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Extent of myocardial damage after open-heart surgery assessed from serial plasma enzyme levels in either of two periods (1975 and 1980)

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SUMMARY Perioperative myocardial damage caused by cardiac surgery in 32 patients operated upon in 1980 is quantified in terms of total quantity of alpha-hydroxybutyrate dehydrogenase released from the heart into the circulation, and compared with perioperative myocardial damage in 32 patients operated upon in 1975. In the five year period between 1975 and 1980, various aspects concerning anaesthesia, pharmacological treatment, and myocardial preservation techniques have been subjected to considerable changes. Comparison of calculated myocardial damage in 1980 with that in 1975 shows a general reduction of about 40% in patients having coronary artery bypass grafting, 75% in patients with aortic valve replacement, and 10% in patients with mitral valve replacement.

In an earlier report[1] we described the extent of myocardial damage in 15 patients after coronary artery bypass grafting, in 10 patients after aortic valve replacement, and in seven patients after mitral valve replacement. Cardiac damage was assessed by the enzymatic method in which the activity of an enzyme that has been released by the heart into the circulation is computed. The patients described in the earlier report underwent cardiac surgery in 1975.

Since then, anaesthetic and surgical techniques and procedures have improved considerably. For instance, the introduction of new cardiac preservation techniques, such as hypothermic potassium-induced cardioplegia, has generally proved to be of great value.[2–4] Therefore, the above-mentioned study was repeated in 1980 using the same number of patients in the three surgical groups and the same method to assess myocardial damage.

Subjects and methods

This study comprised two groups each of 32 patients operated upon in 1975 and 1980, respectively. Three subgroups were distinguished in each group: 15 patients having coronary artery bypass grafting, and 10 and seven patients having replacement of aortic and mitral valve, respectively. Table 1 shows the clinical data.

Surgical techniques with respect to the patients operated upon in 1975 were previously described.[1] In 1975 and in 1980 cardiac surgery was performed with standard cardiopulmonary bypass techniques. In both years mild systemic hypothermia, haemodilution, and topical myocardial cooling with iced saline were employed. While in 1975 patients had anoxic cardiac arrest (coronary artery bypass grafting group) or coronary perfusion with hypothermic blood (aortic and mitral valve replacement groups) all patients operated upon in 1980 had hypothermic potassium-induced cardioplegia using St. Thomas's Hospital cardioplegic solution,[5] infused at a pressure of about 40 mmHg and repeated every half an hour.

Table 1 shows the duration of cardiopulmonary bypass and aortic cross-clamping as well as minimal body temperature. A standard 12 lead electrocardiogram was recorded before operation and repeated at least once daily after operation. The only electrocardiographic criterion used to assess perioperative myocardial infarction was the appearance of new or deeper Q waves of at least 0·04 s duration.[6 7]

ENZYME ASSAYS

Venous blood samples were obtained before, just before the start of cardiopulmonary bypass (time

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zero), immediately after termination of cardiopulmonary bypass, and subsequently every six hours for 36 hours. Blood was drawn on trisodium citrate and centrifuged twice at 1174 x g for 10 minutes. The plasma activity of alpha-hydroxybutyrate dehydrogenase was assayed with alpha-keto-butyrate as a substrate[8] using a test kit (Boehringer, 124818). Alpha-hydroxybutyrate dehydrogenase activity represents the activity of the H subunits of lactate dehydrogenase (LDH, EC 1.1.1.27), and is expressed in units per litre plasma, in which 1 unit of alpha-hydroxybutyrate dehydrogenase catalyses the conversion of 1 μmol substrate per minute at 25°C.

MATHEMATICAL CALCULATION OF MYOCARDIAL DAMAGE BASED ON PLASMA ALPHA-HYDROXY-BUTYRATE DEHYDROGENASE (HBDH)

The quantity of enzyme released per litre of plasma during the first 36 hours after operation, denoted as A_{HBDH} (36), is taken as a measure of perioperative myocardial damage. As discussed by Norris *et al.*,[9] this quantity should be preferred as a clinical index to the quantity of enzyme expressed in grams of destroyed tissue. For purposes of quantification the plasma HBDH activity was determined at various times after onset of injury. It can be assumed from the low plasma levels of HBDH seen immediately after operation that no significant haemolysis occurs during operation. The calculation and the mathematical model used are described in a previous paper[1] and in more detail elsewhere.[10] The variable values of the two-compartment model used have recently been estimated with greater precision by Willems *et al.*[11] A fixed mean value of 0·015 h^{-1} was used for the clearance constant of HBDH.[11] As the 32 patients operated upon in 1975 were analysed earlier with slightly different variable values, calculation of individual values of A_{HBDH} (36) was repeated for these patients. A more common procedure on quantification of myocardial injury followed by many investigators uses creatine kinase (CK) or CK MB.[12-14] When applying a fixed rate for the enzyme's clearance constant k, it appears that a considerable interindividual variation in the value of k produces only small variations in the calculated total quantity of an enzyme released, provided the enzyme is cleared from the circulation slowly.[15] This important condition is fulfilled by choosing HBDH. The fast disappearance kinetics of CK and CK MB, as calculated by Willems *et al.*,[11] make them less appropriate for purposes of quantitative assessment of the extent of myocardial damage.

STATISTICAL METHODS

Statistical significance of differences between means of two groups of values was calculated using Student's t test when samples proved to have a normal distribution. When values were not distributed normally, median values ± 95% confidence limits were given, and for testing differences between two groups of values the Wilcoxon rank test was employed. Linear regression analysis was employed to detect whether a linear correlation existed between pairs of values of two normally distributed variables. When variables were not distributed normally Spearman's rank test was used to disclose a rank correlation. For analysis of statistical significance between two groups of data on the incidence of a *yes-or-no* phenomenon (for example mortality) the χ^2-test has been used.

Results

The Fig. shows the median values ± 95% confidence limits of calculated total quantity of HBDH released (A_{HBDH}) as a function of time for the six groups of patients dealt with in this study. In fact, these curves represent the time-dependent release of HBDH activity into the plasma corrected for (1) preoperative plasma HBDH values, (2) clearance of HBDH activity from the plasma, and (3) extravasation of HBDH activity. The six curves depicted in the Fig. show that at 24 hours after the start of extracorporeal circulation (t=0) HBDH release from the injured heart into the circulation has almost come to a stop. As the aortic valve replacement group of 1975 still shows some progression of HBDH release in the next 12 hours, the A_{HBDH} values as calculated 36 hours after the start of extracorporeal circulation have been taken to represent the ultimate myocardial damage resulting from cardiac surgery.

Comparison of the results of 1980 with those of 1975 discloses a significant ($p<0·05$) reduction in myocardial damage in the coronary artery bypass graft group of about 40%, and a highly significant ($p<0·01$) reduction in the aortic valve replacement group of about 75%.

The greater degree of damage in 1975 compared with 1980 in the coronary artery bypass graft group corresponds to a higher incidence of new Q waves in the electrocardiogram and a higher mortality in the first postoperative week in the patients operated on in 1975 when compared with those operated on in 1980 (see Table 1).

When we correlate enzymatic heart damage with duration of extracorporeal circulation in patients operated on in 1975 and 1980 no correlation was found (correlation coefficients of 0.28 and −0·07, respectively) using Spearman's rank test. When A_{HBDH} (36) is correlated with duration of aortic occlusion the correlation coefficients are −0·15 and 0·09, respectively, using the same test.

Although the period of aortic occlusion was longer in 1980 than in 1975 by a factor of 1·6 (see Table 1)

cardiac surgery produced less cardiac damage in 1980 than in 1975. In the coronary artery bypass graft group the longer duration of aortic occlusion in 1980 compared with 1975 can be ascribed to grafting of more distal anastomoses (3·1 vs. 1·9; $p<0·01$) on the coronary artery system in 1980. In the aortic valve replacement group the reduction of myocardial damage in 1980 compared with 1975 is associated with a shortening of the duration of extracorporeal circulation (92 vs. 156 minutes; $p<0·01$).

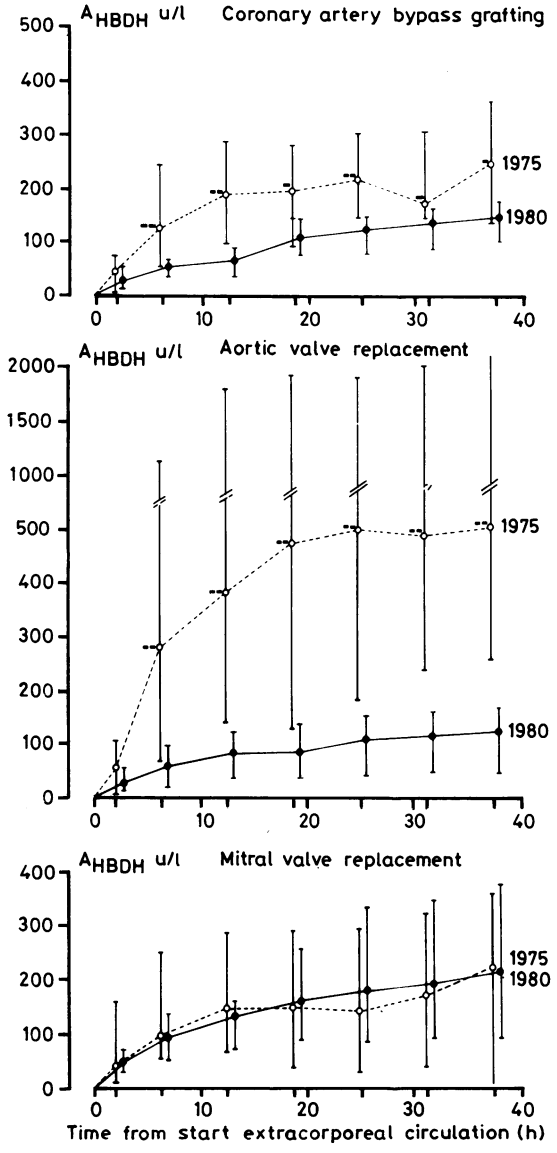

Fig. *Time course of the calculated quantity of alpha-hydroxybutyrate dehydrogenase (HBDH) released per litre plasma (A_{HBDH} u/l) in the patients operated upon in 1975 (o) and 1980 (•) for coronary artery bypass grafting (n=15 in each year), aortic valve replacement (n=10 in each year), and mitral valve replacement (n=7 in each year). Indicated are medians ± 95% confidence limits. Differences between 1975 and 1980 are tested with a two-tailed Wilcoxon rank test: ■p<0·05 and ■■p<0·01.*

Although an increase in the number of bypassed obstructions in the coronary artery bypass graft group and a decrease in duration of extracorporeal circulation in the aortic valve replacement group will be of benefit to the surgically treated patients the pronounced difference in perioperative myocardial damage as found in 1975 and 1980 is, most probably, to be ascribed to other factors as well. Also to be excluded are age and preoperative exercise tolerance of patients as well as the indications for cardiac surgery and body temperature during extracorporeal circulation (see Table 1) since they were not essentially different in 1980 when compared with 1975. Factors which are considered as likely to be responsible for the reduction of myocardial damage in patients operated on in 1980 compared with those operated on in 1975 are: the anaesthetic procedure, the pharmacological treatment, topical cooling of the heart, and use of cardioplegia instead of (intermittent) coronary perfusion.

ANAESTHESIA

Several changes in the anaesthetic regimen have been implemented between 1975 and 1980. Table 2 provides information about the anaesthetic procedures employed.

The improvement in the whole anaesthetic regimen is aimed at avoiding large variations in blood pressure and heart rate to permit an optimal balance between myocardial oxygen supply and demand.

PHARMACOLOGICAL THERAPY AND CIRCULATORY SUPPORT

Pharmacological treatment before, during, and after cardiac surgery has changed in several respects between 1975 and 1980. In 1975 all patients in the coronary artery bypass graft group who were on beta-receptor blocking drugs (14/15) stopped this treatment two to three days before operation. In the years after 1975, patients of the coronary artery bypass graft group who used beta-receptor blocking drugs continued to use these drugs till the very day of cardiac surgery. It is believed that the oxygen-sparing effects of beta-blocking agents in patients with severe coronary artery lesions is beneficial particularly during cardiac surgery. Table 3 shows the number of patients receiving respiratory support, cardiac pacemaker, intra-aortic counterpulsation, and certain drugs acting on heart and circulation, such as beta-adrenergic agonists, digitalis, vasodilators, calcium antagonists, and beta-adrenergic blocking agents.

Table 1 *Three groups of patients operated upon in 1975 compared with three groups of patients operated upon in 1980: coronary artery bypass grafting, aortic valve replacement, and mitral valve replacement*

	Coronary artery bypass graft			*Aortic valve replacement*			*Mitral valve replacement*		
	1975	*1980*	*p†*	*1975*	*1980*	*p†*	*1975*	*1980*	*p†*
No. of patients	15	15		10	10		7	7	
Sex Male	12	13		8	7		2	0	
Female	3	2		2	3		5	7	
Age Mean (y)	50·5	57·4		46·5	52		58	51·2	
Range (y)	35–62	37–69		22–69	18–66		46–68	21–70	
Preoperative II	1	2		4	4		0	0	
exercise III	13	12		6	5		5	5	
tolerance* IV	1	1		0	1		2	2	
			AS	2	2	MS	1	4	
Valvular			AR	3	5	MR	3	2	
abnormality¶			AS+AR	5	3	MS+MR	3	1	
No. of distal anastomoses‡	1·9±0·7	3·1±1·1	<0·01						
Range	1–3	1–5							
Period of extra-corporeal circulation‡ (min)	118±50	127±38	NS	156±67	92±15	<0·01	120·0±38·0	89±22	NS
Period of aortic cross clamping‡ (min)	34±16	61±22	<0·01	48±38	62±14	NS	36·0±8·0	58±16	<0·05
Minimal body temperature‡ (°C)	28·2±3·2	27·1±1·2	NS	28·3±1·6	28·3±0·3	NS	25·1±3·4	28±0·6	<0·05
New Q waves in electrocardiogram§	4/15	0/15		2/10	0/10		0/7	0/7	
Mortality in first postoperative week	2/15	0/15		1/10	0/10		0/7	0/7	

*Classification according to the New York Heart Association.
†Using the two-tailed Student's t test.
‡Mean value ± SD.
§Indicative of perioperative infarction.
¶AS: aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation.

Table 2 *Data concerning anaesthesia of two groups of patients operated on in 1975 and 1980*

Drugs administered	*1975 CABG*	*AVR*	*MVR*	*All patients*	*1980 CABG*	*AVR*	*MVR*	*All patients*	*Relative change in 1980 compared with 1975*
Premedication									
Opiates	15/15	10/10	7/7	32/32	8/15	8/10	4/7	20/32	↓
Atropine	14/14†	10/10	7/7	31/31†	8/15	3/10	4/7	15/32	↓
Lorazepam	0/15	0/10	0/7	0/32	15/15	9/10	7/7	31/32	↑↑
Induction of anaesthesia									
Thiopentone	14/15	10/10	7/7	31/32	9/15	8/10	3/7	20/32	↓
Nicomorphine	0/15	0/10	1/7	1/32	6/15	5/10	3/7	14/32	↑↑
Muscle relaxant*	15/15	10/10	7/7	32/32	15/15	10/10	7/7	32/32	—
Calcium chloride	14/15	9/10	7/7	30/32	6/15	2/10	0/7	8/32	↓↓
Fentanyl	0/15	0/10	0/7	0/32	12/15	7/10	5/7	24/32	↑↑
Maintenance of anaesthesia									
100% O_2	15/15	10/10	7/7	32/32	7/15	4/7†	2/6†	13/28†	↓
O_2/N_2O	0/15	0/10	0/7	0/32	8/15	5/8†	3/5†	16/28†	↑↓
Halothane	15/15	7/10	5/7	27/32	0/15	0/10	0/7	0/32	↓↓
Enflurane	0/15	3/10	2/7	5/32	6/15	5/10	37	14/32	↑
Nicomorphine	15/15	10/10	7/7	32/32	4/15	2/10	2/7	8/32	↓↓
Fentanyl	0/15	0/10	0/7	0/32	13/15	10/10	7/7	30/32	↑↑

*For example, pancuronium bromide and succinyl choline.
†Complete data not available.
CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement.

From 1975 to 1980 one can distinguish a shift in the use of positive inotropic interventions to interventions that lead to decreased peripheral resistance and negative-inotropic responses.

TOPICAL COOLING OF HEART

A number of patients received topical cooling of the heart with ice-cold saline during operation, either once or continuously by means of Topical Cooling Device (Cobe). Statistical analysis using the χ^2 test reveals that topical cooling of the heart was applied more often in 1980 than in 1975 in the coronary artery bypass graft group (15/15, instead of 10/15; $p<0·05$), aortic valve replacement group (10/10, instead of 4/10;

$p<0.01$), and mitral valve replacement group (5/7, instead of 1/7; $p<0.05$).

MYOCARDIAL PRESERVATION TECHNIQUE

In all 32 patients operated on in 1980 cardiac arrest during open-heart surgery was induced and maintained by hypothermic potassium-induced cardioplegia. In 1975 patients from the coronary artery bypass graft group had intermittent coronary perfusion with hypothermic blood. In 1975 patients from the aortic valve replacement group had continuous coronary perfusion with hypothermic blood by selective cannulation of the coronary ostia. This method has a number of disadvantages: narrow or calcified ostia of the coronary artery are often the cause of improperly fitting perfusion cannulae. In addition, proximal side branches of the coronary artery system can easily be obstructed by the inserted perfusion cannulae. In 1975 patients from the mitral valve replacement group had continuous coronary perfusion with hypothermic blood via a needle inserted in the aorta proximally of the cross-clamp.

Discussion

The results presented in this study demonstrate that in a five year interval (1975 to 1980) cardiac injury after coronary artery bypass grafting and aortic valve replacement had decreased considerably. This finding was previously reported by Kouchoukos *et al.*[16] who compared mortality from coronary artery bypass grafting in the period 1970 to 1973 with that in the period 1974 to 1977. They reported that 30 day mortality as well as incidence of definite or probable perioperative myocardial infarction in the two periods fell from 2·7% to 1·2% ($p<0.01$) and 11·4% to 2·4% ($p<0.001$), respectively, despite the fact that in the period 1974 to 1977 more vessels were grafted (mean number 2·9) than in the period 1970 to 1973 (mean number 1·9). In the present study the decrease of the extent of perioperative myocardial injury was more pronounced in the group of patients having aortic valve replacement than in the group of patients with coronary artery bypass grafting. Earlier[1] we proposed that selective coronary artery perfusion of the hearts in which the aortic valve had to be replaced might have been inadequate in perfusing the subendocardial layers of the heart, because of the hypertrophied state of the hearts of the aortic valve replacement group. The tremendous decrease of perioperative myocardial injury in the aortic valve replacement group possibly means that development of extensive subendocardial ischaemia has been prevented. In this context the change of myocardial preservation technique to hypothermic, potassium-induced cardioplegia may be considered as the factor responsible for the significant improvement of perioperative cardiac damage. In the coronary artery bypass graft group several factors can be held responsible for the improvement of perioperative myocardial injury. Apart from a change in preservation technique, changes in medical treatment, such as continued administration of beta-blocking agents till the day of operation, as well as changes in anaesthetic regimen may have helped to optimise the balance between oxygen supply and energy requirements of the heart. Hypothermic, potassium-induced cardioplegia is not the only factor responsible for improvement of perioperative myocardial injury, for in the mitral valve replacement group no significant improvement in the interval 1975 to 1980 could be demonstrated. Though the mitral valve replacement groups contained only seven patients it was shown earlier[1] that in this group myocardial damage after surgery was small when compared with cardiac damage in the groups of patients undergoing coronary artery bypass grafts and aortic valve replacement. Therefore, we believe that in the mitral valve replacement group medical care, anaesthetic treatment, and surgical techniques were relatively optimal already, so that the improvements mentioned before did not result in a further decrease of perioperative myocardial damage.

Table 3 *Pharmacological treatment and circulatory support given perioperatively to two groups of patients operated on in 1975 and 1980*

Treatment	*1975*	*1980*	*Relative change in 1980 compared with 1975*
Respiratory support (postop.)	29/32	31/32	—
Pacemaker	7/32	9/32	—
Intra-aortic balloon pump	4/32	1/32	↓
Adrenaline/isoprenaline	24/32	0/32	↓↓
Dopamine/dobutamine	9/30*	9/32	—
Cardiac glycosides	18/32	29/32	↑
Vasodilators‡	0/32	11/32	↑↑
Antiarrhythmic drugs§	5/32	6/32	—
Nifedipine	0/32	2/32	↑
Beta-receptor blocking agents¶	2/32†	17/30*	↑↑

*Complete data not available.
†Patients from the coronary artery bypass grafting group treated with beta-receptor blocking agents preoperatively (14/15) did not receive these drugs in the last two to three days before operation.
‡For example, nitroprusside and glyceryl trinitrate.
§For example, lignocaine and disopyramide.
¶For example, propranolol, atenolol, metoprolol, and acebutolol.

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