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ASPIRIN INHIBITS THE EARLY MYOCARDIAL RELEASE OF THROMBOXANE B_2 AND VENTRICULAR ECTOPIC ACTIVITY FOLLOWING ACUTE CORONARY ARTERY OCCLUSION IN DOGS

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Acute coronary artery occlusion in anaesthetized open-chest greyhounds led to early release of thromboxane B_2 (TxB_2) into venous blood draining the ischaemic region. No release occurred from the remainder of the left ventricular wall (coronary sinus sampling). TxB_2 release and ventricular ectopic activity were positively correlated (r = 0.863) 2 min post-occlusion. Aspirin (3 mg/kg i.v.) suppressed both local TxB_2 release and ectopic activity and prevented ventricular fibrillation. It is suggested that TxB_2 release is a factor contributing to early post-infarction arrhythmias.

Introduction Although there is still doubt about the effectiveness of 'low-dose' aspirin in the prevention of sudden cardiac death (from ventricular fibrillation) following reinfarction (Lancet editorial, 1980), there is good experimental evidence in anaesthetized dogs that this drug reduces post-infarction arrhythmias (e.g. Moschos, Haider, DeLa Cruz, Lyons & Regan, 1978). We have recently demonstrated (Coker, Ledingham, Parratt & Zeitlin, 1981) the early release of thromboxane B_2 (TxB_2) from the acutely ischaemic myocardium of anaesthetized greyhounds at a time when ventricular ectopic activity is pronounced. The purpose of the present experiments was to determine, in the same model, whether aspirin modified this release or altered ventricular ectopic activity following non-thrombotic coronary artery occlusion.

Methods Greyhound dogs were prepared as previously described (Marshall & Parratt, 1980) and respired with oxygen. Catheters were placed, under fluoroscopic control, in the aorta, coronary sinus and pulmonary artery and were used for blood sampling, pressure measurement and for the determination of cardiac output. Following a left thoracotomy, the heart was suspended in a pericardial cradle and a thread placed around the anterior descending branch of the left coronary artery. The vein adjacent to this artery was catheterized so that the tip lay within the ischaemic area (Marshall, Parratt & Ledingham, 1974). Blood samples were taken from the various sites just before acute coronary artery occlusion and at 2, 10 and 30 min after. They were analysed for blood gases, pH and lactate (Marshall *et al.*, 1974), and for TxB_2 using radioimmunoassay techniques developed by us (Coker, Clarke & Zeitlin, unpublished). Briefly, blood samples for TxB_2 assay were immediately placed in plastic tubes containing indomethacin and disodium edetate and kept on ice until centrifugation (2000 *g* for 10 min). The plasma was removed and stored at −20°C until assay. After acidification, aliquots of plasma were extracted with redistilled ethyl acetate and evaporated to dryness under reduced pressure at 37°C. The recovery of TxB_2 was monitored by means of tritiated internal standards. Sample extracts and standards were redissolved in phosphate buffered saline and tritiated TxB_2 (New England Nuclear) added, followed by the appropriate specific antibody (Pasteur Institute, Paris). After overnight incubation at 4°C, the antibody-bound and free TxB_2 were separate by use of dextran-coated charcoal. An aliquot of the antibody-bound fraction was placed in Bifluor scintillant (New England Nuclear) and counted in a Packard Tri-Carb 460 liquid scintillation counter. With the above procedures the detection limit for TxB_2 was 15 pg.

In six of the dogs aspirin (3 mg/kg, dissolved in 0.9% w/v NaCl solution) was administered intravenously 30 min before coronary artery occlusion.

Results The haemodynamic, metabolic and electrocardiographic effects of coronary artery occlusion in the present experiments were similar to those previously described (Marshall *et al.*, 1974; Marshall & Parratt, 1980). The main purpose of the present communication is to describe the effects of aspirin on the time course of TxB_2 release from the ischaemic region of the left ventricular wall. In dogs not treated with aspirin, TxB_2 release occurred within 2 min of acute coronary artery occlusion (Figure 1); there was no such release from essentially normal regions of the

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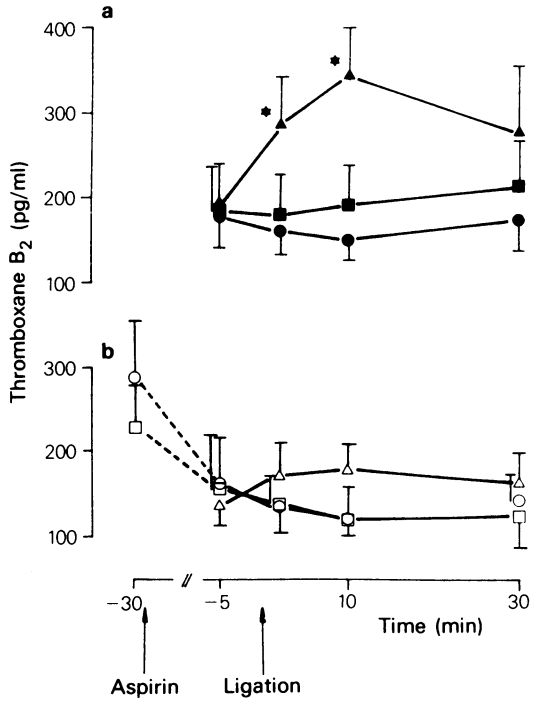

Figure 1 Thromboxane B_2 (TxB_2) concentrations in the aorta (●), coronary sinus (■) and local coronary vein (▲) before, and after, coronary artery ligation in control animals (a, closed symbols, $n = 9$) and in dogs pretreated with aspirin 3 mg/kg i.v. (b, open symbols, $n = 6$) Mean values are shown; vertical lines indicate s.e. mean; $^*P < 0.05$.

left ventricular wall (assessed from coronary sinus sampling) nor was there, under basal conditions, any difference between the arterial and coronary venous (or sinus) levels of TxB_2. In this series of dogs, ventricular ectopic activity began immediately after coronary artery occlusion and in the control series, a total of 69 ± 37 ventricular ectopic beats (range 0–188) had occurred by 2 min. At this time there was a significant positive correlation between the number of ectopic beats and the release of TxB_2 into coronary venous blood ($r = 0.863$).

The only significant haemodynamic effect of intravenously administered aspirin was a reduction in coronary blood flow (from 49 ± 7 to 40 ± 6 ml/min; $P < 0.05$); there were no significant changes in coronary sinus Po_2, Pco_2 or pH. However, there was a reduction in both arterial and coronary sinus levels of TxB_2 (from 293 ± 63 and 230 ± 49 pg/ml respectively before aspirin to 168 ± 51 and 163 ± 57 pg/ml respectively 30 min after aspirin). Aspirin also prevented the early rise in coronary venous TxB_2 levels (Figure 1) and suppressed early ventricular ectopic activity. Thus the number of ventricular ectopic beats that had occurred by 2 min in the aspirin-treated group was only 7 ± 6. None of the dogs treated with aspirin fibrillated after coronary artery occlusion whereas in a total of 12 control dogs, occlusion resulted in ventricular fibrillation in 3 of them. This is similar to the results of a previous control group (Marshall & Parratt, 1980) when the incidence was 5/14.

Discussion This study demonstrates that the thromboxane, which is released within a few minutes of coronary artery occlusion, comes only from the ischaemic region (Figure 1). Further, ventricular ectopic activity was most marked in those dogs in which TxB_2 release was especially pronounced. Although this does not necessarily imply that thromboxane release is responsible for the arrhythmias (the release could be a consequence of pronounced ectopic activity), the results with aspirin could certainly be adequately explained on the basis that TxB_2 release *precedes* ventricular ectopic activity. Thus it is possible that the TxB_2 is derived from platelets aggregating behind the occluded coronary artery (Folts, Crowell & Rowe, 1976). This TxB_2 would have two effects on the coronary microcirculation that might well have serious repercussions for the myocardium. Firstly, it could cause local coronary vasoconstriction, by an action on vascular smooth muscle, and secondly there could be mechanical obstruction in small blood vessels as a result of TxB_2-induced platelet aggregation. The result could be a further reduction in blood flow to an already compromised myocardium; this might well trigger ventricular ectopic activity.

We are not of course suggesting that TxB_2 release is the only mechanism by which ventricular ectopic activity arises after coronary artery occlusion. However, the fact that ventricular fibrillation is much reduced by aspirin (Moschos *et al.*, 1978 and present results) suggests that it is certainly an important contributary factor.,

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