THE USE OF AMINOPHYLLINE FOR CORRECTION OF HAEMODYNAMIC REPERCUSSIONS OF CLAMPING OF THE AORTA

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OLIGURIA AND AZOTAEMIA often follow occlusion of the aorta for infrarenal aortic surgery. According to many authors^{1,2,3} these complications occur in 20 to 40 per cent of cases and if organic renal failure supervenes it is associated with a high mortality rate.⁴

Numerous explanatory hypotheses have been formulated and although the results of renal arterial flow measurements are contradictory, recent findings⁵⁻⁹ show that infrarenal aortic clamping in the dog is accompanied by an important reduction in cortical perfusion. Abbott found that cortical flow decreases from 67 to 24 per cent of the total renal blood flow after three hours of clamping.⁵ This author considers many hypotheses to explain the shunting of blood away from renal cortex, such as modification of aortic pressures due to clamping, modification of blood flow characteristics in the renal artery, and modification of cardiac output.

In animal experiment, Perry has shown a decrease of cardiac output by 20 per cent following the clamping of infrarenal aorta.¹⁰ In a previous human investigation we have demonstrated important haemodynamic changes in the first minutes of aortic occlusion.¹¹ These changes were a 15 per cent increase in arterial systolic pressure, a 28 per cent increase in vascular systemic resistance and a 15 per cent reduction in cardiac output. The magnitude of these disturbances seemed important enough to justify the use of a vasodilator drug which does not induce severe arterial hypotension; in that respect we have studied the effects of aminophylline.

MATERIAL AND METHODOLOGY

Twelve patients requiring surgery of the abdominal aorta were included in this study. None presented clinical evidence of cardiac insufficiency or dysrhythmia before operation. They were divided at random into two groups of six, the control series being designated by A- and the treated series designated by A+. Anthropometric data from patients in each group are summarized in Table I.

Induction of anaesthesia was carried out with thiopentone (5 mg/kg) and pancuronium (0.15 mg/kg) was given for intubation and muscular relaxation. Maintenance was with nitrous-oxide oxygen and fentanyl according to analgesic requirements. Droperidol (0.1 mg/kg) was also given before the surgical incision.

Under general anaesthesia, the left radial artery was cannulated after testing

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TABLE I
ANTHROPOMETRIC DATA

Group*	Age	Sex	Height cm	Weight kg	BSA m ²	Surgery
A -	57	M	160	63.5	1.66	Leriche
A -	60	M	167	70	1.78	Leriche
A +	75	M	165	68.5	1.75	Aneurysm
A -	65	M	164	59	1.64	Leriche
A +	77	M	168	54.5	1.61	Aneurysm
A +	65	M	175	57	1.70	Leriche
A +	48	M	165	67	1.74	Leriche
A +	61	M	160	55	1.56	Leriche
A +	60	F	150	52	1.45	Leriche
A -	73	F	150	63.5	1.57	Aneurysm
A -	68	F	160	49	1.49	Leriche
A -	64	M	163	77	1.83	Leriche

*Group A +: patient pretreated with aminophylline. Mean age 64.5 (SD 5.6).

Group A -: without aminophylline - control group. Mean age 64.3 (SD 10.6).

There is no difference in age.

for adequacy of cubital artery compensatory function. A catheter was placed in the right atrium through the internal jugular vein; its position was ascertained by threading to the right ventricle and withdrawal into the atrium, the characteristic pressure signal being displayed on an oscilloscope.

All patients were placed on controlled ventilation with a tidal volume of 10 ml/kg at a frequency of 12/min. A control arterial blood gas analysis was performed routinely at the beginning of the procedure. Necessary adjustments to maintain P_{aCO_2} and P_{aO_2} within normal limits were rapidly applied. Fluid intake was adjusted to 20 ml/kg/hr before aortic clamping, half the volume consisting of 5 per cent glucose in water and the other half 5 per cent glucose with 0.45 per cent NaCl. A rather liberal fluid intake was administered prior to clamping in order to ascertain that hypovolemia would not explain the hemodynamic changes. Furthermore, in patients with over twelve hours of water restriction, it is important to prevent an augmentation of serum osmolality with subsequent release of antidiuretic hormone. Following occlusion of the aorta, fluid intake was reduced to 6 ml/kg/hr. Blood loss was replaced as accurately as possible.

Haemodynamic data (E.K.G., arterial and right atrial pressure curves and dilution curve) were inscribed on a polygraph recorder (Mingograph EMT 81 - Elema-Schonander). Pressures were recorded continuously from the amplified signals of Statham P23dB transducers. Mechanical and electrical calibrations were obtained and checked regularly during the investigation.

Cardiac output was determined by injection of indocyanine green dye into the right atrium and detection of the resulting dye dilution curve in the arterial blood by a Waters D-400 densitometer. The surface under the curve was calculated by computer from ordinates taken at one-second intervals. The recirculation was eliminated by extrapolating the exponential portion of the curve using a least square method. A special program was written which permitted us to obtain results as well as statistics from the computer, thus eliminating human bias (varian 73). Derived variables were obtained as follows:

$$SVR = \overline{AP} - \overline{RAP} / C.O. \times 79.92 \text{ dynes.sec.cm}^{-5}$$

$$SV = C.O. / HR = \text{ml}$$

$$C.I. = C.O. / m^2$$

$$LVSWI = \overline{AP} (SI) 1.36 \times 10^{-2} = \text{g.m.m}^{-2}$$

$$PTI = HR \times \text{syst. AP} = 10^{-3}$$

Where SVR is the systemic vascular resistance expressed in dynes.sec.cm⁻⁵; SV is the stroke volume in ml; LVSWI is the left ventricular stroke-work index in gram-meter and PTI, the pressure time index.

In the control group the study was conducted as follows: pressure signals and the second derivation of the EKG were recorded continuously; three cardiac output determinations were obtained just before the clamping of the aorta and every two minutes for the first ten minutes after aortic occlusion. In the treated group the chronological sequence of observations was identical but, after control measurements of pressure and cardiac output, a single 250-mg dose of aminophylline was injected slowly intravenously before clamping the aorta. We shall limit our initial observations to the results obtained in the first ten minutes following clamping, interpretation of later readings presenting certain difficulties due to individual variations in blood losses and replacement. Statistical analysis of the data used two-tailed t-tests for comparisons within groups and unpaired t-tests for comparisons between groups; unless otherwise mentioned, only statistically significant variations will be presented and discussed.

RESULTS

The results are presented in the tables using the mean of the six readings in all patients, with standard error in brackets. Significant variations within the group ($p < 0.05$) as related to the control are followed by an asterisk and the statistically valid variations between the two groups ($p < 0.05$) are indicated by a cross.

Table II shows the variations in cardiac frequency. Whereas frequency is not modified in the controls, on the other hand, treated patients show a mean increase of 15 per cent. This tachycardia appears early and is sustained.

The behavior of arterial systolic pressure is shown in Table III. In both series it displays a significant increase; however, as compared proportionately to the initial level, the increase is slightly less in treated subjects (12 per cent for A+ and 16 per cent for A-).

Table IV indicates modifications in right atrial pressure which are not significant in either of the two series.

Table V elicits the variations in cardiac index. The controls undergo a fall after clamping; the cardiac output decreases by 14 per cent immediately after clamping and 28 per cent after ten minutes. Pretreatment with aminophylline causes all significant variations to disappear, cardiac index being maintained at control value during the ten-minute observation period. A significant difference between the two groups is noted after 2, 4, 8 and 10 minutes.

In treated patients, stroke index (Table VI) is not modified by clamping while it diminishes progressively in control subjects; after ten minutes, the systolic indices

TABLE II
CHANGES IN HEART RATE FOLLOWING AORTIC
OCCLUSION (MEANS $\pm$ SE) N = 12

Time	A +	A -
0	77.5 (± 3.6)	77.5 (± 6.7)
2'†	91.6 (± 1.6)*	79.1 (± 7.8)
4'†	91.6 (± 1.6)*	79.1 (± 8.8)
6'†	88.3 (± 2.4)*	79.2 (± 8.6)
8'†	88.3 (± 2.7)*	78.3 (± 8.4)
10'†	88.3 (± 3.8)*	82.5 (± 9.5)

*P < 0.05 within each group.

†P < 0.05 between the two series.

Patients were studied before (T = 0) and after aortic clamping (T = 2').

TABLE III
CHANGES IN SYSTOLIC ARTERIAL PRESSURE DUE TO
AORTIC OCCLUSION (MEANS $\pm$ SE) N = 12

Time	A +	A -
0	177 (± 3.7)	161 (± 9.8)
2'	197 (± 9.1)*	179 (± 13.5)*
4'	206 (± 9.6)*	190 (± 11.2)*
6'	196 (± 8.7)*	186 (± 11.2)*
8'	192 (± 9.5)	190 (± 14.5)*
10'	199 (± 8.9)*	190 (± 10.4)*

*P < 0.05 within each group.

Patients were studied before (T = 0) and after aortic clamping (T = 2').

TABLE IV
CHANGES IN RIGHT ATRIAL PRESSURE DUE TO
AORTIC OCCLUSION (MEANS $\pm$ SE) N = 12

Time	A +	A -
0	6.6 (± 1.9)	7.6 (± 2.0)
2'	6.0 (± 2.2)	6.1 (± 2.3)
4'	5.5 (± 2.1)	6.8 (± 2.0)
6'	4.6 (± 2.2)	6.3 (± 2.1)
8'	4.6 (± 2.2)	6.3 (± 2.1)
10'	4.6 (± 2.2)	6.3 (± 2.0)

Patients were studied before (T = 0) and after aortic clamping (T = 2').

being at 74.5 per cent of the control value. When comparing the two groups, no significant variations are found except at the second minute.

Table VII exhibits modifications which occur in systemic arterial resistances. In the control patients the resistances increase by 38 per cent during the clamping. The pretreatment with aminophylline effectively prevents increase in afterload since we do not find any increase in vascular resistance after aortic occlusion in that group. There is a significant difference between the two groups.

The evolution of the systolic ventricular work index is retraced in Table VIII. Short-lived increase in the systolic work index occurs in treated patients, this in-

TABLE V
CHANGES IN CARDIAC INDEX DUE TO AORTIC
OCCLUSION (MEANS $\pm$ SE) N = 12

Time	A +	A -
0	3.22 (± 0.49)	2.59 (± 0.17)
2'†	3.84 (± 0.34)	2.22 (± 0.15)*
4'†	3.74 (± 0.38)	2.18 (± 0.15)*
6'	3.45 (± 0.44)	2.10 (± 0.18)*
8'†	3.43 (± 0.47)	1.99 (± 0.16)*
10'†	3.30 (± 0.38)	1.87 (± 0.16)*

*P < 0.05 within each group.

†P < 0.05 between the two series.

Patients were studied before (T = 0) and after aortic clamping (T = 2').

TABLE VI
CHANGES IN STROKE INDEX DUE TO AORTIC
OCCLUSION (MEANS $\pm$ SE) N = 12

Time	A +	A -
0	40.58 (± 5.6)	33.99 (± 2.2)
2'†	42.08 (± 4.00)	29.3 (± 3.50)*
4'	40.72 (± 4.03)	29.4 (± 4.10)
6'	39.45 (± 5.48)	28.6 (± 4.12)
8'	38.92 (± 5.93)	25.59 (± 3.54)*
10'	36.79 (± 5.08)	25.34 (± 3.67)*

*P < 0.05 within each group.

†P < 0.05 between the two series.

Patients were studied before (T = 0) and after aortic clamping (T = 2').

TABLE VII
CHANGES IN SYSTEMIC VASCULAR RESISTANCE
DUE TO AORTIC OCCLUSION (MEANS $\pm$ SE) N = 12

Time	A +	A -
0	2013 (± 574)	2152 (± 128)
2'†	1614 (± 235)	2742 (± 281)*
4'†	1699 (± 280)	2957 (± 284)*
6'†	1854 (± 331)	2976 (± 308)*
8'†	1900 (± 386)	3352 (± 454)*
10'†	2001 (± 359)	3122 (± 213)*

*P < 0.05 within each group.

†P < 0.05 between the two series.

Patients were studied before (T = 0) and after aortic clamping (T = 2').

crease being observed at the second and fourth minute is in the order of 15 per cent. At the start of clamping a difference is noted between the two groups (T 2' and T 4').

In Table IX myocardial oxygen consumption, indirectly evaluated by the product of peak systolic pressure and heart rate, is shown to increase in treated patients whereas it is not modified in control subjects.

TABLE VIII

CHANGES IN LEFT VENTRICULAR STROKE WORK
INDEX DUE TO AORTIC OCCLUSION (MEANS $\pm$ SE)
N = 12

Time	A +	A -
0	61.11 (± 6.83)	54.65 (± 2.8)
2†	70.8 (± 5.21)*	49.33 (± 5.72)
4†	69.94 (± 5.24)*	51.70 (± 5.55)
6'	65.43 (± 8.45)	49.44 (± 7.31)
8'	63.21 (± 8.65)	45.75 (± 6.04)
10'	61.17 (± 6.74)	44.51 (± 7.74)

*P < 0.05 within each group.

†P < 0.05 between the two series.

Patients were studied before (T = 0) and after aortic clamping (T = 2').

TABLE IX

CHANGES IN PRESSURE TIME INDEX DUE TO
AORTIC OCCLUSION (MEANS $\pm$ SE) N = 12

Time	A +	A -
0	13.92 (± 0.79)	12.3 (± 2.19)
2'	18.47 (± 1.06)*	12.9 (± 2.42)
4'	18.73 (± 0.88)*	13.9 (± 2.86)
6'	17.53 (± 0.81)*	13.49 (± 2.40)
8'	17.08 (± 0.95)*	14.80 (± 3.18)
10'	17.61 (± 0.89)*	13.26 (± 2.20)

*P < 0.05 within each group.

†P < 0.05 between the two series.

Patients were studied before (T = 0) and after aortic clamping (T = 2').

DISCUSSION

Aminophylline or ethylene-diamine theophylline is a methylxanthine whose activity is predominant over myocardial, vascular and renal functions.¹² On the myocardium it exerts an inotropic and chronotropic activity, the increase in cardiac output thus obtained being in the order of 20 to 30 per cent,^{13,14} and it follows immediately after intravenous injection and persists for approximately 30 minutes. Vasodilating activity is important on pulmonary and systemic circulations, the fall in arterial resistance being approximately 20 per cent. In man its coronary vasodilating effect is probably secondary to an increase in myocardial oxygen extraction.¹⁵ The effect of theophylline and its derivatives on the kidney is to increase diuresis by improving haemodynamic conditions and by decreasing sodium reabsorption.¹⁹ As to their mode of action, xanthines¹⁶ have been demonstrated to behave similarly to β -mimetic agents by increasing the cellular level of 3'-5' cyclic AMP but, while the former activate adenylcyclase, theophylline inhibits the destruction of cyclic AMP by phosphodiesterase. More recent studies^{17,18} attribute a determinant role to the variations in calcium concentrations as a result of xanthine activity. Methylxanthines are excreted in the urine, 10 per cent being

CARDIAC INDEX ($\pm$ S.E) N=12

FIGURE 1. Aminophylline effectively prevents the decrease in cardiac output seen in the control group (Δ) following clamping of abdominal aorta.

eliminated unchanged in their active form, while the rest is deactivated by demethylation and oxidation to 1-3 demethyluric acid.

Our results are in accordance with the known pharmacological effects of aminophylline and are such that it is possible to say that this drug has distinct advantages. The potentially dangerous increase in systemic resistance produced by aortic occlusion is prevented; the vasodilating action of aminophylline effectively neutralizes the increase in afterload (Figures 1 & 2). Moreover, a positive inotropic action can be inferred from the increase in stroke volume and left ventricular systolic work (Figures 3 and 4), though the latter could be discussed on the ground of not using the left ventricular filling pressure in its determination. This inotropic effect nevertheless is brief and moderately active as shown by the small 8 per cent increase in systolic work load. The positive chronotropic action on the contrary is sustained and more important as shown by a 15 per cent increase in heart rate after aminophylline injection (Figure 5).

With this therapeutic approach four points must be stressed. First, the drug must be withheld in patients with arrhythmia, particularly premature contractions. Aminophylline, acting as a β -mimetic, may enhance irritability. We have now used this xanthine in twelve patients under continuous monitoring and in one subject with hypokalaemia the drug elicited junctional premature contractions, although

SYSTEMIC VASCULAR RESISTANCES ($\pm$ SE) N=12

FIGURE 2. While in the control group ($\triangle$) there is a significant increase in systemic vascular resistance following the clamping of abdominal aorta; in the aminophylline pre-treated patients the vascular resistance does not change.

these were easily corrected with lidocaine. Secondly, it must be remembered that our patients had a generous fluid intake up to the moment of clamping. We feel that the use of a potent vasodilating agent in an hypovolaemic patient could lead to decreased venous return and hypotension. Its positive inotropic effect could not then counterbalance the decreased filling pressure.

However, from the observation of the first ten minutes of clamping, one cannot infer what will subsequently happen to cardiac output. Previous experience had shown us¹¹ that there is in fact a steady deterioration of cardiac function, probably due to progressive hypovolaemia associated with major vessel surgery and, not infrequently, metabolic acidosis and hypothermia. Aminophylline has distinct

FIGURE 3. The stroke volume is maintained in the treated patients while it decreases progressively in the control group. This difference reaches statistically significant values only at two minutes after clamping, indicating the short lived inotropic effect of aminophylline.

advantages at the moment of acute stress imposed by aortic occlusion. Should its evanescent action be a drawback, we cannot tell, though we feel that it is used when most needed, immediately after imposing an increased afterload. When its action has ceased, after 30 minutes, blood losses from the surgery would most certainly contra-indicate its readministration.

The last but not the least important point to stress concerns the oxygen expenditure of this treatment. One must determine whether the positive inotropic and chronotropic effects are obtained at the expense of a large increase in myocardial oxygen extraction, keeping in mind that our patients often have a precarious coronary circulation.

Many authors,¹⁹⁻²¹ and particularly Kitamura²² in a most sophisticated study, have shown that there is a definite linear correlation between peak systolic arterial pressure times heart rate and myocardial oxygen demand. In our study this index is increased in treated patients while it is not modified in controls (Figure 6). The tachycardia induced by aminophylline is the cause of this augmentation of myocardial oxygen demand, for the increase in systolic pressure, though slightly less in treated patients, is not significantly different in the two groups. We must be aware that any drug that induces tachycardia may reduce coronary perfusion time during

FIGURE 4. There is a short-lived inotropic effect due to aminophylline as shown by the increase in left ventricular stroke work at two minutes and at four minutes after clamping. This figure also demonstrates the significant difference in the two groups.

diastole. In fact we are now evaluating, with the use of the index of subendocardial viability proposed by Buckberg,²³ the effects of clamping on the subendocardial perfusion as well as the value of aminophylline pretreatment.

In conclusion, while it is possible to prevent haemodynamic perturbations due to aortic occlusion by pretreatment with aminophylline, there is still to be demonstrated that it is not at the expense of too great an increase in myocardial oxygen demand. We have presently demonstrated the validity of Abbott's hypothesis that shunting away of blood from the renal cortex could be due in part to a decrease in cardiac output and we are now looking at the effects it may have on renal function.

SUMMARY

Occlusion of the abdominal aorta induces an increased impedance to ejection, leading to a reduction in cardiac output. The magnitude of the haemodynamic disturbances seemed important enough to justify the use of a vasodilator drug. In that respect the use of aminophylline was evaluated in twelve patients. The

FIGURE 5. Aminophylline has definite and sustained chronotropic effect. In these patients the heart rate never exceeded 15 per cent.

potentially dangerous increase in systemic resistance is prevented by aminophylline, which effectively neutralizes the increase in afterload. Moreover, a positive inotropic action can be inferred from the increase in stroke volume and ventricular systolic work. It must be stressed that this drug must be withheld in patients with cardiac irritability, for it has a β -mimetic action.

RÉSUMÉ

L'occlusion même distale de l'aorte provoque une augmentation de l'impédance aortique. Les réflexes cardiaques vasomoteurs étant amortis par l'anesthésie générale le volume systolique diminue parfois de façon alarmante (Meloche, *et al.*). Ces modifications hémodynamiques nous ont paru assez importantes pour tenter de les prévenir au moyen d'un vasodilatateur. Nous avons dans ce but utilisé l'aminophylline dont les effets β mimétiques paraissaient avantageux. Injecté en bolus de 250 mg immédiatement avant le clampage de l'aorte, l'aminophylline neutralise l'augmentation de la post-charge de façon évidente. De plus, l'augmentation du volume systolique et du travail ventriculaire laisse soupçonner un effet inotropique positif expliquant en partie le maintien du débit cardiaque. Il faut souligner que les effets β mimétiques peuvent provoquer des arrhythmies ventriculaires chez certains patients.

PRESSURE - TIME INDEX

($\pm$ S E) N = 12

FIGURE 6. The myocardial oxygen extraction, indirectly evaluated by the pressure time index, is increased in the aminophylline pre-treated patients. This augmentation is due to the positive chronotropic action of the drug.

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ABBREVIATIONS

- AP = arterial pressure
- $\bar{AP}$ = mean arterial pressure
- CI = cardiac index
- CO = cardiac output
- HR = heart rate
- LVS $\overline{WI}$ = left ventricular stroke work index
- RAP = mean right atrial pressure
- SI = stroke index
- SVR = systemic vascular resistance

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