

## Protective effect of methylprednisolone on ischaemic myocardium assessed by ventricular function

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**Krause, B. L., Hassan, M. A., McMillan, A. B., and Hedley Brown, A. (1977). Thorax, 32, 185-193. Protective effect of methylprednisolone on ischaemic myocardium assessed by ventricular function.** Intracardiac surgical procedures are best carried out when the heart is still and bloodless. This condition, however, produces myocardial cellular damage with loss of contractility and compliance unless some protection can be provided. Myocardial contractility and compliance is best studied by isovolumic ventricular function tests, which were used to evaluate the protective effect of methylprednisolone on the isolated cross-perfused canine heart made ischaemic for 2 hours. Control experiments included 2 hours of ischaemia without methylprednisolone, and 2 hours of continuous normothermic cross-perfusion.

The methylprednisolone-treated hearts had probably significantly better ventricular function after 2 hours of ischaemia than did hearts without the methylprednisolone, while the cross-perfused hearts were best overall. This work suggests that methylprednisolone may have a protective effect on the ischaemic myocardium of the intact canine heart.

Protection of the myocardium during cardiac surgery is less than optimal (Maloney and Nelson, 1975). Myocardial cellular damage still occurs to some degree and affects the function of the myocardium after operation.

It is clear that normal myocardial metabolism is almost exclusively aerobic with the chemical energy stored as high energy phosphates, ATP and creatine phosphate (Lundesgaard-Hansen, 1966). The hypoxic heart is more dependent on anaerobic metabolism than normal (Scheuer, 1967). The function of the ischaemic heart is severely depressed (Sarin *et al.*, 1968; Willman and Barner, 1969), and the ultrastructure of the myocardium becomes deranged permanently after about 30 minutes (Buja *et al.*, 1971; Jennings and Ganote, 1972; Balibrea *et al.*, 1975). After the first 6-7 minutes the myocardial creatine phosphate has disappeared (Lundesgaard-Hansen, 1966) and as the ischaemia continues there is glycogen depletion (Scheuer, 1967) and an increasing dependence on lipid metabolism (Moffitt *et al.*, 1970). Residual depression of total high energy nucleotides prevents recovery of normal contractility on reperfusion (Levitsky and Feinberg, 1975).

Hypothermia prevents this disordered metabolism to some extent, reducing the excessive loss of glycogen and creatine phosphate (Hall *et al.*, 1960), so protecting against ischaemia (Mundth *et al.*, 1969; Tyers *et al.*, 1974; MacGregor *et al.*, 1975), and doubling the duration of anoxia without loss of contractility (Enright *et al.*, 1970). But hypothermia may cause oedema of the myocardium and this reduces compliance (Salisbury *et al.*, 1961) and is inferior to continuous normothermic perfusion (Brown *et al.*, 1974). However, continuous perfusion has its hazards also (Shaw *et al.*, 1962; Blackstone *et al.*, 1968; Brown *et al.*, 1969).

It is evident that mechanical and thermal protection alone are insufficient and so biochemical and pharmacological techniques are being investigated (Hickey, 1975).

Mannitol improves perfusion and thus organ function; the hyperosmolality has been shown to improve myocardial contractility (Weisfeldt *et al.*, 1973). Prostaglandin PGA improves coronary blood flow (Bloor *et al.*, 1975). Glucagon has also been shown to improve myocardial contractility without inducing arrhythmias and independent of digitalis administration (Levine *et al.*, 1969). Beta-

blocking drugs have a protective effect on the myocardium (Libby *et al.*, 1973b). Propranolol decreases S-T segment elevation, a criterion of ischaemic damage (Maroko *et al.*, 1971). When propranolol is combined with glucose-potassium-insulin infusion, an increased survival time from asphyxia has been reported, the probable mechanism being a slowing of ATP depletion (Wildenthal *et al.*, 1973). Retrograde insufflation of gaseous oxygen into the coronary sinus has been shown to preserve ventricular function better than ischaemia (Brown *et al.*, 1972c) while ATPase inhibition and provision of high energy phosphates showed no significant advantage over simple hypothermia (Brown *et al.*, 1972b).

Corticosteroids were reported to have a beneficial effect in limiting the size of experimentally produced myocardial infarcts (Johnson *et al.*, 1953), but this was not confirmed by others (Hepper *et al.*, 1955). Further investigations showed that glucocorticoids, as distinct from mineralocorticoids (Lefer and Martin, 1969), have a beneficial effect on the heart, and early trials on experimental canine infarctions and in 38 clinical cases showed an increased vascularity and a decreased mortality rate (Gerisch and Compeau, 1958). More recent experiments have shown a reduction in size or a decrease in spread of infarcts after administration of hydrocortisone (Libby *et al.*, 1973a), dexamethasone (Spath and Lefer, 1975), and methylprednisolone (Spath *et al.*, 1974); all three trials used elevation of S-T segments and creatine phosphokinase (CPK) levels as criteria of ischaemia. Clinical trials also differ in their conclusions on the benefit of high doses of hydrocortisone in infarction (Dall and Peel, 1963; Scottish Society of Physicians Scientific Subcommittee, 1964; Barzilai *et al.*, 1972) and shock (Lefer and Martin, 1969; Lefer, 1974).

The mechanisms of the reported beneficial effects of corticosteroids on the heart are still largely unknown. Increases in cardiac output (Sambhi *et al.*, 1965) have suggested an inotropic effect, but even though corticosteroids appear structurally related to known inotropic agents this has not been confirmed (Spath *et al.*, 1973; Lefer, 1974). Reports of systemic (Dietzman *et al.*, 1970; Dietzman *et al.*, 1975) and coronary (Hinshaw *et al.*, 1974) vasodilatation appear to show an action on blood vessels, and although there are reports to the contrary (Spath and Lefer, 1975), there may be an inhibition of catecholamine-induced vasoconstriction (Altura *et al.*, 1974). An increase in myocardial contractility has been produced—directly (Carter and Thomas, 1970), by increased coronary perfusion (Hinshaw *et al.*,

1974) and by the augmentation of the catecholamine response to stress (Replogle *et al.*, 1962; Alexander *et al.*, 1969), the effect of the steroids being absent in adrenalectomised dogs (Tecklenberg *et al.*, 1973). Other studies, however, have shown no potentiation or sensitisation to catecholamines by corticosteroids (Lefer, 1974).

The protective effect of corticosteroids is said to arise from the 'stabilisation of membrane structures', particularly lysosomes, which may release hydrolytic enzymes and damage the cell (Weissman and Thomas, 1964; Brachfeld, 1969; Shannon and Courtice, 1975). This has been reported as a mechanism of myocardial necrosis (Brachfeld and Gemba, 1965). The stabilisation of lysosomal membranes would explain the reduction of pathological increase of known lysosomal enzymes in the plasma and the reduction of necrosis by steroid treatment of myocardial infarction (Spath and Lefer, 1975), pancreatic ischaemia (Ferguson *et al.*, 1972), hepatic ischaemia (Figuroa and Santiago-Delpín, 1975), and haemorrhagic shock (Spath *et al.*, 1973). Recently, however, this theory also has been challenged (Persellin and Ku, 1974; Wiener *et al.*, 1975).

Whatever the mechanism, a protective effect against ischaemia probably exists and should guard the myocardium against ischaemia arising during cardiopulmonary bypass. This protective effect has been reported, enhancing recovery after anoxia in the papillary muscle (Jewitt *et al.*, 1972), and reducing the compliance deficit of the left ventricle of an isolated heart (Toyama and Reis, 1975) and the contractility deficit of in-situ ventricles (Busuttill *et al.*, 1975). These preparations involve cardiopulmonary bypass with the heart in situ; the steroid may be protecting against deleterious effects of whole-body perfusion and extracorporeal oxygenation (Brown *et al.*, 1972a). So far there has been no report of this protective effect on contractility in the intact isolated cross-perfused heart.

### Form of the investigation

Isolated perfused hearts are stable when cross-perfused (Londe, 1969) and can therefore be used in experiments determining myocardial contractility. Although no preparation is perfect, because the function of isolated papillary muscle and the isolated heart varies according to pre-load, after-load, and heart rate (Jochim and Behrendt, 1975), the isovolumic tests carried out on isolated hearts are closer to the clinical situation.

Isovolumic ventricular function tests carried out

by means of a balloon fixed in the ventricle were performed before and after a 2-hour period of uninterrupted normothermic cross-perfusion (group 1); ischaemia (group 2); and ischaemia with methylprednisolone given before the ischaemic period (group 3). Variables measured included peak systolic pressure, end-diastolic pressure, rate of rise of pressure (dp/dt), and the pressure at which dp/dt was maximal. Regression slopes of end-diastolic volume, peak systolic pressure, and peak dp/dt were calculated against end-diastolic pressure. These values, representing contractile force, velocity, and compliance (Brown *et al.*, 1977), could then be compared at a standard end-diastolic pressure of 1.33 kPa (10 mmHg), expressing all values after the experimental period relative to those before it.

## Method

Mongrel dogs, weighing from 14 to 32 kg, were premedicated with acetylpromazine, 5–10 mg intramuscularly, and after 15 minutes were anaesthetised with 30–40 mg/kg sodium pentobarbital, intubated, and ventilated with 60/40 N<sub>2</sub>O/O<sub>2</sub> from a respirator. The chest was opened by a median sternotomy and the heart exposed by excision of the pericardium. Heparin, 5 mg/kg, was administered intravenously; the aortic root was cannulated for monitoring and perfusion via the subclavian arteries and the right ventricle via the right atrial appendage. The second dog was similarly premedicated, anaesthetised, intubated, ventilated, and heparinised, and its femoral arteries and vein were cannulated for bypass and pressure monitoring. The arterial cannula was connected to a calibrated pump which led to the aortic cannula of the experimental heart and a pressure-limiting side arm which overflowed when 13.30 kPa (100 mmHg) was exceeded. The venous cannula of the second dog was connected to the right heart cannula of the experimental heart and to a funnel in which the heart was to lie and into which the arterial overflow was fed. The circuit was primed with 5% dextrose in distilled water which was exchanged with the blood of the support dog. The cavae of the experimental heart were tied and, while the heart emptied itself, the aorta below the subclavian artery, the brachiocephalic artery, and the pulmonary artery were then tied in that order. The isolated heart's circulation was begun and its venous cannula unclamped. The heart was thus perfused continuously with minimal mixing of the blood of the two dogs. The heart was fibrillated electrically, its attachments divided, and the

free heart placed in the funnel. A fine Latex balloon was held in the left ventricle by a purse-string suture around the free edge of the mitral valve, which was tightened around a flange connecting the balloon to pressure transducers and a graduated syringe. Measured fluid was then placed in the balloon to raise the end-diastolic pressure above 0.665 kPa (5 mmHg) when electrical defibrillation was performed. The heart was paced at a rate of 100 beats/min if necessary and ECG leads and a temperature probe were attached to the right heart (Fig. 1). Fluid was added in 2.5 ml increments to raise the end-diastolic pressure in the ventricle from 0–1.33 kPa (0–10 mmHg), recording a few beats at each volume. The experimental technique to be applied to a particular dog was chosen at random. This was: group 1, continuous normothermic cross perfusion for 2 hours; group 2, 2 hours of ischaemia attained by terminating pump action, thus stopping perfusion of the heart; group 3, ischaemia attained similarly with methylprednisolone sodium succinate, 30 mg/kg, given slowly intravenously into the support dog before terminating perfusion of the heart, with time allowed for circulation to the isolated heart. In all cases there was sufficient fluid left in the balloon to keep the end-diastolic pressure above zero.

After the 2 hours, in groups 2 and 3, the hearts were again perfused, starting at very low perfusion pressures and gradually increasing to levels similar to the initial ones. Time was allowed for these hearts to regain as much function as possible, and once they were stable a further series of ventricular function tests were recorded in all three groups. After the recordings had been taken perfusion was stopped, and the ventricle was dissected from the rest of the heart; its weight and volume by displacement were then measured as well as the weight of the dog from which it came.

## Results

### PEAK SYSTOLIC PRESSURE

The hearts maintained by continuous normothermic cross-perfusion developed a higher pressure relative to the initial level than those of the other two groups. The hearts given the methylprednisolone before ischaemic arrest showed a probably significantly higher force than those not given the methylprednisolone. The difference between the continuous normothermic cross-perfused hearts and the ischaemic hearts with and without the methylprednisolone was significant (Table 1; Fig. 2).

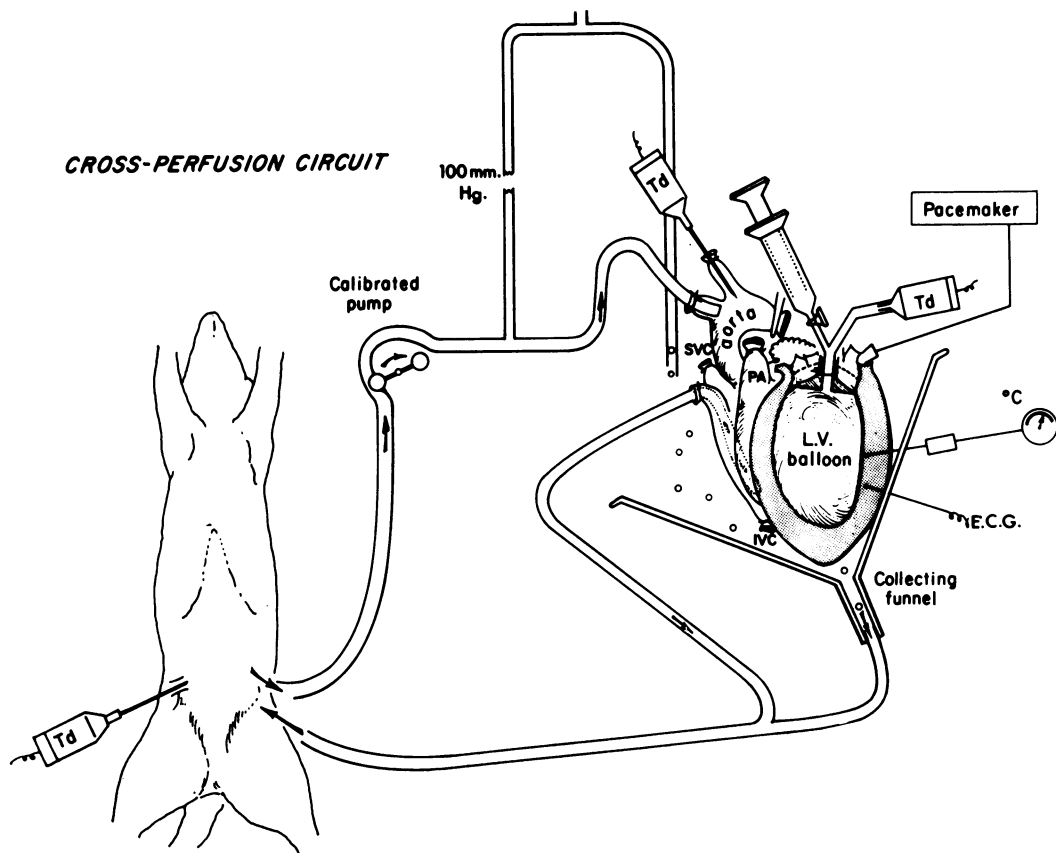


Fig. 1 A diagram of the experimental layout: Td=pressure transducer; ECG=electrocardiogram; SVC=superior vena cava; IVC=inferior vena cava; PA=pulmonary artery.

Table 1 Peak systolic pressure at end-diastolic pressure of 1.33 kPa (10 mmHg) after 2 hours of preservation, expressed as percentages of initial values

Group	No.	Mean	SE	P values		
				1	2	3
1 Continuous normothermic perfusion	19	137	17.665	< 0.001	< 0.001	
2 Ischaemia	10	35	4.7434			< 0.05
3 Ischaemia with methylprednisolone	13	48	3.8829			

The group, number of animals, mean of this variable, and standard error of the mean for each of the three groups is shown against a table of the probability (P) that the apparent superiority of continuous normothermic perfusion over ischaemia or ischaemia with methylprednisolone prior to ischaemia is due to chance.

#### CONTRACTILE VELOCITY

The rate of rise of pressure at an end-diastolic pressure of 1.33 kPa (10 mmHg) at the end of the 2-hour period relative to the initial values was

highest in the continuously perfused hearts (group 1) followed by the hearts treated with methylprednisolone (group 3) and the ischaemic hearts (group 2) respectively. The differences between the constantly perfused hearts and the other two groups was significant (Table 2; Fig. 2).

#### COMPLIANCE OF THE VENTRICLES

The difference in volume in the ventricle between the end-diastolic pressures of 0–1.33 kPa (0–10 mmHg) at the end of the experimental period of 2 hours was highest in the continuously cross-perfused hearts (group 1), next highest in the methylprednisolone-treated hearts (group 3), and lowest in the ischaemic hearts (group 2). The differences between group 1 and the other two groups were significant (Table 3; Fig. 2).

#### OEDEMA OF THE MYOCARDIUM

The oedema of the myocardium was calculated as

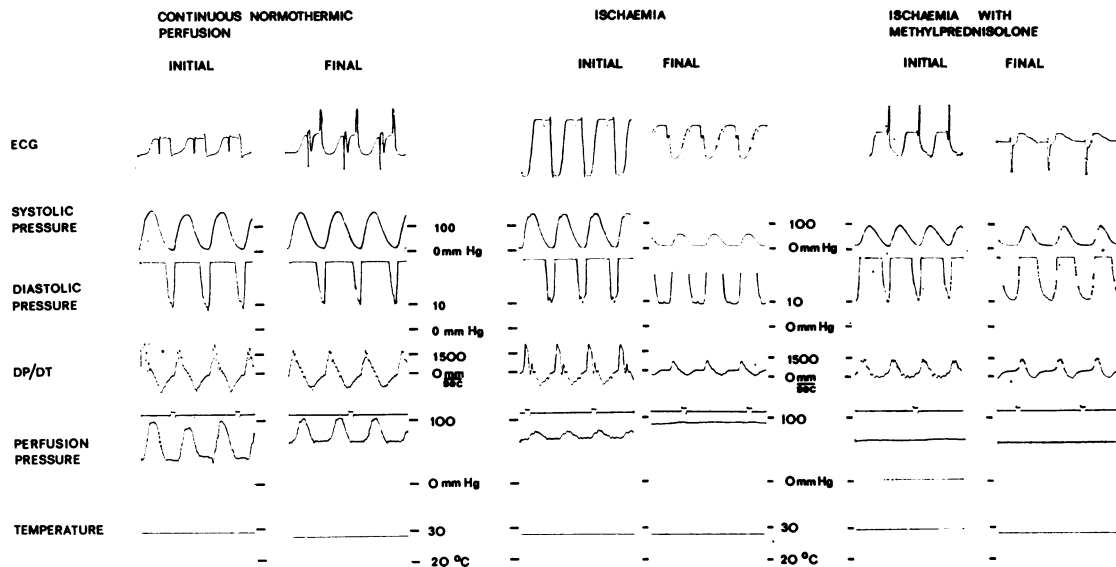


Fig. 2 Initial and final traces as representations of the three experimental groups.

Table 2 Contractile velocity at end-diastolic pressure of 1.33 kPa (10 mmHg) after 2 hours of preservation, expressed as percentages of initial values

Group	No.	Mean	SE	P values		
				1	2	3
1 Continuous normothermic perfusion	19	143	20.42	< 0.001	< 0.001	
2 Ischaemia	10	32	7.589			NS
3 Ischaemia with Methylprednisolone	13	39	5.269			

As in Table 1, the P-values representing the probability that the difference between continuous normothermic perfusion and the other techniques was due to chance. NS, difference between the ischaemic groups is not significant.

a ratio of the weight of the animal to the weight of the dissected left ventricle after the 2-hour experimental period. No difference reached statistical significance (Table 4).

## Discussion

These experiments have shown that methylprednisolone administered before an ischaemic insult to the myocardium probably improves recovery of ventricular function as measured by peak systolic pressure after 2 hours of preservation. The validity of these results must be considered in the light of the experimental preparation and any possible clinical applications they might have.

Table 3 Compliance of the ventricles after the experimental period, expressed as percentage of initial values

Group	No.	Mean	SE	P values		
				1	2	3
1 Continuous normothermic perfusion	19	109.5	10.989		0.0053	0.023
2 Ischaemia	10	57.4	8.1903			NS
3 Ischaemia with methylprednisolone	13	69.0	10.76			

As for Table 2.

Table 4 Oedema of the myocardium, expressed as weight of LV/kilogram of animal

Group	No.	Mean	SE	P values		
				1	2	3
1 Continuous normothermic perfusion	19	5.7756	0.503		NS	NS
2 Ischaemia	10	5.4	0.221			NS
3 Ischaemia with methylprednisolone	13	5.579	0.329			

There are no significant differences between the groups for this variable.

## THE PREPARATION

Isolated perfused hearts are satisfactory preparations for assessing ventricular function (Blackstone *et al.*, 1968; Londe, 1969) and, when cross-perfused, are free from the inherent deterioration

of oxygenator preparations. Although non-invasive methods of assessing myocardial contractility have been devised for use in patients (Levitsky and Merchant, 1973; Hardason *et al.*, 1974), isovolumic function tests permit a more satisfactory estimate of ventricular function (Brown *et al.*, 1969). Isolated papillary muscle preparations are also used to estimate myocardial contractility, and although the function of these preparations like that of intact isolated hearts varies with pre-load, after-load, and heart rate (Mason *et al.*, 1971; Jochim and Behrendt, 1975), further assumptions concerning the geometry of the ventricle (Levitsky and Merchant, 1973) are necessary to extrapolate data obtained from the experiments (Sonnenblick, 1962; Levine and Britman, 1964). The isolated heart does not have this problem and is therefore more suitable for ventricular function tests.

Myocardial contractility may be approached and investigated in several ways (Levitsky and Merchant, 1973). Ventricular end-diastolic pressure, systolic pressure, and stroke volume give only indirect information (Braunwald *et al.*, 1967), while wall tension, stress, and contractile velocity, although difficult to calculate, give a theoretically better estimation of myocardial contractility. The direct measurements of systolic pressure, rate of rise of pressure, and diastolic pressure/volume relationships as indices of contractile force, velocity, and compliance are as efficient in discriminating excellence of myocardial preservation as are the derived data (Brown *et al.*, 1977).

The regime of administration of the methylprednisolone was based on previous work using the steroid (Blinderman *et al.*, 1962; Jewitt *et al.*, 1972; Dietzman *et al.*, 1975). It has been shown that the vehicles of some preparations of methylprednisolone have a toxic effect on cardiac function (Vargish *et al.*, 1974) but the solution used in these experiments (Solumedrol, Upjohn Ltd) did not contain the chemical involved. It has also been shown that sodium succinate *per se* has no effect on cardiac index, peripheral resistance, or oxygen consumption of the myocardium (Dietzman *et al.*, 1973). To affect the amount of ischaemic damage the steroid must be given before the onset of ischaemia (Spath *et al.*, 1974), which was the procedure used in these experiments.

#### CLINICAL APPLICATIONS

Depressed myocardial function is often observed after open-heart surgery and is due mainly to ischaemic injury to the myocardium (Cooper, 1975; Maloney *et al.*, 1975). After cardiopulmonary bypass patients may show a 'low output syndrome' as a result of depressed ventricular

function (Dietzman *et al.*, 1969; Buckberg *et al.*, 1975). Increased peripheral resistance also occurs after operations, and this is of special importance after cardiac operations as it adds further stress to the already damaged myocardium (Matthews *et al.*, 1974). This means that the demand upon the heart may be beyond its reserves (Wisheart, 1975). Myocardial oedema may also play a part in the cycle of further myocardial depression by impairing oxygen diffusion to the cell (Wisheart, 1975) and by decreasing the compliance of the heart (Cross *et al.*, 1961; Salisbury *et al.*, 1961).

Methylprednisolone has already been shown to affect the postischaemic function of the myocardium in terms of tension development (Jewitt *et al.*, 1972) by reducing the compliance deficit that normally accompanies ischaemic arrest (Toyama and Reis, 1975) and the contractility deficit of *in-situ* ventricles (Busuttill *et al.*, 1975). The steroid has been shown to have a beneficial effect in reducing the added stress of a peripheral vasoconstriction if it is given before the onset of bypass (Replogle *et al.*, 1966). The results of the experiments reported here add evidence to the postischaemic protection of the myocardium and to the observed vasodilator effects reported by others (Dietzman *et al.*, 1970; Dietzman *et al.*, 1975).

The determination of the mechanism of action of methylprednisolone on the myocardium was not one of the objects of these experiments. However, it seems clear from published reports that there is some effect on membranes. Myocardial contractility depends on the integrity of membranes of cells and subcellular organelles as well as on ATPase and calcium (Brown *et al.*, 1969). Any protection that can be afforded to stop dysfunction of the cell by lysosomal damage would therefore improve ventricular contractility after injury. Recent evidence supports the 'membrane stabilisation' theory, as labelled steroid does localise in lysosomes and lysosomal membranes (Wilson, 1974). The effect of the steroid is seen in the alteration of permeability characteristics of the lysosomal membrane (Ignarro, 1972; Goldstein, 1975).

Methylprednisolone has been shown here to promise better protection of the myocardium during open-heart surgery.

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