membrane action potential of anoxic papillary muscle. J Gen Physiol **48**:887, 1965.
22. Kardesch M, Hogancamp CE, Bing RJ: The effect of complete ischemia on the intracellular electrical activity of the whole mammalian heart. Circ Res **6**:715, 1958.
23. Goldstein S, deJong JW: Changes in left ventricular wall dimensions during regional myocardial ischemia. Am J Cardiol **34**:56, 1974.
24. Yamaguchi I, McCullen A, Mandel WL: The electrophysiological and mechanical time-course after graded reduction in coronary flow and reperfusion (abstr). Am J Cardiol **39**:312, 1977.
25. Upton MT, Rerych SK, Newman GE, Port S, Cobb FR, Jones RH: Detecting abnormalities in left ventricular function during exercise before angina and ST-segment depression. Circulation **62**:341, 1980.

Effect of BW755C in an occlusion-reperfusion model of ischemic myocardial injury

BW755C is a new antiinflammatory agent which predominantly inhibits lipoxygenase over cyclooxygenase. Effects of BW755C have been examined in a canine, occlusion-reperfusion, model of ischemic myocardial injury. In pentobarbital anesthetized open-chest dogs, the proximal left circumflex coronary artery (LCX) was occluded for 90 minutes and slowly reperfused using a micrometer-driven occluder. Thirty minutes before occlusion, animals randomly received BW755C, 3 mg/kg (n = 7), or 10 mg/kg (n = 8), or saline (n = 16) by intravenous infusion. The thoracotomy was closed and the animals subsequently were killed at 24 hours. Infarct size and anatomic area dependent on the occluded LCX were determined by a dual staining technique using triphenyltetrazolium and Evan's blue. Both doses of BW755C significantly reduced the ultimate extent of irreversible myocardial ischemic injury, whether results were expressed as grams of infarcted tissue or as percent of risk region infarcted. No difference in risk region size was observed between groups. No effects of BW755C on heart rate, arterial pressure, or left circumflex flow were observed. BW755C (10 mg/kg) did not significantly inhibit ex vivo platelet aggregation in response to collagen, adenosine diphosphate, or arachidonic acid. These results suggest that inhibition of lipoxygenase may reduce the extent of ischemic damage to the heart. (Am Heart J 106:8, 1983.)

Stanley R. Jolly, Ph.D.,* and Benedict R. Lucchesi, Ph.D., M.D. *Ann Arbor, Mich.*

BW755C (3-amino-1-[m(trifluoromethyl) phenyl]-2-pyrazoline) is a novel nonsteroidal anti-inflammatory agent (NSAIA). Unlike other NSAIAs, BW755C is a dual inhibitor of both the lipoxygenase and cyclooxygenase pathways of arachidonic acid metabolism.[1-3] Because of its effective inhibition of lipoxygenase, studies with BW755C may give further insight into the role of lipoxygenase-derived leukotriene B_4 and subsequent leukotrienes[1,3,4] in various pathophysiologic conditions. In this report, effects of BW755C on the ultimate extent of myocardial ischemic injury have been examined in a canine model involving occlusion-reperfusion of the left circumflex coronary artery.[5,6]

From the Department of Pharmacology, The University of Michigan Medical School.

This study was supported by National Institutes of Health Grants HL-27817 and HL-19782.

Received for publication May 10, 1982; revision received Oct. 22, 1982; accepted Nov. 12, 1982.

Reprint requests: Benedict R. Lucchesi, M.D., Dept. of Pharmacology, M6322 Medical Science Bldg. I, The University of Michigan, Ann Arbor, MI 48109.

*Dr. Jolly is a postdoctoral fellow of the Pharmaceutical Manufacturers' Association.

METHODS

Occlusion-reperfusion model of myocardial infarction. Ischemic myocardial injury was produced in dogs using techniques detailed in previous publications.[5,6] Male mongrel dogs (10 to 15 kg) were anesthetized with pentobarbital sodium (30 mg/kg intravenously), intubated, and ventilated with room air *via* a Harvard respirator. Catheters for drug infusion and arterial pressure measurement were implanted in the left jugular vein and left carotid artery and were exteriorized at the back of the neck. A thoracotomy was performed at the fifth left intercostal

space, the heart was suspended in a pericardial cradle, and the left circumflex coronary artery (LCX) was isolated distal to its atrial branch and proximal to any major ventricular branches. An electromagnetic flowprobe and a micrometer-driven coronary occluder[7] were placed on the LCX. ECG limb lead II and phasic arterial pressure were recorded continuously on a Grass Model 7 polygraph.

Dogs were assigned randomly to treated or control groups. Thirty minutes before occlusion, LCX flow was recorded and dogs received an infusion of saline or BW755C (3 or 10 mg/kg). Data from control dogs for the two groups have been pooled. BW755C was dissolved in saline. Five minutes before occlusion, the occluder was adjusted so that resting flow was unchanged, but the peak flow increment (reactive hyperemic response) following a 10-second complete occlusion was decreased by more than 70%. Myocardial ischemia was produced by adjusting the occluder to interrupt flow completely for 90 minutes. The drug infusion was completed 30 minutes after occlusion. After 90 minutes of ischemia, flow was restored gradually over 30 minutes and the critical stenosis was retained for an additional 10 minutes. A third flow measurement was made at 45 minutes after reperfusion. At this time the occluder had been removed for at least 5 minutes and flow was stable. In expressing flow measurements, electromagnetic flowprobe results have been divided by the mass of the anatomic risk region determined after the animal was killed.

The thoracotomy was closed and the animal was allowed to recover from the surgical procedure. On the following day, the ECG and arterial pressure were monitored for 1 hour with the dog resting quietly in a sling. Subsequently, the animals were reanesthetized and the original thoracotomy incision was reopened to expose the heart. The heart was fibrillated electrically and removed rapidly for postmortem quantification of infarct size. Only animals which survived occlusion by at least 20 hours were included. Overnight mortality and thrombotic reocclusion of the artery resulted in a loss of 5 of 36 dogs not included in data analysis.

Postmortem quantification of infarct size. Myocardial infarct size was quantified using an in vitro dual perfusion technique described previously.[6] Cannulas were inserted into the LCX immediately distal to the site of LCX occlusion and into the aorta above the coronary ostia. The LCX coronary bed was perfused with 1.5% triphenyltetrazolium hydrochloride (TTC) in 20 mM potassium phosphate buffer (pH 7.4, 38° C). The aorta was perfused in a retrograde manner with 0.5% Evans blue. Both the LCX region and the remainder of the heart were perfused with their respective stains at a constant pressure of 100 mm Hg for 5 minutes. The heart was cut into six equal sections, approximately 1.0 cm thick, perpendicular to the apex-base axis. The area of the left ventricle at risk of infarction due to its anatomical dependence on the LCX for blood flow was identified by the lack of Evans blue in this region. The regions of infarcted myocardium within the area at risk were demarcated by the lack of staining of the tissue when perfused with TTC.

Transverse ventricular sections were traced carefully onto clear plastic overlays. Planimetry was used to determine the amount of left ventricle infarcted and at risk. Ventricular sections were then trimmed of right ventricular, valvular, and fatty tissue. Total left ventricle, area at risk, and infarct were carefully dissected and weighed. Planimetric and gravimetric determinations of percent left ventricle infarcted and percent left ventricle at risk agreed closely. The planimetric (P) and gravimetric (G) estimates of percent risk region infarcted were related as follows: $P = 0.89 \times G + 7.5\%$; $r = 0.94$.

Effects of BW755C on platelet function. Ex vivo platelet aggregation: assessment of platelet function was accomplished by established spectrophotometric methods[8] with a PAP-3 platelet aggregometer (Bio/Data Corp., Willow Grove, PA). Aggregation was initiated by the addition of 50 μl of collagen (1:80 dilution of Ethicon collagen dispersion in TD 150) to 450 μl of diluted platelet-rich plasma (PRP). Aggregation in response to 5.0 μg of adenosine diphosphate (ADP) in 50 μl and 0.65 mM arachidonic acid plus 0.55 mM epinephrine in 10 μl were also examined. PRP was prepared by collecting venous blood in 1.5 ml of 3.0% sodium citrate to a total of 15 ml. This was centrifuged at 310 × g for 3 minutes to obtain the PRP fraction and then 2200 × g for 10 minutes to obtain the platelet poor fraction (PPP). PRP was diluted with PPP to a platelet count of 200,000 per mm^3 before aggregation assays. All platelet samples were assayed less than 2 hours from the time of collection. Values are expressed as percentage of light transmission standardized to the PRP and PPP samples yielding 0% to 100% light transmission, respectively. Comparisons are made between platelet activity before treatment and at 1 hour after the conclusion of BW755C infusion, after animals had received 10 mg/kg.

Statistics. All data are expressed as mean ± SEM. Differences were considered significant when $p < 0.05$. One-way analysis of variance followed by Duncan's multiple range test was used to determine the level of significance of differences between BW755C dose groups and nontreated groups. Multiple measurements within a group were compared using two-way analysis of variance followed by Duncan's multiple range test.

RESULTS

Hemodynamic parameters. A total of 31 dogs were studied with 16 control, seven low-dose, and eight high-dose experiments being successfully completed. Animal weight was similar in these groups (control 12.5 ± 0.7; BW755C (3 mg/kg), 13.0 ± 0.8; BW755C (10 mg/kg) 13.3 ± 0.6, $\bar{X}$ ± SEM, $p > 0.05$).

No significant differences in hemodynamic parameters were observed between control and BW755C groups, although heart rate and coronary flow values were somewhat higher in the control group (Table I). BW755C produced no significant effects on hemodynamic parameters during the first

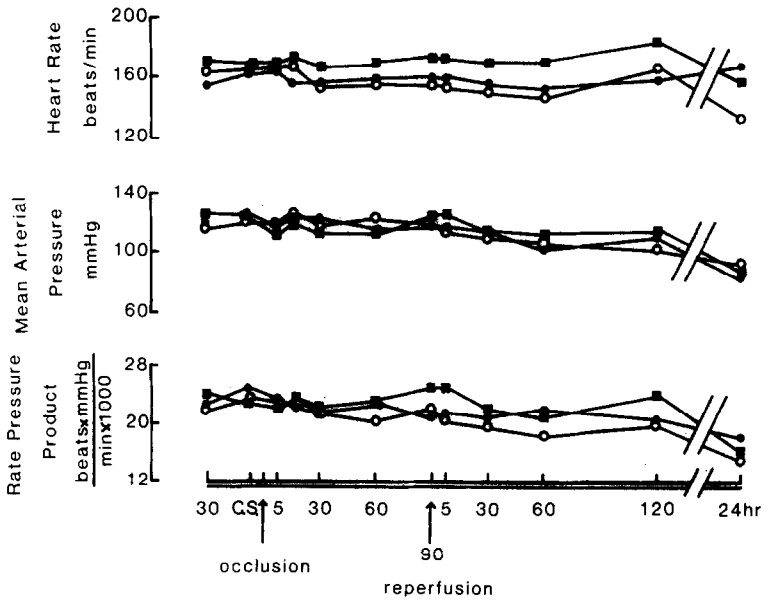

Fig. 1. Heart rate, mean arterial pressure, and the rate-pressure product in saline *(solid squares)* and BW755C (3 mg/kg = *open circles* and 10 mg/kg = *closed circles*) groups. Mean values from 16, seven, and eight experiments per group in saline and BW755C low and high doses are given. Standard errors (not shown) were similar to those in Table I. No significant differences between groups were observed using one-way analysis of variance and Duncan's multiple range test comparing at any given time point.

Table I. Effect of BW755C on hemodynamic parameters before drug infusion (A) and at the time of critical stenosis (B)

		Mean arterial pressure (mm Hg)		*Heart rate (bpm)*		*Circumflex coronary blood flow* (ml/min/gm)*		*Rate-pressure product (bpm × mm Hg × 1000)*	
	No.	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Control	16	125 ± 10†	125 ± 11	170 ± 11	172 ± 10	0.96 ± 0.12	0.92 ± 0.13	24.2 ± 2.3	24.6 ± 2.5
BW755C									
3 mg/kg	7	119 ± 6	125 ± 5	166 ± 16	171 ± 14	0.91 ± 0.15	0.90 ± 0.16	22.0 ± 2.3	23.7 ± 2.3
10 mg/kg	8	122 ± 9	125 ± 10	155 ± 10	164 ± 10	0.83 ± 0.11	0.80 ± 0.12	22.4 ± 2.8	25.0 ± 2.6

*Values given are derived by dividing left circumflex flow (ml/min) by anatomic risk region mass.
†No significance, $\bar{X}$ ± SEM of n animals are given; no significant differences were observed between time points using two-way analysis of variance followed by Duncan's multiple range test or between groups using one-way analysis of variance followed by Duncan's multiple range test.

15 minutes of infusion at either dose (Table I). Heart rate, arterial pressure, and the rate pressure-product during the experimental course are shown in Fig. 1. Control dogs and the BW755C treated groups responded similarly to LCX occlusion and reperfusion. Although BW755C did not appear to affect resting coronary blood flow (Table I), LCX flow at 45 minutes after reperfusion in the absence of a stenosis was increased slightly after BW755C by 9 ± 8% and 10 ± 8% ($\bar{X}$ ± SEM) in the 3 mg/kg and 10 mg/kg groups and decreased in the control group by 14 ± 6% ($\bar{X}$ ± SEM). Because of the large variability, however, this difference between groups was not significant ($p > 0.05$ by one-way analysis of variance and comparison of percent change from initial flow).

Reduction of myocardial infarct size. BW755C and saline treated groups showed no significant differences in left ventricular mass or myocardial mass anatomically dependent on the occluded LCX for flow (Table II). BW755C significantly decreased the ultimate extent of irreversible ischemic myocardial injury at both doses with slightly greater effect at 10 mg/kg. Results have been normalized as percent of left ventricle and percent of area at risk (Fig. 2, *A*). Infarct size in individual experiments is shown in Fig. 2, *B* as percent risk region infarcted vs percent left ventricle at risk. The small variation in risk

Table II. Effect of BW755C on ultimate infarct size in a canine model of regional myocardial ischemia

	No.	*Total left ventricle (gm)*	*Risk region (gm)*	*Infarct (gm)*
Saline	16	68.1 ± 4.2*	26.7 ± 2.0	11.5 ± 1.0
BW755C				
10 mg/kg	8	70.3 ± 4.1	28.7 ± 2.7	6.1 ± 1.3†
3 mg/kg	7	71.3 ± 5.3	27.2 ± 3.2	7.2 ± 1.7†

*$\bar{X}$ ± 1 SEM.
†$p < 0.05$ between saline and BW755C by one-way analysis of variance followed by Duncan's multiple range test.

Table III. Ex vivo platelet aggregation before and after BW755C (10 mg/kg) treatment

	Addition		
	Collagen 1:80	*ADP 5 μg/ml*	*Arachidonic acid 0.65 mM*
Control	63.2 ± 5.1*†	52.5 ± 3.3	45.8 ± 13.5
BW755C	55.0 ± 13.7	60.5 ± 3.6	39.6 ± 17.6

ADP = adenosine diphosphate.
*All values are percent light transmission at peak aggregation following each addition.
†Mean ± SEM of five dogs is given. Paired *t* comparison showed no significant differences between control and BW755C values.

region size for all three groups is evident. The separation of individual data points shows that variability of myocardial infarction in dogs, but the general separation of BW755C and saline clusters shows the drug effect. Dependency of infarct size upon the area at risk was not observed, possibly because of the small variation in risk region size. Similar results were obtained by planimetric measurement of traced ventricular segments. Area at risk by planimetry was: control 39.0 ± 3.2%; BW755C (10 mg/kg) 40.5 ± 3.0% of the left ventricle ($\bar{X}$ ± 1 SEM; $p > 0.05$). Infarct size by planimetry was: control 50.8 ± 4.0%, BW755C (10 mg/kg) 25.4 ± 4.7% of area at risk ($\bar{X}$ ± 1 SEM; $p > 0.05$). The low-dose group and its matched eight controls were not analyzed planimetrically.

Platelet aggregation ex vivo. Platelet aggregation was studied from blood samples obtained from five LCX occlusion-reperfusion dogs before and after the high dose of 10 mg/kg BW755C. BW755C did not significantly inhibit aggregation due to arachidonic acid plus epinephrine, collagen, or ADP (Table III).

DISCUSSION

BW755C reduction of infarct size. The present study shows that BW755C can reduce the ultimate extent of myocardial injury resulting from 90

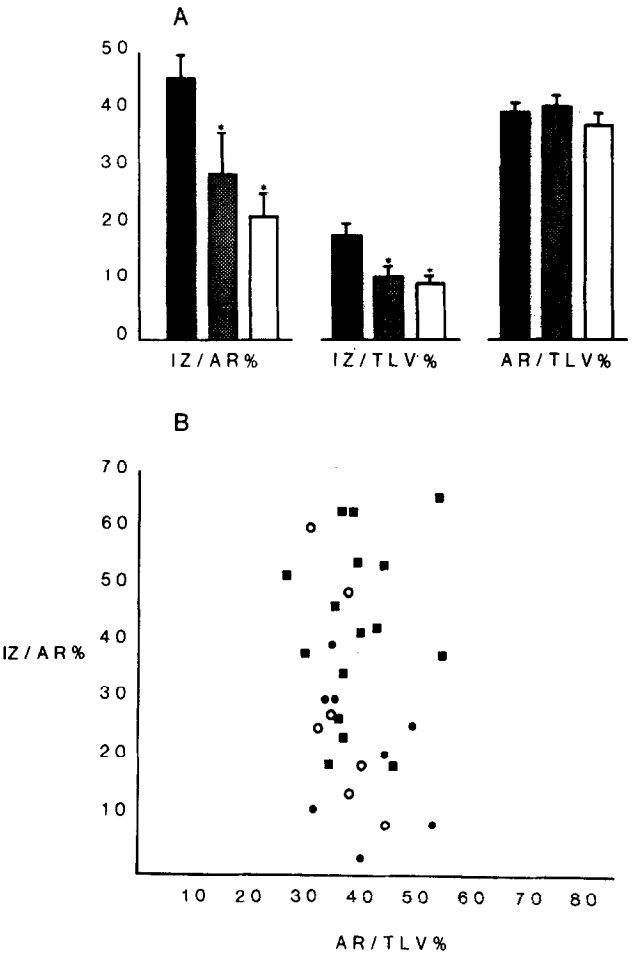

Fig. 2. Effects of BW755C and 24-hour myocardial infarct size. *A*, Shows infarcted zone normalized as a percent of area at risk *(IZ/AR%)*, or as a percent of total left ventricle *(IZ/TLV%)* and area at risk as a percent of total left ventricle *(AR/TLV%)*. *Solid bars* indicate saline treatment (n = 16); *hatched bars* are the BW755C low doses, 3 mg/kg (n = seven); *open bars* are the BW755C high doses, 10 mg/kg (n = eight). *Stars* indicate significant differences compared to the saline control group by one-way analysis of variance followed by Duncan's multiple range test. No differences in area at risk between groups were observed. *B*, Shows a scattergram of saline *(closed squares)*, BW755C 3 mg/kg *(open circles)* and 10 mg/kg *(closed circles)*. The reduction of infarct size by BW755C can be seen in the downward separation of individual experiments compared to saline treated controls.

minutes' occlusion of the LCX followed by reperfusion and sacrifice at 24 hours. BW755C had no measurable hemodynamic effects, so it is difficult to attribute the protective action of the drug to a reduction in myocardial oxygen demand. BW755C did not affect resting coronary bloow flow, as determined by measurements of LCX coronary flow before and after reperfusion. Neither regional myocardial blood flow nor coronary collateral flow were examined in this study. If BW755C increased is-

chemic myocardial blood flow, reduction of ischemic injury could be attributed to increased oxygen supply. Although differences between 3 and 10 mg/kg BW755C were not statistically significant, it appeared that the action was dose-dependent.

Mechanism of BW755C effect. Studies with other nonsteroidal anti-inflammatory agents have not supported an important role of collateral blood flow in their effects on ischemic myocardium. Reduction of ischemic injury by ibuprofen[9,10] and increased damage after indomethacin[11] occurred without changes in myocardial blood supply to the jeopardized region. On the other hand, increased epicardial collateral blood flow has been reported after aspirin and sulfinpyrazone[12] treatment without significant changes in the extent of ischemic injury.[13,14] It appears more likely that protection by BW755C is due to the antiinflammatory effects mediated *via* alterations in arachidonic acid metabolism rather than to improvement in myocardial oxygen supply.

Critical stenosis model. The experimental LCX occlusion-reperfusion model utilizing a critical stenosis and slow reperfusion is a useful method for detecting agents which have the potential to protect ischemic myocardium. Previous studies by this laboratory have shown that LCX occlusion reduces flow in the central ischemic subendocardium to less than 10% of control.[10,15] The presence of a critical stenosis upon reperfusion reduces the severity of arrhythmias upon reflow.[5] Furthermore, reperfusion through a critical stenosis has been shown to reduce severity of myocardial hemorrhage[5,6] and ventricular fibrillation.[5] Reduction of reperfusion arrhythmias by a critical stenosis has also been reported by Sheehan and Epstein.[16] Antiarrhythmic agents such as lidocaine were not used in the study because of possible effects on ischemic injury.[17] Finally, examination of the myocardial infarct at 24 hours ensured that the ischemic event was largely completed,[18] suggesting that protection by BW755C was not due to delayed expression of ischemic injury.[19]

BW755C attenuation of leukocyte activity by lipoxygenase inhibition. Since BW755C inhibits both cyclooxygenase and lipoxygenase, results obtained in this study cannot be simply attributed to effects on either system. Even though platelet aggregation ex vivo did not reveal significant inhibition by BW755C, the true degree of cyclooxygenase inhibition in vivo may have differed, since ex vivo aggregometry employs conditions which are markedly different from those in vivo and since potentially critical interactions between platelets and the vascular endothelium are absent.[20,21] Platelets may exacerbate myocardial injury by aggregating in the microvasculature supplying the involved region[22-24] and by releasing vasoactive substances, particularly TXA_2.[21] Leukocytes possess lipoxygenase activity and respond to lipoxygenase products, especially leukotriene B_4, in very low concentrations.[1,25,26] Leukocytes also enter ischemic tissue[24,27,28] and may influence the development of ischemic injury by microembolism[28] and by release of inflammatory mediators, lysosomal enzymes, and oxygen-free radicals.[29] An important role of these blood-borne components in myocardial ischemic injury has been suggested.[30] Entry of both platelets and leukocytes is increased by reperfusion,[23,24] suggesting that drug effects on these blood components could be an important mechanism for protection in this model.

Studies with other NSAIAs suggest a poor correlation between protection of ischemic myocardium and cyclooxygenase mediated antiplatelet effects. Although indomethacin and ibuprofen both decrease platelet aggregation, the former increases[11] and the latter decreases[9,10,20] the ultimate extent of myocardial injury. Furthermore, platelet inhibitory doses of sulfinpyrazone and naproxen have recently been shown not to affect myocardial infarct size.[14] Recent work in this laboratory has shown that reduction of infarct size by ibuprofen was associated with equivalent accumulation of 111-Indium labelled autologous platelets compared to controls, but with significantly reduced accumulation of 111-Indium labelled autologous leukocytes into ischemic reperfused myocardium.[24] BW755C has been shown to decrease neutrophil migration into carrageenan impregnated sponges implanted in rats.[31] Direct effects of leukotrienes on ischemic myocardium must also be considered. Leukotrienes have been shown to increase vascular resistance and microvascular permeability in guinea pig skin.[32] Recently, leukotrienes have been shown to produce coronary vasoconstriction in isolated guinea pig hearts.[33] If leukotrienes indeed contribute to the development of myocardial ischemic injury, perhaps the varied effects of other NSAIAs can be explained, in part, by substrate diversion of arachidonic acid away from cyclooxygenase into the lipoxygenase pathway. Enhanced production of slow reacting substance of anaphylaxis (SRS-A) after indomethacin has been observed in rat granulomatous inflammatory reactions.[34] Furthermore, concentrations of indomethacin which only block cyclooxygenase have been shown to potentiate leukocyte migration into an active inflammatory region.[31]

Conclusions. While this report was being prepared and extended by addition of results from the low-dose treatment group, the observation of myocardial protection by BW755C was independently confirmed by Mullane and Moncada.[35] Using a 60-

minute occlusion of the left anterior descending coronary artery with treatment (10 mg/kg) 30 minutes after reperfusion, infarct size was decreased to a degree similar to that seen with the high dose in this study. Treatment after reperfusion removes the possibility that drug protection was due to effects on myocardial oxygen supply and demand. It provides further evidence for an anti-inflammatory mechanism of BW755C's action by interference with an interaction between potentially viable tissue and cells migrating into the area and activated by injured myocardium.

The authors wish to thank the Burroughs Wellcome Company for the generous supply of BW755C. We acknowledge the excellent technical assistance of Messrs. Marc B. Bailie, William J. Kane, and Lewis R. Weiner; and express appreciation for secretarial help from Mrs. Dixie Thomas.

REFERENCES

1. Mullane KM, Flower RI: The interaction of antiinflammatory drugs with arachidonic acid metabolism. Mater Med Pol **12**:195, 1980.
2. Blackwell GJ, Flower RJ: 1-Phenyl-3 pyrazolidone: An inhibitor of cyclooxygenase and lipoxygenase pathways in lung and platelets. Prostaglandins **16**:417, 1978.
3. Armour CL, Hughes JM, Seale JP, Temple DM: Effect of lipoxygenase inhibitors on release of slow reacting substances from human lung. Eur J. Pharmacol **72**:93, 1981.
4. Hedqvist P, Dahlen SE, Gustafson L, Hammerstrom S, Samuelsson B: Biological profile of leukotrienes C_4 and D_4. Acta Physiol Scand **110**:331, 1980.
5. Lucchesi BR, Burmeister WE, Lomas TE, Abrams GD: Ischemic changes in the canine heart as affected by the dimethyl analog of propranolol, UM-272 (SC-27761). J Pharmacol Exp Ther **199**:310, 1978.
6. Jolly SR, Abrams GD, Romson JL, Bailie MB, Lucchesi BR: Effects of lodoxamide on ischemic reperfused myocardium. J Cardiovasc Pharmacol **4**:441, 1982.
7. Hosko MJ, Gross GJ, Warltier DC: Technique for precise graded arterial stenosis and occlusion. Basic Res Cardiol **72**:651, 1977.
8. Mills D, Roberts G: Membrane active drugs and the aggregation of human blood platelets. Nature **213**:35, 1967.
9. Jugdutt BI, Hutchins GM, Bulkley BH, Becker LC: Salvage of ischemic myocardium by ibuprofen during infarction in the conscious dog. Am J Cardiol **46**:74, 1980.
10. Romson JL, Bush LR, Jolly SR, Lucchesi BR: The cardioprotective effect of ibuprofen in experimental regional and global myocardial ischemia. J Cardiovasc Pharmacol **4**:187, 1982.
11. Jugdutt BI, Hutchins GM, Bulkley BH, Becker LC: Effect of indomethacin on collateral blood flow and infarct size in the conscious dog. Circulation **59**:734, 1979.
12. Davenport N, Goldstein RE, Capurro N, Lipson LC, Bonow RO, Shulman NR, Epstein SE: Sulfinpyrazone and aspirin increase epicardial coronary collateral flow in dogs. Am J Cardiol **47**:848, 1981.
13. Bonow RD, Lipson LC, Sheehan FH, Capurro NL, Isner JM, Roberts WC, Goldstein RE, Epstein SE: Lack of effect of aspirin on myocardial infarct size in the dog. Am J Cardiol **47**:258, 1981.
14. Bolli R, Goldstein RE, Davenport N, Epstein SE: Influence of sulfinpyrazone and naproxen on infarct size in the dog. Am J Cardiol **47**:841, 1981.
15. Bush LB, Romson JL, Ash JL, Lucchesi BR: Effect of diltiazem on the extent of ultimate myocardial injury resulting from temporary coronary artery occlusion in dogs. J Cardiovasc Pharmacol **4**:285, 1982.
16. Sheehan FH, Epstein SE: Determinants of arrhythmic death due to coronary spasm: Effects of pre-existing coronary artery stenosis on the incidence of reperfusion arrhythmias. Circulation **65**:259, 1982.
17. Boudoulas H, Karayannacos PE, Lewis RP, Kakos GS, Kilman JW, Vasko JS: Potential effect of lidocaine on ischemic myocardial injury: Experimental and clinical observations. J Surg Res **24**:469, 1978.
18. Cox JL, McLoughlin VW, Flowers NC, Horan LG: The ischemic zone surrounding acute myocardial infarction; its morphology as determined by dehydrogenase staining. Am Heart J **76**:650, 1968.
19. Hofmann M, Hofmann M, Schaper W: Influence of hyaluronidase on infarct size following experimental coronary occlusion of short (90) or long (24 hrs) duration. Bas Res Cardiol **75**:340, 1980.
20. Moncada S, Vane JR: Prostacyclin, platelet aggregation and thrombosis. *In* deGaetano G, Garattini S, editors: Platelets: A multidisciplinary approach. New York, 1978, Raven Press, pp 239.
21. Romson JL, Bush LR, Haack DW, Lucchesi BR: The beneficial effects of oral ibuprofen on coronary artery thrombosis and myocardial ischemia in the conscious dog. J Pharmacol Exp Ther **215**:271, 1980.
22. Ruf W, McNamara JJ, Suehiro A, Suehiro G, Wickline SA: Platelet trapping in myocardial infarct in baboons: Therapeutic effect of aspirin. Am J Cardiol **46**:405, 1980.
23. Laws KH, Clanton JA, Starnes VA, Lupinetti FM, Collins JC, Oates JA, Hammon JW: Kinetics of 111-Indium labelled platelet uptake in experimental myocardial infarction. Circulation **64**(suppl IV):154, 1981.
24. Romson JL, Hook BG, Rigot VM, Schork MA, Swanson DP, Lucchesi BR: The effect of ibuprofen on accumulation of 111-Indium labelled platelets and leukocytes in experimental myocardial infarction. Circulation **66**:1002, 1982.
25. Goetzl EJ, Pickett WC: The human PMN leukocyte chemotactic activity of complex hydroxyeicosatetraenoic acids (Hetes). J Immunol **125**:1789, 1980.
26. Palmblad J, Malmsten CL, Uden AM, Radmark O, Engstedt L, Samuelsson B: Leukotriene B_4 is a potent and stereospecific stimulator of neutrophil chemotaxis and adherence. Blood **58**:658, 1981.
27. Weiss ES, Ahmed SA, Thakur MJ, Welch MJ, Coleman RE, Sobel BE: Imaging of the inflammatory response in ischemic canine myocardium with 111-Indium labelled leukocytes. Am J Cardiol **40**:195, 1977.
28. Engler R, Schmid-Schoenbein GW, Pavela R: Role of leukocyte capillary plugging in preventing myocardial reperfusion. Circulation **64**(suppl IV):138, 1981.
29. Weissmann G, Smolen JE, Korchak HM: Release of inflammatory mediators from stimulated neutrophils. N Engl J Med **303**:27, 1980.
30. Schaper J: Ultrastructure of the myocardium in acute ischemia. *In* Schaper W, editor: The pathophysiology of myocardial perfusion. New York, 1979, Elsevier-North Holland Press, pp 581.
31. Higgs GA, Eakins KE, Mugridge KG, Moncada S, Vane JR: The effects of non-steroidal antiinflammatory drugs on leukocyte migration in carrageenan-induced inflammation. Eur J Pharmacol **66**:81, 1980.
32. Williams TJ, Piper PJ: The action of chemically pure SRS-A on the microcirculation *in vivo*. Prostaglandins **19**:779, 1980.
33. Tershita ZI, Fukui H, Hirata M, Terco S, Olikawa S, Nishikawa K, Kikachi S: Coronary vasoconstriction and PGI_2 release by leukotrienes in isolated guinea pig hearts. Eur J Pharmacol **73**:357, 1981.
34. Koshihara Y, Nagasaki I, Mirota S-I: Production of slow reacting substances in rat granulomatous inflammation. Biochem Pharmacol **30**:1781, 1981.
35. Mullane KM, Read N, Salmon JA, Moncada S: The role of leukocytes in acute myocardial infarction in anesthetized dogs: Mechanism of myocardial salvage by antiinflammatory drugs. (In press, 1983)