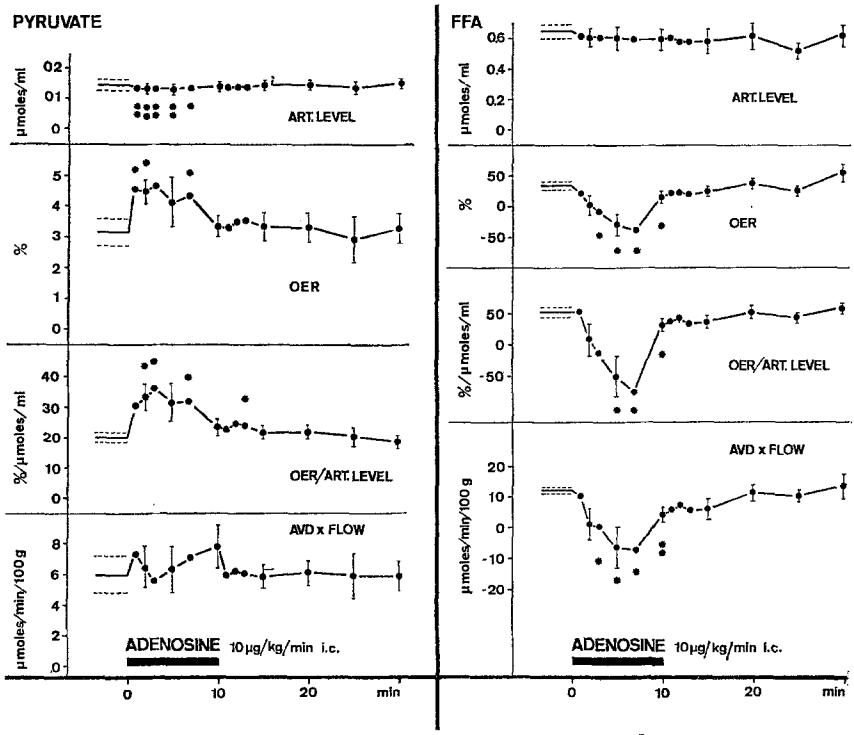


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Fig. 4a. Experiments on 7 dogs (Urethane/Chloralose/N_2O). Average curves and standard error mean of: pyruvate arterial level and OER, OER/art. level and AVD × flow prior to, during and following an intracoronary infusion of 10 µg/kg/min adenosine. For significance symbols see Fig. 1a

Fig. 4b. Experiments on 7 dogs (Urethane/Chloralose/N_2O). Average curves and standard error of mean of: FFA arterial level and OER, OER/art. level and AVD × flow prior to, during and following an intracoronary infusion of 10 µg/kg/min adenosine. For significance symbols see Fig. 1a

OER and OER/A values for pyruvate increased significantly during the early infusion period, but had almost returned to the starting values at the end of the infusion (Fig. 4a). Myocardial pyruvate balance showed a tendency towards a net increase in uptake during the infusion, but the changes were not significant (Fig. 4a).

Arterial *free fatty acid* (FFA) levels were not significantly altered during the i.c. infusion of adenosine (Fig. 4b). However, the myocardial OER values and the net cardiac balance of FFA both changed significantly from positive values in the pre-infusion period to increasingly negative values during the infusion, indicating a myocardial FFA mobilizing effect of adenosine (Fig. 4b). This effect reached its maximum

during the 7th min of infusion and thereafter regressed steadily until the end of infusion, when positive values were recorded once again (Fig. 4b).

Discussion

The present investigation once again confirms the wellknown specific effects of adenosine on coronary haemodynamics [5,22,24,33,59]. However, minor effects of adenosine on the systemic circulation became apparent in spite of the fact that the intracoronary route was employed for administration and these were probably caused by backflow of adenosine into the aorta during cardiac systole. As a consequence, the cardiac output, heart frequency and heart work rose slightly during the infusion, but as an interesting and unexpected result the myocardial oxygen consumption was found to be reduced significantly at the same time and the aerobic efficiency of the heart therefore rose significantly during the first 7 min of the adenosine infusion (Fig. 1b). Evidence for an actual decrease in aerobic metabolism of the heart during the first minutes of the adenosine infusion was furthermore provided by the significant decrease in total myocardial CO_2 release registered at the 2nd min (Fig. 2b). Hence, it must be concluded that additional energy was supplied to the heart by anaerobic metabolic processes during the initial period of intracoronary adenosine administration. In accordance with such an assumption, the myocardial lactate uptake decreased immediately and was significantly reduced throughout the adenosine infusion whilst the steep, significant increase in glucose uptake was recorded after a lag period of 2 min (Figs. 3a, 3b). On calculating the individual changes in glucose and lactate uptake during each minute (Table) it became apparent that in spite of the different time course, the total myocardial uptake of glucose over the first 5 min exceeded the pre-infusion values by 34 μmoles/100 g, whilst the total uptake of lactate was reduced by 63 μmoles/100 g over the same period. It is interesting to note that the ratio of the increased glucose uptake to the decreased

Table. *Changes in myocardial glucose and lactate uptake occurring during the first 5 min of an intracoronary infusion of 10 μg/kg/min adenosine (average values)*

	Additional myocardial glucose uptake/min in μmoles/100 g	Reduction in myocardial lactate uptake/min in μmoles/100 g
1st min	+ 0.9	− 6.9
2nd min	+ 0.4	−11.3
3rd min	+ 7.0	−14.6
4th min	+11.0	−15.0
5th min	+15.0	−15.4
Changes in total uptake for the 5-min period	+34.3	−63.2

lactate uptake is approximately 1 : 2, suggesting that an amount of glucose equivalent to the quantitiy of this substrate taken up in excess by the heart was converted anaerobically to lactate. The lag between the increase in glucose, and decrease in lactate uptake may be explained by an initial glycogenolysis, which was superseded after 2 min by an increase in glucose uptake, which served to replenish the glycogen stores and act as substrate for increased glycolysis. These results bring convincing evidence for the assumption of increased anaerobic myocardial glycolysis triggered off by the i.c. infusion of adenosine. This assumption is furthermore supported by the observed tendency to an increase in the respiratory quotient above unity between the 2nd and 5th min and by an increased myocardial H^+ release, which was significant during the first minute of the infusion if corrected for the concomitant reduction in the release of "H^+ equivalent of CO_2" (see Results, Fig. 2b).

Similar results were obtained by Lundholm [41] on i.a. infusion of epinephrine into forelegs of cats, with a resulting increase in lactic acid production, accompanied by a rise in the respiratory quotient to a value of 1.74 and a fall in oxygen consumption amounting to 16% of the pre-infusion value. A decrease in myocardial oxygen consumption as a consequence of pharmacogenic stimulation of myocardial glycolysis may occur by feed back inhibition via changes in the myocardial ATP/ADP ratio. Such a proposed "reversed Pasteur effect" should first involve the "luxury" formation ot ATP by glycolysis initiated by adenosine and, hence, an increase in the cytoplasmic ATP/ADP ratio with a secondary effect on the mitochondrial ATP/ADP ratio and corresponding decrease in isocitrate dehydrogenase activity [1]. In fact, an increase in tissue ATP consequent to epinephrine administration has been observed in rabbit gastric muscle [39], in mesenteric arteries [43,44] and in guinea pig taenia coli [11,12] and also following the administration of coronary dilators which are considered to act via an adenosine mechanism in myocardial tissue [25,34]. There are striking similarities between the metabolic effects of epinephrine on resting smooth and skeletal muscle and those of adenosine on the heart in situ which may point to a common molecular mechanism of the metabolic effects of both substances. Such considerations lead necessarily to 3,5-AMP as the intracellular messenger of the glycolytic and lipolytic effects of catecholamines. It is obvious that the majority of the observed effects of adenosine too on myocardial substrate metabolism strongly resemble those of 3,5-AMP. This applies to the increase in glucose uptake [16] and to the stimulation of glycolysis [2,4] and especially to the activation of tissue lipolysis by 3,5-AMP [4,9,27]. A stimulation of myocardial lipolysis as a consequence of i.c. adenosine infusion was indicated by the observed reversal of the myocardial FFA balance in the present investigation

(see Fig. 4b). The question now arises whether, in general, the observed effects of adenosine on myocardial metabolism and on cardiac blood supply may be induced by stimulation of the production of 3,5-AMP. Adenosine is rapidly taken up in isolated perfused hearts [29,49] and to a large extent immediately converted into ATP [29,23]. Possibly such an increase in ATP could occur within the myocardial cell membrane and result in a shift in the dynamic ATP/3.5-AMP equilibrium [50] in direction of an increased intracellular release of 3,5-AMP.

A further question to be discussed is the nature of a possible connection between the observed metabolic changes with the observed coronary vasodilatory action of adenosine. A causal connexion between stimulation of glycolysis and vasodilatation was put forward for epinephrine by Lundholm [41] on the basis of his findings of a significant correlation between the increase in CO_2 production and in blood flow. According to Lundholm [41] and also to Griffith *et al.* [21] an increase in glycolysis and hence in lactic acid production should result in a release of CO_2 from the bicarbonate in the cells and intercellular fluid and finally lead to vasodilatation. In the present experiments the potent coronary dilatory action of i.c. administered adenosine was accompanied not only by an increase in the myocardial glucose uptake and decrease in the lactate uptake but also by an increase in the RQ values and increase in negativity of AVD-pCO_2/AVD-O_2 values and an increase in myocardial H^+ release (Figs. 2a, 2b). These findings point to the appearance of a metabolic acidosis concomitant with the increased glycolysis at least during the first 5 min of the adenosine infusion. In Fig. 5 the temporal course of the increase in coronary blood flow and in myocardial glucose uptake and of the decrease in lactate uptake obtained during i.c. infusion with adenosine are presented. A correlation analysis revealed highly significant correlation coefficients for the regression lines of all three parameters of Fig. 5 over the whole infusion period.

From the above findings and considerations a metabolic theory of the coronary dilatory action of adenosine is proposed, involving a primary step concerned with the myocardial uptake of adenosine and production of 3,5-AMP leading to an increase in myocardial glycolysis and lipolysis. As a consequence, intracellular acidosis becomes apparent which is mediated by changes in pCO_2 across the cell barriers to the extracellular space and, finally, to the receptors of the smooth muscles of the coronary vasculature. In principle, a similar chain of events may occur as a consequence of a direct action of adenosine on the coronary smooth muscle fibres as was demonstrated for epinephrine on isolated bovine coronaries by Lundholm and Mohme-Lundholm [42]. The whole spectrum of effects of adenosine on myocardial metabolism and cardiac blood supply fits in well with the picture of a myocardial emergency reaction.

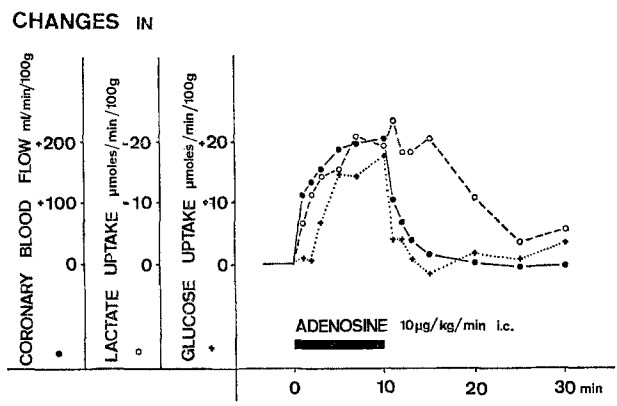

Fig. 5. Experiments on 7 dogs (Urethane/Chloralose/N_2O). Comparison of the increase in coronary blood flow with the corresponding increments in myocardial glucose uptake and decrements in myocardial lactate uptake occuring during and following an intracoronary infusion of 10 µg/kg/min adenosine (average values)

This applies to the extra supply of energy in form of anaerobically-produced ATP and to an increase in substrate supply by an increase in glucose turnover and by lipolysis and finally by the proposed feed-back mechanism which serves to increase the cardiac blood supply. In accordance with such a concept is the proposition put forward by Berne [3], Olsson [48], Rubio *et al.* [52] and Winbury *et al.* [61] of adenosine as the physiological regulator of the coronary blood flow by adapting the cardiac oxygen supply to myocardial oxygen requirements.

However, on account of the metabolic effects of adenosine observed in the present study, the molecular mechanism of the regulatory function of adenosine seems to be more complex than a simple transmitter function between myocardial metabolism and coronary vascular receptors. Adenosine arising intracellularly following the breakdown of mitochondrial ATP owing to anoxia, may exert the following secondary effects: 1. A release of 3,5-AMP during diffusion through the cell membranes with a consequent feed-back activation of glycolysis and lipolysis and enhancement of intracellular acidosis and 2. direct metabolic effects on other myocardial regions and on the smooth muscle cells of the coronary resistance vessels by outflow into the extracellular space. Coronary vasodilatation might then be induced by a rise in the H^+ concentration in the vicinity of the contractile system of vascular smooth muscles as a result of increased glycolysis within the cells of the coronary vessels. This vasodilatation may be enhanced by a positive feed-back effect resulting from an increase in extracellular pCO_2 which, in turn, arises from metabolic acidosis within the myocardial cells.

The similarity of the observed effects of adenosine on myocardial metabolism to those of some long acting-coronary dilatory substances, especially dipyridamol [50] and hexobendine [35,36], seems to be further support for the "adenosine theory" of the coronary effects of these substances, thought to be caused by an inhibition of adenosine re-uptake by the myocardial cells [31,49,58].

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