Effect of Aminophylline on Myocardial Reactive Hyperemia[1] (36830)

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(Introduced by A. M. Lefer)

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Adenosine, a powerful coronary vasodilator, is present in coronary sinus blood (1) and cardiac tissue (2) during reactive hyperemia following brief periods of coronary occulsion and has been proposed as a physiological mediator of metabolic regulation of coronary blood flow (3). The possibility that adenosine is the mediator of reactive hyperemia has been investigated by the use of aminophylline, a drug that attenuates the coronary vasodilation produced by exogenous adenosine (4–9). However, it has been reported that the drug does not affect the peak flow during reactive hyperemia (4, 9) nor the total hyperemic blood flow following coronary artery occlusion (5, 6). These findings have been interpreted as opposing the concept that adenosine is involved in the regulation of coronary blood flow. The present study was undertaken to reinvestigate the effects of aminophylline on reactive hyperemia with consideration of the duration and magnitude of blood flow increase as well as peak flow after brief occlusions of a coronary artery.

Materials and Methods. Five healthy mongrel dogs were anesthetized with pentobarbital (30 mg/kg) and respired with air via an endotracheal cannula. A left thoracotomy was performed in the fourth intercostal space and the left circumflex coronary artery was cannulated and supplied with blood from the left subclavian artery. Coronary blood flow was measured with a Biotronex electromagnetic flowmeter and pressure was measured with a Statham transducer. Pressure and flow measurements were recorded with a Honeywell Visicorder.

Adenosine and aminophylline were dissolved in isotonic saline and injected into the tubing leading to the cannulated coronary artery. Adenosine was administered at the desired concentration in a volume of 0.1 ml and aminophylline was given as 5 or 10 mg doses in a volume of 0.2 ml. Control observations of increases in coronary blood flow induced by coronary occlusions and by adenosine administration were recorded and were then repeated after aminophylline had been given. The volume of coronary blood flow from the onset of reactive hyperemia to the point where flow had returned to 50% of peak flow (VCBF) was determined by planimetry. The duration of VCBF as well as the magnitude of peak flow were also calculated.

Results. Aminophylline produced a decrease of approximately 41% in VCBF and 11% in the duration of VCBF during hyperemia produced by various doses of adenosine (Table I, Fig. 1). Similar observations were made on the effect of aminophylline on the magnitude and duration of reactive hyperemia following brief periods of left coronary artery occlusion. After aminophylline, periods of occlusion from 5 to 60 sec produced a decrease in VCBF during reactive hyperemia of approximately 42% associated with a reduction in the duration of VCBF of 31% (Table II, Fig. 1). These changes were statistically significant for the 10 and 20 sec occlusions where sufficient data were obtained.

Data on peak flow, from the same experiments shown in Tables I and II, are shown in Table III. With peak flow measurements, the effect of aminophylline on the hyperemia produced by ischemia was more variable and not statistically significant. For example, in Expt. 3 there was no decrease in hyperemic peak flow after administration of aminophylline whereas a pronounced decrease in VCBF

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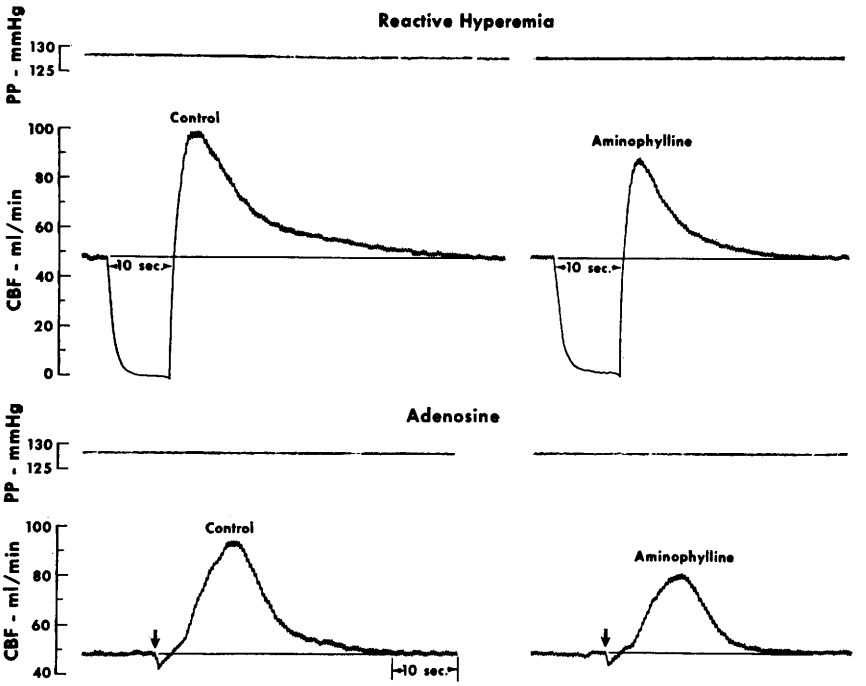

FIG. 1. Effect of intracoronary administration of aminophylline on coronary blood flow during myocardial reactive hyperemia and intracoronary adenosine administration. The arrows indicate points of adenosine injection (4 μg in 0.1 ml saline).

was observed. However, the average data indicate that after aminophylline administration there was a decrease in peak flow produced by injected adenosine of approximately 19% and by ischemia of approximately 9%.

Discussion. The data indicate that aminophylline attenuates both the vasodilator effect of adenosine and reactive hyperemia following different periods of coronary occlusion. These findings are in agreement with those of Afonso (7), Afonso and O'Brien (8), Afonso *et al.* (9), Juhran and Dietmann (4), Juhran *et al.* (5), and Bittar and Pauly (6) with respect to the effect of aminophylline on adenosine-induced hyperemia. However, they are not in agreement with these investigators (4–6, 9) concerning the effect of aminophylline on reactive hyperemia produced by ischemia (4–6) or hypoxia (9). This discrepancy may be attributed to the long periods of coronary occlusion used in some of the previous studies (5, 6). It is possible that the duration of coronary occlusion and the degree of hypoxia may be important factors in determining whether aminophylline inhibits coronary blood flow. If the ischemic or hypoxic periods are of such duration that high concentrations of endogenous adenosine are produced, then aminophylline may not be able to attenuate the reactive hyperemia whereas it is effective in partially blocking the vasodilator effect of small amounts of exogenous or endogenous adenosine.

Even with short periods of coronary occlusion Juhran and Dietmann (4) reported that theophylline failed to attenuate reactive hyperemia following coronary occlusion. However, their original record shows that theophylline produced approximately a 32% decrease in peak coronary blood flow during hyperemia after a 15 sec coronary artery occlusion.

With hypoxia (5–8% O_2 in the inspired air), Afonso *et al.* (9) found that peak coronary sinus outflow was 9% greater during hypoxia before aminophylline than after admin-

TABLE I. Effect of Intra-arterial Injection of Adenosine on Blood Flow in the Left Circumflex Coronary Artery at Constant Perfusion Pressure Before and after Intracoronary Administration of Aminophylline

			Adenosine (μg)									
			2		4		8		16		32	
Expt.		(mg)	Vol.[a] (ml)	Duration[b] (sec)	Vol. (ml)	Duration (sec)	Vol. (ml)	Duration (sec)	Vol. (ml)	Duration (sec)	Vol. (ml)	Duration (sec)
1	Control		3.7	14.2			4.2	16.5			6.8	18.5
	Amphy,	5	1.2	12.2			1.4	13.0			2.0	16.3
2	Control						4.6	15.9			7.8	17.4
	Amphy,	5					1.1	9.3			3.7	15.0
		10									3.9	15.2
3	Control		5.3	14.8	8.3	15.9	11.6	18.5				
	Amphy,	5	1.9	11.7	5.2	13.3	10.1	14.9				
		10	1.1	10.4			5.7	15.2				
4	Control		4.6	15.2	7.3	16.9	11.2	18.9				
	Amphy,	5	2.2	18.0	2.7	14.9	5.9	19.3				
		10	1.8	13.7	2.5	14.4	5.7	16.7				
5	Control		4.0	12.2	7.0	14.4	11.1	16.7	14.6	18.5	16.2	18.9
	Amphy,	10	2.5	10.7	4.6	13.3	7.6	15.2	11.7	17.0	14.3	18.1
	Control, av[c]		4.4	14.1	7.5	15.7	8.5	17.3	14.6	18.5	10.3	18.3
	Amphy, av[c]		1.8	12.8	3.8	14.0	5.5	14.9	11.7	17.0	6.0	16.2
	% Decrease[c]		59.1	9.2	49.3	10.8	35.9	13.9	19.9	8.1	41.7	11.5
	p[d]				.02–.05	.02–.05	<.001	.02–.05				

[a] Volume of flow in milliliters above control flow from the onset of reactive hyperemia to the point where flow had returned to 50% of peak flow. Numbers represent averages from 1 to 4 trials.

[b] Duration of volume flow in seconds from the onset of hyperemia to the point where flow had returned to 50% of peak flow.

[c] The control and combined 5 and 10 mg aminophylline volume and duration values for all dogs in each category was averaged. The percentage decrease was calculated from the average values.

[d] p = significance of means of the differences between control and aminophylline.

TABLE II. Effect of Intracoronary Administration of Aminophylline on Coronary Blood Flow During Reactive Hyperemia Following Different Periods of Left Circumflex Coronary Artery Occlusions.

		Occlusion (sec)									
		5		10		20		30		60	
Expt	(mg)	Vol.[a] (ml)	Duration[b] (sec)	Vol. (ml)	Duration (sec)	Vol. (ml)	Duration (sec)	Vol. (ml)	Duration (sec)	Vol. (ml)	Duration (sec)
1	Control			8.3	24.4	16.0	41.0				
	Amphy, 5			3.1	21.1	7.5	24.8				
2	Control			4.3	9.0	13.4	21.5				
	Amphy, 5			3.2	7.3	5.4	10.0				
	10			3.4	8.9	8.7	12.6				
3	Control			9.2	13.6	20.3	20.0				
	Amphy, 5			6.4	9.2	17.0	16.1				
	10			6.6	10.0	14.8	15.2				
4	Control	2.6	11.5	8.8	13.7	17.8	17.8				
	Amphy, 5	1.8	9.1	5.8	12.4	11.5	18.0				
	10	2.9	10.7	5.1	10.7	10.9	15.2				
5	Control	3.6	10.7	7.0	11.9	20.0	23.3	39.5	38.5	58.7	54.1
	Amphy, 10	1.1	5.9	3.3	7.4	9.0	11.9	17.2	19.3	37.7	43.7
	Control, av[c]	3.1	11.1	7.5	14.5	17.5	24.7	39.5	38.5	58.7	54.1
	Amphy, av[c]	1.9	8.7	4.6	10.9	10.6	15.5	17.2	19.3	37.7	43.7
	% Decrease[c]	38.7	21.6	38.7	24.8	39.4	37.1	56.5	49.9	35.8	19.2
	p[d]			.01–.02	.01–.02	.001–.01	.02–.05				

[a] Volume of flow in milliliters above control flow from the onset of reactive hyperemia to the point where flow has returned to 50% of peak flow. Numbers represent averages from 1 to 4 trials.

[b] Duration of volume flow in seconds from the onset of hyperemia to the point where flow has returned to 50% of peak flow.

[c] The control and combined 5 and 10 mg aminophylline volume and duration values for all dogs in each category were averaged. The percentage decrease was calculated from the average values.

[d] p = significance of means of the differences between control and aminophylline.

TABLE III. Effect of Aminophylline on Peak Coronary Blood Flow During Reactive Hyperemia and Intra-arterial Injection of Adenosine.

		Peak flow (ml/min)									
		Occlusion (sec)					Adenosine (μg)				
Expt	(mg)	5	10	20	30	60	2	4	8	16	32
1. CF, 57[b]; CP, 108[c]	Control		104.1	114.4			97.4		96.6		109.6
	Amphy, 5		80.9	87.9			71.3		74.8		87.0
2. CF, 47; CP, 100	Control		93.8	119.7					76.3		91.2
	Amphy, 5		88.6	98.9					58.1		70.1
	10		83.2	111.7							71.8
3. CF, 54; CP, 112	Control		117.7	144.5			92.0	110.7	126.4		
	Amphy, 5		120.0	151.5			69.9	94.4	122.2		
	10		116.5	145.6			65.3		95.5		
4. CF, 34; CP, 105	Control	52.9	73.9	103.2			56.7	72.9	88.0		
	Amphy, 5	51.6	73.4	94.1			44.9	49.9	62.4		
	10	56.7	70.8	90.1			44.5	49.6	66.8		
5. CF, 45; CP, 128	Control	72.0	93.5	116.0	126.0	126.0	74.0	90.0	107.0	116.0	118.0
	Amphy, 10	61.0	83.0	106.0	116.0	112.0	65.0	76.0	90.0	106.0	113.0
	Control, av[a]	62.5	96.6	119.6	126.0	126.0	80.0	91.2	98.9	116.0	106.3
	Amphy, av[a]	55.3	89.6	110.7	116.0	112.0	60.2	67.5	81.8	106.0	85.5
	% Decrease[a]	11.5	7.2	7.4	7.9	11.1	24.7	26.0	17.3	8.6	19.6
	p[d]		.1–.2	.05–.1				.02–.05	<.001		

[a] The control and combined 5 and 10 mg aminophylline peak flow values for all dogs in each category were averaged. The percentage decrease was calculated from the average values.

[b] Control flow (ml/min).

[c] Control perfusion pressure (mm Hg).

Numbers represent averages from 1 to 4 trials.

[d] p = significance of means of the differences between control and aminophylline.

istration of the drug. In the present study a similar difference of approximately 9% was found between the hyperemic flow before and after aminophylline when measured as peak flow, but this difference increased about 4-fold when measured as VCBF. As shown by Juhran *et al.* (5), the duration of reactive hyperemia is also important in evaluating the effect of theophylline. They found that the duration of hyperemic flow produced by adenosine and ischemia was reduced after administration of this drug.

To what degree the differences in results with reactive hyperemia can be attributed to the dose and route of administration of aminophylline or theophylline is difficult to resolve. The amounts of aminophylline we used were 5–10 mg injected into the coronary artery, whereas other investigators used 100–320 mg intravenously. Since these compounds enhance myocardial oxygen consumption and hence can produce myocardial hypoxia and possibly greater adenosine formation, it is conceivable that with large doses of aminophylline attenuation of reactive hyperemia is masked by the overriding effect of high concentrations of endogenous vasoactive metabolites.

The mechanisms whereby aminophylline curtails the increased coronary blood flow produced by adenosine or following brief periods of coronary occlusion may be due to cyclic 3′,5′-AMP accumulation as a result of aminophylline-induced inhibition of phosphodiesterase, the enzyme that catalyzes conversion of cyclic 3′,5′-AMP to 5′-AMP (10). A greater vascular smooth muscle concentration of cyclic 3′,5′-AMP could evoke

contraction of the coronary arterioles, possibly via Ca^{2+} release, thereby reversing some of the smooth muscle relaxing effect of the adenosine. It is also possible that aminophylline causes a direct release of bound Ca^{2+} in the vascular smooth muscle in a manner similar to the effect of caffeine in skeletal muscle (11).

Summary. The effect of aminophylline on the coronary vasodilator effect of adenosine and myocardial reactive hyperemia following different periods of coronary occlusion was studied in 5 anesthetized dogs. It has been shown that aminophylline decreases the volume and duration of hyperemic flow produced by adenosine approximately 41 and 11%, respectively, and by ischemia, approximately 42 and 31%, respectively. These results support the concept that adenosine is possibly a metabolic mediator in the regulation of coronary blood flow.

1. Katori, M., and Berne, R. M., Circ. Res. **19**, 420 (1966).

2. Olsson, R. A., Circ. Res. **26**, 301 (1970).

3. Berne, R. M., Amer. J. Physiol. **204**, 317 (1963).

4. Juhran, W., and Dietmann, K., Pfluegers Arch. **315**, 105 (1970).

5. Juhran, W., Voss, E. M., Dietmann, K., and Schaumann, W., Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol, **269**, 32 (1971).

6. Bittar, N., and Pauly, T. J., Amer. J. Physiol. **220**, 812 (1971).

7. Afonso, S., Circ. Res. **26**, 743 (1970).

8. Afonso, S., and O'Brien, G. S., Amer. J. Physiol. **219**, 1672 (1970).

9. Afonso, S., Ansfield, T. J., Berndt, T. B., and Rowe, G. G., J. Physiol. (London) **221**, 589 (1972).

10. Butcher, R. W., and Sutherland, E. W., J. Biol. Chem. **237**, 1244 (1962).

11. Weber, A., and Herz, R. J., J. Gen. Physiol. **52**, 750 (1968).

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