

## Effects of external counterpulsation on enzymatically estimated infarct size and ventricular arrhythmia<sup>1</sup>

SIDDHESH K. GOWDA, THOMAS A. GILLESPIE, JOSEPH D. BYRNE, H. DIETER AMBOS, BURTON E. SOBEL, AND ROBERT ROBERTS

*From the Cardiovascular Division, Washington University School of Medicine, St. Louis, Missouri, U.S.A.*

**SUMMARY** To determine whether external counterpulsation influences the evolution of injury in ischaemic myocardium, we analysed 20-hour continuous electrocardiographic recordings and plasma creatine kinase (CK) time-activity curves in 39 patients with acute myocardial infarction and 10 normal subjects. CK values projected from observed changes during the first 7 hours after admission in patients with infarction were used to predict infarct size before implementation of counterpulsation for 30-minute intervals separated by 10-minute rest periods for 12 to 18 hours. CK values during the 72-hour interval after admission were compared with values projected before counterpulsation to determine whether the intervention changed the ratio of enzymatically estimated observed to predicted infarct size. Counterpulsation augmented systemic arterial diastolic pressure and decreased pulmonary arterial occlusive pressure consistently but affected CK activity in normal subjects only minimally (mean peak 0.060 IU/ml). Among patients with infarction treated with counterpulsation, the incidence and rate of premature ventricular complexes, couplets, and runs did not differ significantly from values in control patients matched for early ventricular arrhythmia despite a slight transitory decrease of ventricular arrhythmia within the first hour of counterpulsation ( $P < 0.01$ ). The ratio of observed to predicted infarct size was virtually identical in treated compared with control patients matched for predicted infarct size. Thus, external counterpulsation initiated 7 hours after an increase in plasma CK activity did not lead to apparent salvage of ischaemic myocardium despite a transitory improvement in ventricular rhythm.

Most deaths occurring in patients admitted to hospital for acute myocardial infarction result from pump failure associated with extensive myocardial necrosis (Harnarayan *et al.*, 1970; Page *et al.*, 1971; Sobel *et al.*, 1972; Shell and Sobel, 1973b). Thus, it is likely that reduction of mortality in this group of patients will require limitation of the extent of myocardial damage. Evolution of myocardial infarction appears to be a dynamic process with its ultimate extent related in part to the balance between myocardial oxygen supply and demand (Maroko *et al.*, 1971; Braunwald and Maroko, 1973; Roberts *et al.*, 1975b). Thus, by modifying factors that influence myocardial oxygen consumption, it has been possible to produce corresponding directional changes in the extent of damage in experimental animals. Attempts to reduce infarct size in

clinical studies have involved decreasing myocardial oxygen consumption by reducing heart rate or ventricular afterload (Braunwald *et al.*, 1969; Shell and Sobel, 1973a, 1974); increasing cardiac output, coronary perfusion, and myocardial oxygen supply with agents with positive inotropic effects (Gillespie *et al.*, 1975); augmenting myocardial perfusion by emergency coronary bypass grafting (Keon *et al.*, 1973), mechanical circulatory assist (DeLaria *et al.*, 1974); or augmenting substrate supply to enhance anaerobic glycolysis (Maroko *et al.*, 1972b).

Early reperfusion of ischaemic myocardium produces favourable results in experimental animals (Maroko *et al.*, 1972a) and circulatory assist with intra-aortic balloon counterpulsation is associated with reduction of left ventricular systolic pressure, increased systemic arterial diastolic pressure, increased coronary flow (Brown *et al.*, 1967; Mueller *et al.*, 1971; Shaw *et al.*, 1974), decreased myocardial ischaemic injury (Gill *et al.*, 1973), and delayed evolution of myocardial necrosis (DeLaria *et al.*, 1974). Circulatory assist with this technique requires

<sup>1</sup>Supported in part by National Institutes of Health Grants in Ischemic Heart Disease; and in Prediction and Prevention of Sudden Cardiac Death.

surgical insertion of a balloon into the aorta entailing potential hazards in acutely ill patients. Attempts have been made to avoid such risks by augmenting diastolic arterial pressure with external counterpulsation (performed with a Cardioassist<sup>R</sup> device) (Soroff *et al.*, 1964). Augmentation of diastolic blood pressure and coronary flow similar to that seen with intra-aortic balloon counterpulsation has been achieved with this technique.

The present study was undertaken to evaluate effects of external counterpulsation (Cardioassist<sup>R</sup>) on enzymatically estimated infarct size and ventricular arrhythmia during the acute phase of myocardial infarction. Diastolic pressure was augmented noninvasively in 13 patients with acute myocardial infarction, and infarct size was estimated enzymatically based on serial changes in plasma creatine kinase activity as previously described (Sobel *et al.*, 1972). The difference between infarct size predicted before external counterpulsation and infarct size estimated from all plasma CK values (before and after external counterpulsation) was compared with the corresponding difference between predicted and observed infarct size in 13 control patients (not treated with counterpulsation), matched for predicted infarct size.

The effect of external counterpulsation on ventricular arrhythmia was assessed by comparing the frequency of premature ventricular complexes before external counterpulsation with their frequency during treatment to analogous results in corresponding intervals in a second group of 13 other control patients with acute myocardial infarction matched for ventricular arrhythmia during the first 7 hours after admission.

## Methods

### PATIENT SELECTION

Thirty-nine patients with documented acute myocardial infarction admitted to the Barnes Hospital Cardiac Care Unit and 10 normal volunteers without cardiac disease were studied, including 28 men and 11 women with a mean age of 57 years (42 to 65, range). All patients were admitted within 6 hours of the onset of symptoms with initial plasma total creatine kinase values  $<0.075$  IU/ml. None had been treated with digitalis or antiarrhythmic agents before admission. Thirteen patients were treated with external counterpulsation. Patients were excluded if age exceeded 65 years, systolic hypertension was more than 160 mmHg; or if there was peripheral vascular disease, obesity, previous skeletal injury, severe arrhythmia, or heart block. Thirteen control patients with infarction were selected on the basis of comparable predicted infarct size and

treated conventionally. A second control group of 13 patients with infarction was selected retrospectively on the basis of comparable frequency and incidence of premature ventricular complexes compared with treated patients during the first 7 hours (the interval before counterpulsation in treated patients).

Effects of external counterpulsation on the lower extremities may have caused release of creatine kinase from skeletal muscle that might affect estimation of observed infarct size. For this reason, 10 normal volunteers with no history of cardiac disease were studied to determine whether external counterpulsation altered plasma creatine kinase levels, white blood cell count, haemoglobin, haematocrit, or vital signs.

### EXTERNAL COUNTERPULSATION

The device used in this study was a Cardioassist<sup>R</sup> external pressure circulatory assist system (Soroff *et al.*, 1964), which applies circumferential compression to the thighs during diastole, with compression relieved during systole. Electrocardiographic triggering of compression provides synchronisation to the diastolic phase of the cardiac cycle. Compression of the arterial bed in the legs increases diastolic aortic pressure (Fig. 1) and may increase coronary perfusion during diastole. Arterial runoff is enhanced after the compression phase, during systole. Afterload and diastolic pressure are, therefore, reduced after compression ceases at the onset of systole.

Thirteen patients were treated with external counterpulsation for 30-minute intervals alternating with 10 minutes of rest for 12 to 18 hours. External counterpulsation was initiated immediately after data were obtained sufficient for prediction of infarct size from serial changes in plasma creatine kinase activity during the first 7 hours. Treatment was tolerated by 9 patients for the entire 18 hours and by 4 for only 12 hours. Eight normal volunteers underwent external counterpulsation for 8 hours and 2 for 18 hours.

### ENZYMATIC ESTIMATION OF INFARCT SIZE

Blood samples for determination of creatine kinase activity were obtained via an indwelling Heparin lock to avoid repetitive venepuncture. Samples were collected hourly for the first 10 hours, every 2 hours thereafter until creatine kinase activity had returned to baseline ( $<100$  mIU/ml). Blood samples were collected and neutralised with EGTA (0.005 M, pH 7.4) and centrifuged at 2000 *g* for 10 minutes after which mercaptoethanol (0.005 M) was added to protect enzyme activity during storage. Samples were analysed for creatine kinase activity spectro-

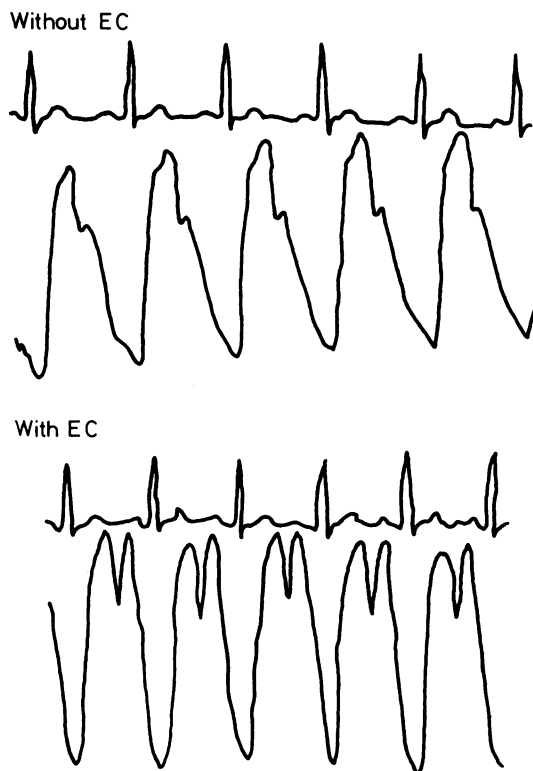


Fig. 1 The top panel shows the electrocardiographic tracing and pressure recorded from an intra-arterial catheter from a patient before counterpulsation. The panel below shows the electrocardiogram and arterial pressure tracing from the same patient during counterpulsation and illustrates the diastolic augmentation typically seen with counterpulsation.

photometrically according to the Rosalki method either immediately or after storage at 0–4° C. Samples stored under these conditions do not lose activity for at least 6 weeks (Roberts *et al.*, 1974). MB creatine kinase isoenzyme activity was determined quantitatively by a fluorometric kinetic method previously described (Roberts *et al.*, 1974).

Infarct size was predicted from projected plasma creatine kinase values obtained from the log normal curve best fitting the values of creatine kinase activity during the first 7 hours after the initial plasma creatine kinase rise (Shell *et al.*, 1973). Observed infarct size expressed in CK-gram-equivalents was calculated from all creatine kinase values with the patient's own individual creatine kinase disappearance rate ( $k_d$ ), determined from the terminal portion of the time-activity curve (Roberts *et al.*, 1975b).

In treated patients, infarct size predicted was estimated from data obtained during the 7 hours

before external counterpulsation. Comparison of infarct size predicted to infarct size observed was used as an index of the effect of external counterpulsation on ischaemic myocardium.

#### QUANTIFICATION OF VENTRICULAR ARRHYTHMIA

Continuous recordings of the electrocardiogram during the first 20 hours were obtained on magnetic tapes, with recordings initiated in all cases within one hour after hospital admission. All tapes were digitised and processed by the Argus/H computer system designed for automated high speed analysis of ventricular arrhythmia with human editor verification (Nolle *et al.*, 1974). This system shows 1 per cent reproducibility after digitisation, true positive sensitivity of approximately 90 per cent and essentially no false positives. Tapes were analysed for the total number of premature ventricular complexes, and the number of couplets and runs of ventricular tachycardia. The effects of counterpulsation on ventricular arrhythmia were assessed by determining the rate per hour of premature ventricular complexes (including couplets and runs of ventricular tachycardia) in the first 7 hours to the rate observed in the subsequent 13 hours and comparing results with corresponding results in control patients matched for ventricular arrhythmia during the initial 7 hours. In addition, the number of premature ventricular complexes (PVCs) occurring during the hour before counterpulsation (seventh hour) was compared with the number occurring during the first hour of counterpulsation (eighth hour) in treated patients. Data were compared also with the corresponding premature ventricular contraction rates during the seventh and eighth hours in control patients. Treatment with bolus injections of lignocaine (1 mg/kg i.v.) was given to all patients when the rate of ventricular premature complexes exceeded 10 per minute for 3 consecutive minutes or when runs of ventricular tachycardia occurred (more than 3 ventricular premature complexes in a row). Lignocaine requirements were similar for treated and control patients. No other anti-arrhythmic agents were used.

#### EVALUATION OF HAEMODYNAMICS

Systemic arterial pressure was monitored continuously in all patients treated with external counterpulsation with the use of finger plethysmography calibrated by direct intra-arterial pressure and cuff pressure and validated by comparison of serial changes with results of percutaneous catheterisation of the radial artery in 6 patients. Swann-Ganz thermodilution catheters were used in 9 treated patients to evaluate changes in cardiac output, and

right atrial pulmonary artery occlusive pressure for at least 3 hours before counterpulsation and at 2-hour intervals during counterpulsation. Plasma electrolytes and arterial blood gases were monitored every 6 hours.

## Results

### EFFECTS OF EXTERNAL COUNTERPULSATION ON NORMAL VOLUNTEERS

Counterpulsation of normal volunteers resulted in a mean increase of 60 mIU/ml in plasma creatine kinase among the 8 volunteers treated for 12 hours. No additional increase occurred in the other 2 patients who were treated for 18 hours. Mean white blood cell count increased from 5960 cells per mm<sup>2</sup> to 9530 cells per mm<sup>2</sup> following counterpulsation for 12 hours. WBC count returned to normal within 16 hours after cessation of external counterpulsation. Modest haemoconcentration occurred (mean haemoglobin increased from 15.4 g of haemoglobin to 16.0). No significant change in plasma LDH levels, body temperature, heart rate, or systolic blood pressure occurred in 10 volunteers treated with counterpulsation.

### EFFECTS OF EXTERNAL COUNTERPULSATION ON HAEMODYNAMICS

The mean increase in diastolic pressure was 30 mmHg. Additional haemodynamic effects included an average decrease of mean pulmonary arterial occlusive pressure of 7 mmHg, an average decrease in systemic arterial systolic pressure of 18 mmHg, and an increase in the mean cardiac index from 2.3 to 3.1 l/min per m<sup>2</sup> during counterpulsation.

### EFFECTS OF EXTERNAL COUNTERPULSATION ON ENZYMATICALLY ESTIMATED INFARCT SIZE

In the control patients matched for predicted infarct size, infarct size predicted was  $36 \pm 9.1$  CK-gram-equivalents, similar to estimates of infarct size observed,  $33 \pm 6.7$  CK-gram-equivalents (Table). This correspondence is typical of that seen in patients with infarction uncomplicated by shock or

intramuscular injection. Similar values of predicted and observed infarct size (38 vs 36 CK-gram-equivalents) (Table) were observed in patients treated with external counterpulsation, indicating that no consistent reduction in enzyme release from the heart, indicative of salvage of myocardium, resulted from this intervention. In view of the results in volunteers, 60 mIU were subtracted from the creatine kinase values obtained in treated patients during counterpulsation, and infarct size was calculated using the corrected creatine kinase values. Since plasma MB creatine kinase comprised 12 to 15 per cent (Roberts *et al.*, 1975a) of total activity in samples with peak total creatine kinase in each treated patient in keeping with the ratio of MB to total creatine kinase in myocardium, substantial release of MM creatine kinase into blood from skeletal muscle could be excluded.

### EFFECTS OF COUNTERPULSATION ON VENTRICULAR ARRHYTHMIA

Analysis of the continuous electrocardiograms showed a distinct decline in the incidence of premature ventricular complexes in the 13 hours after the initial 7-hour interval in both treated ( $n = 13$ ) and control patients ( $n = 13$ ), in keeping with the natural history of ventricular arrhythmias associated with uncomplicated infarction (Roberts *et al.*, 1975c). In the treated patients, an average of 190 premature ventricular complexes occurred in the 7-hour interval before counterpulsation compared with 70 in the subsequent 13 hours during counterpulsation. In control patients matched for frequency of premature ventricular contractions, the ventricular contractions during the first 7 hours averaged 195 compared with 110 in the subsequent 13 hours. These data suggest a possible benefit from external counterpulsation. However, the difference is not statistically significant (Fig. 2).

Comparison of the frequency of premature ventricular complexes in the hour immediately before counterpulsation (seventh hour) with that seen during the first hour of counterpulsation (eighth hour) showed a decrease of 45 per cent, compared with a 10 per cent increase in the control group corresponding time periods (Fig. 3,  $P < 0.05$ ). However, no significant difference was noted between the frequency of couplets before and after the onset of counterpulsation and during the equivalent intervals in controls.

## Discussion

Intra-aortic balloon counterpulsation has been shown to modify the haemodynamics favourably during acute myocardial infarction in experimental

Table Effect of external counterpulsation on infarct size

	N	ISP <sup>1</sup>	ISO <sup>1</sup>	Difference
Controls (ISP matched)	13	$36 \pm 9.1$	$33 \pm 6.7$	NS
External counter- pulsation treated	13	$38 \pm 6.7$	$36 \pm 8.75$	NS

<sup>1</sup>ISP and ISO represent enzymatically estimated predicted and observed infarct size expressed as CK-gram-equivalents (mean  $\pm$  SD).

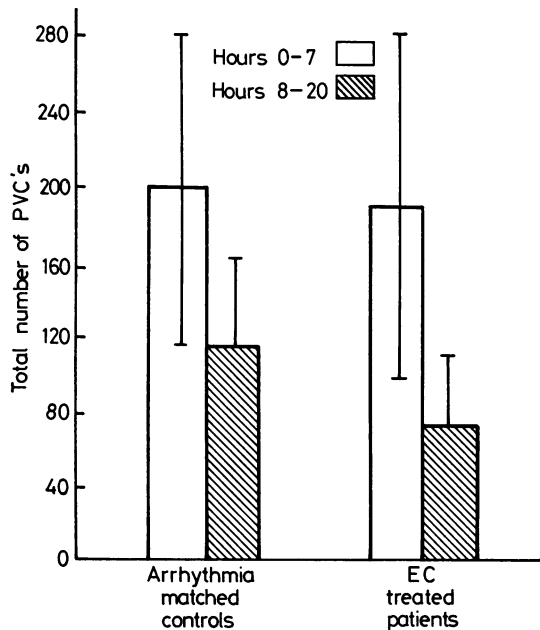


Fig. 2 Premature ventricular contractions (PVCs) present in controls matched for arrhythmia (left panel) compared with PVCs in the treated group (right panel). The slashed bars represent the standard error of the mean. Premature ventricular contractions before counterpulsation during the corresponding interval in the control group are depicted with the open bar, and those during counterpulsation with the shaded bar.

and clinical studies (Goldfarb *et al.*, 1968; Kantrowitz *et al.*, 1968). Nevertheless, despite haemodynamic improvement in patients with severe failure and cardiogenic shock, improvement in survival has not been striking (Scheidt *et al.*, 1973). Because intra-aortic balloon counterpulsation is an invasive procedure, its use has been limited primarily to patients with severe failure or cardiogenic shock (Kantrowitz *et al.*, 1968; Mueller *et al.*, 1971), in whom it is likely that a large portion of myocardium has already been destroyed (Page *et al.*, 1971). External counterpulsation, which can be performed noninvasively, may be more applicable to acutely ill patients because it entails less risk and because haemodynamic effects similar to those seen with intra-aortic balloon counterpulsation can be obtained (Soroff *et al.*, 1971).

The present study was performed with external counterpulsation in patients with uncomplicated acute myocardial infarction to determine its effect on enzymatically estimated infarct size, based on the current concept that augmentation of diastolic blood pressure might increase coronary flow and protect

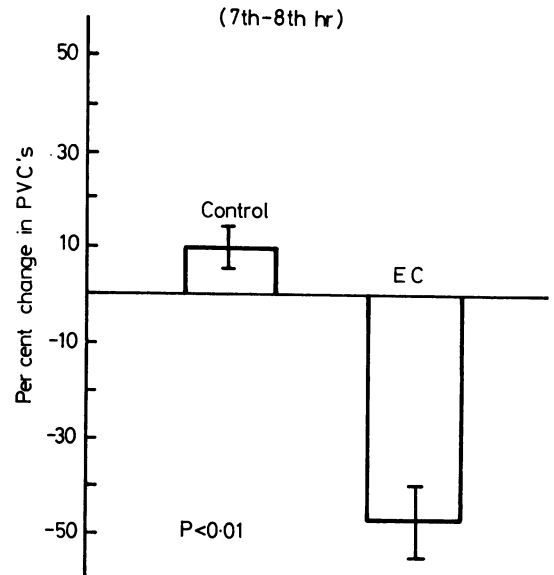


Fig. 3 An hourly increase of 10 per cent in frequency of premature ventricular contraction occurred in the hour corresponding to the hour after onset of counterpulsation in controls compared with a decrease of 48 per cent in patients treated with external counterpulsation (EC). The slashed bars represent the standard error of the mean.

jeopardised ischaemic myocardium. Patients with cardiogenic shock were excluded since death in this situation appears to be virtually inevitable. Treated patients underwent counterpulsation for 12 to 18 hours, with frequent brief rest periods. Most patients tolerated the procedure well. Anxiety was minimised by thorough explanations of the procedure to each patient and the presence at all times of a nurse or doctor at the bedside to provide reassurance and answer questions. With treatment, diastolic arterial pressure increased by an average of 30 per cent, cardiac output increased slightly, and pulmonary arterial occlusive pressure decreased significantly by 7 mmHg. Heart rate did not increase significantly. In spite of these favourable haemodynamic effects, no salvage of myocardium was observed.

Experimental studies with both intra-aortic balloon counterpulsation and external counterpulsation have been shown to increase coronary flow (Shaw *et al.*, 1974). However, in dogs, regional flow to the ischaemic area measured with microspheres is not significantly increased by intra-aortic balloon counterpulsation despite a slight but significant increase in coronary flow in normal zones (Shaw *et al.*, 1974).

It is possible that the lack of an observed effect on infarct size of counterpulsation in the present study was related to failure of the intervention to increase coronary flow in ischaemic regions. This failure may in turn be related to the time elapsing before the initiation of external counterpulsation after the onset of ischaemia. It is possible that maximum vasodilatation had already occurred and that further increase in flow to the ischaemic area was not possible. In experimental animals, integrity of vessels in the ischaemic area becomes much impaired 2 to 4 hours after coronary occlusion (Connors *et al.*, 1976) and increases in coronary flow after this interval may be associated with extravasation of blood into the tissues and deleterious rather than beneficial effects on infarct size (Bresnahan *et al.*, 1974).

In the present study, lack of apparent salvage of myocardium may be the result of the occurrence of most of the myocardial damage induced by ischaemia before the onset of counterpulsation. The potential for any intervention to salvage myocardium might, therefore, be minimal when the onset is delayed. In animals with infarction evaluated electrocardiographically and enzymatically, the evolution of myocardial necrosis was delayed by counterpulsation but the ultimate extent of infarction was similar to that in controls (DeLaria *et al.*, 1974). This suggests that the effect of counterpulsation on ischaemic myocardium retards but does not preclude evolution of infarction. Interventions implemented early in canine and rat preparations modify infarct size favourably but are without effect when implemented more than 5 to 6 hours after coronary occlusion (Hillis *et al.*, 1976; Karlsberg *et al.*, 1976). Since counterpulsation in the present study was not initiated until many hours after the onset of chest pain, substantial salvage of myocardium may no longer have been possible. Unfortunately, however, the frequent late arrival of patients to the coronary care unit may delay implementation of any intervention for comparable intervals.

External counterpulsation significantly decreased ventricular arrhythmia early after its implementation. This effect was seen from the 7th to 8th hours in which the patient served as his own control. However, the benefit was transitory. The decline in the rate of premature ventricular contractions with time in patients with myocardial infarction is well recognised (Roberts *et al.*, 1975c) and may have masked relatively late beneficial effects on ventricular rhythm resulting from external counterpulsation. The significant decrease in premature ventricular contractions in the first hour of counterpulsation may be related to improved flow to ischaemic areas

which may not have been adequate to prevent cell death but may have improved the wash-out of metabolites contributing to ventricular arrhythmia. Though some have argued that external circulatory assist causes increased circulating catecholamines in turn decreasing arrhythmia, no significant increase in heart rate occurred in the present study, and thus increased release of circulating catecholamines appears unlikely. Comparison of the incidence of premature ventricular contractions in control patients versus those treated with counterpulsation showed no significant difference. However, since the number of patients enrolled in each group was small, minor beneficial or deleterious effects may have been masked particularly since the control patients were matched only for ventricular arrhythmias.

In summary, infarct size estimated from the serial plasma CK values was unaltered by external counterpulsation initiated 7 hours after the initial CK elevation. A decrease in ventricular arrhythmia was observed suggesting that external circulatory assist may be of some benefit in patients with refractory arrhythmias, though the effect observed was transitory.

#### References

- Braunwald, E., Covell, J. W., Maroko, P. R., and Ross, J., Jr. (1969). Effects of drugs and of counterpulsation on myocardial oxygen consumption. Observations on the ischemic heart. *Circulation*, **39** and **40**, Suppl. IV, 220-230.
- Braunwald, E., and Maroko, P. R. (1973). Protection of the ischemic myocardium. *Hospital Practice*, **8**, No. 5, 61.
- Bresnahan, G. F., Roberts, R., Shell, W. E., Ross, J., Jr., and Sobel, B. E. (1974). Deleterious effects due to hemorrhage after myocardial reperfusion. *American Journal of Cardiology*, **33**, 82-86.
- Brown, B. G., Goldfarb, D., Topaz, S. R., and Gott, V. L. (1967). Diastolic augmentation by intra-aortic balloon. Circulatory hemodynamics and treatment of severe, acute left ventricular failure in dogs. *Journal of Thoracic and Cardiovascular Surgery*, **53**, 789-804.
- Connors, J. P., West, P. N., Roberts, R., Weldon, C. S., Sobel, B. E., and Williamson, J. R. (1976). Loss of functional integrity of the microvasculature in ischemic myocardium (abstract). *Clinical Research*, **24**, 213A.
- DeLaria, G. A., Johansen, K. H., Sobel, B. E., Sybers, H. D., and Bernstein, E. F. (1974). Delayed evolution of myocardial ischemic injury after intra-aortic balloon counterpulsation. *Circulation*, **49** and **50**, Suppl. II, 242-248.
- Gill, C. C., Wechsler, A. S., Newman, G. E., and Oldham, H. N., Jr. (1973). Augmentation and redistribution of myocardial blood flow during acute ischemia by intraaortic balloon pumping. *Annals of Thoracic Surgery*, **16**, 445-453.
- Gillespie, T. A., Roberts, R., Ambos, H. D., and Sobel, B. E. (1975). Salutary effects of Dobutamine on hemodynamics without exacerbation of arrhythmia or myocardial injury (abstract). *Circulation*, **51** and **52**, Suppl. II, 76.
- Goldfarb, D., Friesinger, G. C., Conti, C. R., Brown, B. G., and Gott, V. L. (1968). Preservation of myocardial viability by diastolic augmentation after ligation of the coronary artery in dogs. *Surgery*, **63**, 320-327.

- Harnarayan, C., Bennett, M. A., Pentecost, B. L., and Brewer, D. B. (1970). Quantitative study of infarcted myocardium in cardiogenic shock. *British Heart Journal*, **32**, 728-732.
- Hillis, L. D., Maroko, P. R., Braunwald, E., and Fishbein, M. C. (1976). Influence of the time interval between coronary artery occlusion and the administration of hyaluronidase on myocardial salvage (abstract). *Circulation*, **53** and **54**, Suppl. II, 161.
- Kantrowitz, A., Tjønneland, S., Freed, P. S., Phillips, S. J., Butner, A. N., and Sherman, J. L., Jr. (1968). Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *Journal of the American Medical Association*, **203**, 113-118.
- Karlsberg, R. P., Sobel, B. E., and Roberts, R. (1976). Appraisal of a calcium antagonist (verapamil) on infarct size and coronary flow (abstract). *Clinical Research*, **24**, 519A.
- Keon, W. J., Bedard, P., Shankar, K. R., Akyurekli, Y., Nino, A., and Berkman, F. (1973). Experience with emergency aortocoronary bypass grafts in the presence of acute myocardial infarction. *Circulation*, **47** and **48**, Suppl. III, 151-155.
- Maroko, P. R., Kjekshus, J. K., Sobel, B. E., Watanabe, T., Covell, J. W., Ross, J., Jr., and Braunwald, E. (1971). Factors influencing infarct size following experimental coronary artery occlusions. *Circulation*, **43**, 67-82.
- Maroko, P. R., Libby, P., Ginks, W. R., Bloor, C. M., Shell, W. E., Sobel, B. E., and Ross, J., Jr. (1972a). Coronary artery reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. *Journal of Clinical Investigation*, **51**, 2710-2716.
- Maroko, P. R., Libby, P., Sobel, B. E., Bloor, C. M., Sybers, H. D., Shell, W. E., Covell, J. W., and Braunwald, E. (1972b). Effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. *Circulation*, **45**, 1160-1175.
- Mueller, H., Ayres, S. M., Conklin, E. F., Giannelli, S., Jr., Mazzara, J. T., Grace, W. T., and Nealon, T. F., Jr. (1971). The effects of intra-aortic counterpulsation on cardiac performance and metabolism in shock associated with acute myocardial infarction. *Journal of Clinical Investigation*, **50**, 1885-1900.
- Nolle, F. M., Oliver, G. C., Kleiger, R. E., Cox, J. R., Jr., Clark, K. W., and Ambos, H. D. (1974). The Argus/H system for rapid analysis of ventricular arrhythmias. In *Computers in Cardiology*, p. 37. Institute of Electrical and Electronics Engineers, Long Beach.
- Page, D. L., Caulfield, J. B., Kastor, J. A., DeSanctis, R. W., and Sanders, C. A. (1971). Myocardial changes associated with cardiogenic shock. *New England Journal of Medicine*, **285**, 133-137.
- Roberts, R., Gowda, K. S., Ludbrook, P. A., and Sobel, B. E. (1975a). Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. *American Journal of Cardiology*, **36**, 433-437.
- Roberts, R., Henry, P. D., and Sobel, B. E. (1975b). An improved basis for enzymatic estimation of infarct size. *Circulation*, **52**, 743-754.
- Roberts, R., Henry, P. D., Witteveen, S. A. G. J., and Sobel, B. E. (1974). Quantification of serum creatine phosphokinase isoenzyme activity. *American Journal of Cardiology*, **33**, 650-654.
- Roberts, R., Husain, A., Ambos, H. D., Oliver, G. C., Cox, J., Jr., and Sobel, B. E. (1975c). Relation between infarct size and ventricular arrhythmia. *British Heart Journal*, **37**, 1169-1175.
- Scheidt, W., Wilner, G., Mueller, H., Summers, D., Lesch, M., Wolff, G., Krakauer, J., Rubenfire, M., Fleming, P., Noon, G., Oldham, N., Killip, T., and Kantrowitz, A. (1973). Intra-aortic balloon counterpulsation in cardiogenic shock. Report of a co-operative clinical trial. *New England Journal of Medicine*, **288**, 979-984.
- Shaw, J., Taylor, D. R., and Pitt, B. (1974). Effects of intra-aortic balloon counterpulsation on regional coronary blood flow in experimental myocardial infarction. *American Journal of Cardiology*, **34**, 552-556.
- Shell, W. E., Lavelle, J. F., Covell, J. W., and Sobel, B. E. (1973). Early estimation of myocardial damage in conscious dogs and patients with evolving acute myocardial infarction. *Journal of Clinical Investigation*, **52**, 2579-2590.
- Shell, W. E., and Sobel, B. E. (1973a). Changes in infarct size following administration of propranolol in the conscious dog (abstract). *American Journal of Cardiology*, **31**, 157.
- Shell, W. E., and Sobel, B. E. (1973b). Infarct size index: an effective predictor of prognosis after myocardial infarction (abstract). *Circulation*, **47** and **48**, Suppl. IV, 39.
- Shell, W. E., and Sobel, B. E. (1974). Protection of jeopardized ischemic myocardium by reduction of ventricular afterload. *New England Journal of Medicine*, **291**, 481-486.
- Sobel, B. E., Bresnahan, G. F., Shell, W. E., and Yoder, R. D. (1972). Estimation of infarct size in man and its relation to prognosis. *Circulation*, **46**, 640-648.
- Soroff, H. S., Birtwell, W. C., Norton, R. L., Cloutier, C. T., Kataoka, K., and Giron, F. (1971). Experimental and clinical studies in assisted circulation. *Transplantation Proceedings*, **3**, 1483.
- Soroff, H. S., Ruiz, U., Birtwell, W. C., and Deterling, R. A., Jr. (1964). Synchronous external circulatory assist. *Transactions. American Society for Artificial Internal Organs*, **10**, 79-88.

Requests for reprints to Dr Robert Roberts, Cardiac Care Unit, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110, U.S.A.