Clinical Assessment of Prolonged Myocardial Preservation for Patients With a Severely Dilated Heart

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Background. The purpose of this study was to compare the myocardial protective effect of histidine-tryptophan-potassium and glucose-insulin-potassium cardioplegic solutions in patients with a dilated heart (left ventricular diastolic diameter > 55 mm, left ventricular systolic diameter > 45 mm) associated with prolonged cross-clamp time (longer than 200 minutes).

Methods. We selected 20 patients with dilated hearts due to severe aortic regurgitation. Glucose-insulin-potassium cardioplegia was used in 11 patients and histidine-tryptophan-potassium cardioplegia was used in 9 patients.

Results. After operation, the cardiac index was significantly increased in the histidine-tryptophan-potassium group (p < 0.05). Postoperative percent fractional shortening was 13.4% ± 3.1% in the glucose-insulin-potassium group and 23.6% ± 2.6% in the histidine-tryptophan-potassium group (p < 0.05). Creatine kinase levels were significantly lower in the histidine-tryptophan-potassium group than in the glucose-insulin-potassium group (p < 0.05). The incidence of ventricular arrhythmia (higher than Lown’s grade 2) was lower in the histidine-tryptophan-potassium group.

Conclusions. These data support the superiority of the histidine-tryptophan-potassium method over the glucose-insulin-potassium method for protection of the dilated heart during prolonged ischemia in open heart operations.

Myocardial preservation during open heart operations has been well established, and various cardioplegic methods have been clinically introduced [1–3]. However, questions still arise as to what method is appropriate for hearts severely injured due to severe valvular disease, and what is the maximum duration of ischemia that can be tolerated by the myocardium. To answer these questions, we focused on patients with a severely dilated heart due to valve disease associated with ischemic time of longer than 200 minutes, and evaluated the efficacy of myocardial preservation using two different cardioplegic methods.

McAinsh and associates [4] indicated that left ventricular hypertrophy and dilatation increase the risk of ischemia and deterioration in function after the ischemia because of an increase in myocardial demand. Kawaguchi and colleagues [5] also demonstrated that the dilated myocardium might require a greater energy supply for cardiac contraction. Taniguchi and associates [6] demonstrated that postoperative mortality was significantly increased in patients whose left ventricular end-systolic volume index was more than 100 mL/m². Borrow and associates [7] also indicated that a left ventricular end-diastolic volume index of more than 180 mL/m² is a significant risk factor for postoperative cardiac failure and may result in poor cardiac protection during ischemia. These studies suggested that myocardial protection in the dilated heart might be difficult during ischemia. Therefore, we selected patients with a severely dilated heart due to valve disease associated with ischemic time of longer than 200 minutes, and evaluated the efficacy of myocardial preservation.

We investigated two different cardioplegic methods. Glucose-insulin-potassium (GIK) solution, in association with continuous cold blood perfusion, is conventionally used at our institute. Histidine-tryptophan-potassium (HTK) solution has been used in European countries and was recently used at our institute [8, 9]. These two cardioplegic solutions are similar in many respects, being calcium-free, intracellular sodium formulations, but differ in the sodium and potassium concentrations, metabolic substrate content, and buffering capacity. The purpose of this study was to investigate whether these differences would be potentially advantageous or disadvantageous for the preservation effect in our patient group.

Patients and Methods

Patients

Twenty patients who had undergone open heart operations at The Heart Institute of Japan between January

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We selected patients with severely dilated hearts due to valve disease associated with prolonged ischemia of more than 200 minutes in each group. The dilated heart was defined as having a left ventricular diastolic diameter (LVDd) of more than 55 mm and left ventricular systolic diameter (LVDs) of more than 45 mm in the preoperative status. There were no significant differences in age, preoperative LVDd, LVDs, percent fractional shortening (%FS), cardiac index (CI), and percent fractional shortening during the intervals between the GIK infusion. Initial infusion. Continuous cold blood perfusion (4°C, 4°C over 5 minutes and an additional dose of 500 mL was infused at the same rate at 30-minute intervals after the initial infusion. Continuous cold blood perfusion (4°C, hematocrit-20%) with low flow (50 mL/L) was also performed during the intervals between the GIK infusion. The selection of cardioplegia was randomly decided by the surgeons.

Assessment of cardiac performance was carried out using the cardiac index and percent shortening fraction during the preoperative and postoperative periods. Cardiac index was measured at 12 hours after weaning from the extracorporeal circulation. An echocardiographic study was performed 3 to 4 weeks after the operation. Biochemical measurements, including creatine kinase and glutamic-oxaloacetic transaminase levels, were measured 12 hours after the operation. During the operation, the initial 10 mL of the cardioplegic coronary effluent was collected from the coronary sinus and the pH was measured during ischemia in both groups. The incidence of postoperative ventricular arrhythmia higher than Lown's grade 2 was investigated using a 24-hour Holter electrocardiogram.

Statistical Analysis
All statistical evaluations were conducted using two-way analysis of variance. The data from the two groups were compared preoperatively with unpaired Student's t test. To evaluate the myocardial protective effects of a certain cardioplegic method, preoperative and postoperation data within the group were compared using paired Student's t test. Data are presented as mean ± standard error of the mean. All differences were regarded as statistically significant if p was less than 0.05.
Results

There was no operative death within 30 days after the operation. The dopamine dose required for weaning from the extracorporeal bypass was $14.6 \pm 3.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ in the GIK group and $13.5 \pm 3.1 \text{ L} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ in the HTK group (not significant). A comparison of the cardiac index between the preoperative and postoperative periods showed that it was decreased in the GIK group, from $3.3 \pm 0.3$ to $2.8 \pm 0.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. However, it was increased in the HTK group, from $2.7 \pm 0.18$ to $3.4 \pm 0.17 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ($p < 0.05$) (Fig 1).

The pH of the coronary effluent was not changed during ischemia in the HTK group. However, pH was decreased as the ischemic time was prolonged in the GIK group (Fig 2). The activity of creatine kinase at 12 hours postoperatively showed significant increases in the GIK group. The glutamic-oxaloacetic transaminase level after the operation was $89.7 \pm 12.4 \text{ IU/dL}$ in the GIK group and $79.9 \pm 16.7 \text{ IU/dL}$ in the HTK group. The creatine kinase level was significantly lower in the HTK group than in the GIK group ($668.1 \pm 73.3$ versus $889.6 \pm 70.9 \text{ IU/dL}; p < 0.05$) (Fig 3). Percent fractional shortening in the postoperative period was $13.4\% \pm 3.1\%$ in the GIK group and $23.6\% \pm 2.6\%$ in the HTK group ($p < 0.05$). Compared with the preoperative value, postoperative percent fractional shortening was significantly decreased in the GIK group ($p < 0.05$) but not in the HTK group (Fig 4).

The frequency of arrhythmia, defined as higher than Lown’s grade 2, was assessed by Holter electrocardiography. The incidence of ventricular arrhythmia higher than Lown’s grade 2 was 72% in the GIK group, but it was lower in the HTK group (33%). Therefore, the postoperative incidence of ventricular arrhythmia was significantly reduced in the HTK group.

Comment

The current growth of interest in the use of various cardioplegic solutions during cardiac operations has resulted in the development of a number of different solutions and various methods [11]. These cardioplegic...
methods have advantages and disadvantages. They should be used appropriately by taking into account the characteristics of myocardial injury and the duration of ischemic time. Suga and associates [12] indicated that the area of the pressure–volume curve significantly correlates to the O2 consumption of the myocardium. Therefore, as the LVEDV increases, the area of the pressure–volume curve and oxygen consumption of the myocardium increases. Thus, the dilated myocardium might require a significantly greater energy supply for cardiac contraction. Several aspects of myocardial protection for the dilated heart should be considered to prevent postoperative cardiac failure [12]. We hypothesized that the buffering effect of histidine may be beneficial for severely injured myocardium in the dilated heart during prolonged ischemia. In this study, therefore, we selected patients with severely dilated myocardium and compared the preservation effects of the HTK and GIK methods.

A major difference between the two cardioplegic methods was their buffering capacity. Histidine buffering to enhance myocardial protection was suggested several years ago by Bretschneider and associates [3]. In 1985, del Nido and colleagues [13] showed that histidine exerted a significant cardiac protective effect. The HTK solution excludes the incorporation of a metabolic substrate but, in contrast, employs a high-capacity buffer system in the form of the amino acid histidine. The more efficient retardation of acidosis with HTK sufficiently delays an increase in the cytosolic calcium ion integrity of the sarcolemmal membrane [14]. This is also affected by the low magnesium ion concentration, resulting in a reduced level of activation of the sarcolemmal ion pumps, thereby further conserving energy reserves. Also, due to the hypokalemic nature of the HTK solution and its low overall ion concentration, provision is made for a significantly higher buffer concentration.

This study demonstrated that a physiologic protein buffer, such as histidine, showed a buffering capacity superior to that of bicarbonate in stabilizing pH and the recovery of postsischemic biochemical and mechanical parameters in the dilated heart. The reason for the effective buffering capacity is that histidine has a borderline pK value of 6.0, but its efficacy as a buffer increases as the tissue pH decreases to less than 7.0. The temperature coefficient of histidine is favorable, because the change in the pK value is in parallel with the change in the pH of water. Therefore, this buffer remains effective over a wide range of temperatures. Although the pK value of bicarbonate is 6.35, the low temperature coefficient indicates that the pH of the bicarbonate buffer alters little with a decline in temperature and does not change with the pN of water during progressive cooling [15, 16]. Heinemeyer and co-workers [17] also reported that intracellular pH in HTK was not changed for 180 minutes of ischemia. However, it declined in St. Thomas’ solution after preservation. Preparations treated with HTK showed complete recovery, whereas those treated with St. Thomas’ solution did not [17]. Our results indicated that the pH was more stable in HTK during prolonged ischemia. Hendry and colleagues also demonstrated that the use of HTK solution resulted in the best recovery of myocardial function after a 24-hour preservation period compared with the Euro-Collins and University of Wisconsin solutions [18–20]. Furthermore, the high buffering capacity of HTK allows for less frequent cardioplegic infusions during the ischemia, thus avoiding the harmful effect on the myocardium caused by multiple infusions of cardioplegia.

As an energy source for prolonging ischemic time, glucose was used in the GIK solution. Hearse and associates [21] reported a deteriorating effect of glucose in cardioplegia because of an increase in lactate production. In contrast, amino acids, such as ketoglutarate and tryptophan, were used in HTK as the energy source. These components generate adenosine triphosphate via the alternative pathway without producing lactate in the cells. Furthermore, the presence of a high histidine concentration outside the cells may also be beneficial because it facilitates H+ removal from the cytosol by anionic carriers such as lactate during the ischemia [22]. These beneficial effects may be the cause of the significant protective effects of HTK solution for prolonged ischemia in the severely injured myocardium. Our study demonstrated that percent fractional shortening after the ischemia was significantly improved and myocardial injury was less in the HTK group. These results suggest a significant effect of the high buffering capacity of histidine in preserving the severely injured myocardium after prolonged ischemia.

In conclusion, the results of the present study suggest that the protective effect of the HTK method may be significant in patients with a severely dilated heart when ischemic time is longer than 200 minutes.

References


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