Assessment of protective effects of Warm Terminal Blood Cardioplegia on Myocardial Protection in CABG.

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Abstract:
Introduction: Coronary artery disease A significant metabolic derangement occurs in the ischaemic-reperfused heart of patients undergoing coronary artery bypass surgery using cold blood cardioplegia . It has been reported that up to one forth of deaths after coronary artery bypass grafting surgery may be caused by Reperfusion injury especially in patients with higher NYHA classes. There are evidences that in adult cardiac operations, a warm cardioplegic reperfusate (hot shot) before removing the aortic cross-clamp improves postbypass myocardial function and metabolic recovery . We randomly assigned 41 consecutive patients undergoing primary, elective CABG into two groups; TWBC Group who received Terminal Warm Blood Cardioplegia just before removing of Aortic cross clamp (n=24) and second group (Control) did not received TWBC (n=17). Among patients in CONTROL group 41% (95% CL: 19-62%) received at least one inotrope, but only 17% (95% CL: 0 - 35%) of patients in TWBC group did so (p = 0.085). Also in respect to EF there was superiority in TWBC group only in patients with low pre operative EF. There was higher rate of spontaneous beating in TWBC group (21 of 24 or 88%) versus Control group (12 of 17 or 70%; P<0.1). Conclusion: it seems prudent to routinely use Terminal Warm Blood Cardioplegia in patients undergoing coronary bypass graft especially in those with reduced ventricular function.

Key words: Cardioplegia, CABG, Myocardial Protection

Introduction: Although blood cardioplegia provides excellent myocardial protection but recovery is delayed. It is now well known that Perioperative MI is most often related to inappropriate myocardial management . Postischemic myocardial dysfunction is attributable, in part, to a phenomenon known as ischemia/reperfusion-induced injury. Clinically, it is manifest by low cardiac output and hypotension, and may be subdivided into two subgroups: reversible injury and irreversible injury. The two are typically differentiated by the presence of ECG abnormalities, elevations in the levels of specific plasma enzymes or proteins such as creatine kinase and troponin I or T, and/or the presence of regional or global echocardiographic wall motion abnormalities. With respect to coronary artery bypass surgery alone, 10% patients may experience myocardial infarction, severe ventricular dysfunction, heart failure, and/or death, despite advances in surgical technique. Technique of Controlled Aortic root reperfusion has been developed to limit reperfusion injury.

Material and Methods:
On a prospective basis, patients undergoing Coronary Arterial Bypass Graft (CABG) were randomly assigned into two groups; Terminal Warm Blood Cardioplegia and Controlled group. Our exclusion criteria were age younger than 30 or older than70 years' old, cross-clamp time of more than 110 minute and need for endarterectomy. Total number of 41 patients were entered the study, of which 24 were in group Terminal Warm Blood Cardioplegia and 17 were in Control group.

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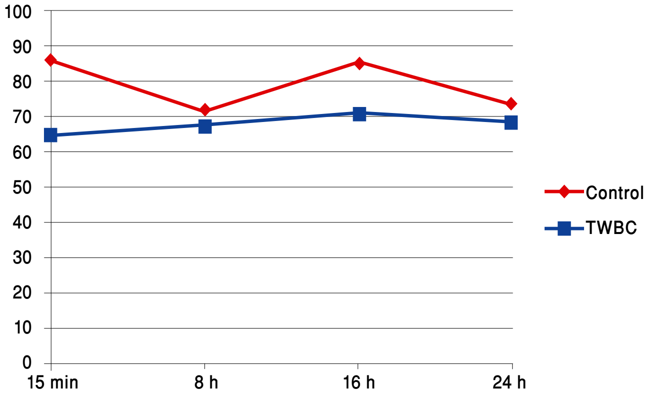
Briefly the technique was as follow: At the conclusion of operation, with the aortic clamp still in place, controlled aortic root reperfusion is begun, initially using warm hyperkalemic blood cardioplegia. The aortic root pressure is kept at 30 mmHg for the first 60 to 120 seconds of the reperfusion. The flow is then increased until the aortic root pressure is 50 to 75 mmHg in adults (or to the normal systemic arterial diastolic pressure in infants and children whose body surface area is less than 1 m2. A total of 500 mL of the blood reperfusate is administered. For patients with a body surface area of less than 1.5 m2, the reperfusate volume = 500 × BSA / 1.5. Once that has been infused, the perfusionist continues the controlled aortic root reperfusion by arranging the circuit so that aortic root perfusion continues with normothermic, normokalemic, unmodified blood. The heart remains flaccid and electromechanically quiescent for 2 to 10 minutes after the onset of the controlled aortic root reperfusion. During this time, the coronary resistance may rise, requiring the perfusionist to reduce the flow rate to maintain a constant aortic root pressure. Controlled aortic root perfusion is continued until sinus rhythm has returned and ventricular contractions are strong. Variables including post-operative ejection fraction, need for inotrope and spontaneous beating after de-clamping of aorta were assessed. Also we measured creatinine phophokinase (CPK) at 15 minute, 8, 16, and 24 hour post operatively. Data were analyzed using univariate tool for scale variables and Binomial regression and chi square tool for nominal variable through "SPSS 16" program.

Results:
Both group were similar in respect to age, sex, preoperative Ejection Fraction and number of grafts (see table 1). Patients in group Terminal Warm Blood Cardioplegia had a lower need for post-operative inotrope (16.7%) support compared to Control group (41.2%, p=0.085). in respect to post-operative Ejection Fraction, when all patients were considered, there were no statistically difference between two groups, but when patients with good preoperative Ejection Fraction excluded (EF ≥ 50 %, table 2) , patients in group Terminal Warm Blood Cardioplegia had better post-operative Ejection Fraction (40%) than in control group (35%, p=0.076), this means patients with lower myocardial function benefits more. this is consistent with current information that maximal benefits of myocardial management is in patients with reduced myocardial function (see figure 1).

Figure 1 *mean levels of Creatin phosphokinase (CPK) in group terminal warm cardioplegia (TWBC) and control group at 15 minute, 8, 16 and 24 hours post-operatively.*



Discussion:
Although hypothermia and potassium infusions remain the cornerstone of myocardial protection during on-pump heart surgery, there are many other cardioprotective techniques and methodologies available . While many of these techniques have been reported to confer superior protection and improve patient outcomes, the ideal cardioprotective technique, solution, and/or method of administration has yet to be found. Fortunately, the majority of cardioprotective strategies now available do allow patients to undergo conventional and complex heart operations with an operative mortality rate ranging from less than 2% to 4%.

Principals of minimizing reperfusion injury include:
1. Electromechanical maintaining electromechanical quiescence during the first to 5 minutes of reperfusion, to permit more rapid repletion of myocardial energy charge, minimize and.
2. Maintaining perfusion pressure at safe levels until the full recovery of the myocardium which is about 30 mmHg during the first 60 to l20 seconds of reperfusion, to minimize endothelial cell damage and swelling, during which time reactive hyperemia, usually present.

Other factors that must be manipulated are

- Providing a large buffering capacity
- Minimizing damage from oxygen-derived free radicals
- Reducing ionized calcium in the initial reperfusate .

Blood: Blood as the reperfusion vehicle has been shown to be superior to crystalloid solutions; the minimal effective

level of the hematocrit in the reperfusate is 0.15 to 0.20
Substrate; c-glutamate and aspartate;
Hydrogen Ion Concentration: hydroxymethyl aminomethane (Tris) and histidine
Calcium: low but should not be totally absent
Potassium: the initial reperfusate should contain sufficient potassium to maintain electromechanical quiescence for at least 2 to 3 minutes, and preferably 5 to 10 minutes. The sufficient concentration is about 12 mmol.
Pressure: about 30 mmHg for the first 60 to) 120 seconds of reperfusion; after the first 60 to 120 seconds, of maintaining reperfusion pressure between 50 and 70 mmHg, or at the preoperative diastolic arterial pressure of the patient, which ever was lower14.
In our study, Creatinine Phosphokinase levels were measured early post-operatively at 15 minute, 8, 16, 24 hours after arrival to Intensive Care Unit (ICU). These levels at any given points were higher in Control group than in Terminal warm blood cardioplegia group (figure 1), but the differences were not significant. Similarly, "Yoshiya Toyoda et al" in a prospective study involving One hundred three consecutive patients who were randomly assigned to TWBC and Control group, showed that Terminal warm blood cardioplegia enhanced myocardial protection in pediatric cardiac surgery by an improvement in aerobic energy metabolism and a reduction of myocardial injury or necrosis . In contrast "Chareonkiat Rergkliang" in a cohort of patients with mitral valve disease (n=40), did not find any difference between terminal warm blood cardioplegia and control group in respect to Troponin T release at 0 and 6 h postoperatively. Also the maximum doses of inotropics, duration of inotropic support, intensive care unit stay, and postoperative left ventricular ejection fraction were similar in both groups on their study .
In our study the percentage of patients who needed inotropic support was higher in Terminal warm blood cardioplegia group (17%) compared to control group (42%, p=0.08).
Spontaneous return of sinus rhythm after removal of aortic cross clamp although was higher in Terminal warm blood cardioplegia group (88%) than control group (71%), but the difference was not significant, although, "Michio Kawasuji" showed a reduction of the incidence of reperfusion arrhythmia using this technique13.
As mentioned earlier post-operative ejection fraction was not significantly different between two groups, but after excluding patients with preserved ejection fraction (EF ≥50%), the difference was more evident (35% versus 40% in control and terminal warm blood cardioplegia, respectively, p=0.076). this is consistent with other reports, as depicted in figure 2, that benefits of myocardial managements are minimal in patients with preserved myocardial function, and maximal in patients with depressed myocardial function.
Conclusion
It is highly advisable to use terminal warm blood cardioplegia and controlled aortic root reperfusion in patients with depressed myocardial function and patients undergoing complex and lengthy procedures.

Table 1 *Comparison of Two groups*

	TWBC		Control		P Value
	Mean	95% CL	Mean	95% CL	
Age	61	57 – 66	61	55 – 67	NS
Number of Grafts	3	2.6 – 3.4	2.9	2.4 – 3.4	NS
Preoperative EF	44	40 – 48	42	37– 47	NS
Post operative EF	41	38 – 44	38	34 -41	NS
Need for inotrope	17%	0 – 38%	42%	19% - 63%	0.08
Spontaneous beating	88%	71 – 100%	71%	51 – 90%	NS
Total CPK	273	200 - 346	318	233 -404	NS
Mortality	0		0		NS

Dependent Variable: *Post -operative EF*
Table 2 *Comparing post-operative Ejection Fraction when patients with good preoperative EF (EF ≥ 50%) are excluded, (P= 0.076).*

Group	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Control	35.000	1.964	30.970	39.030
TWBC	39.875	1.770	36.243	43.507

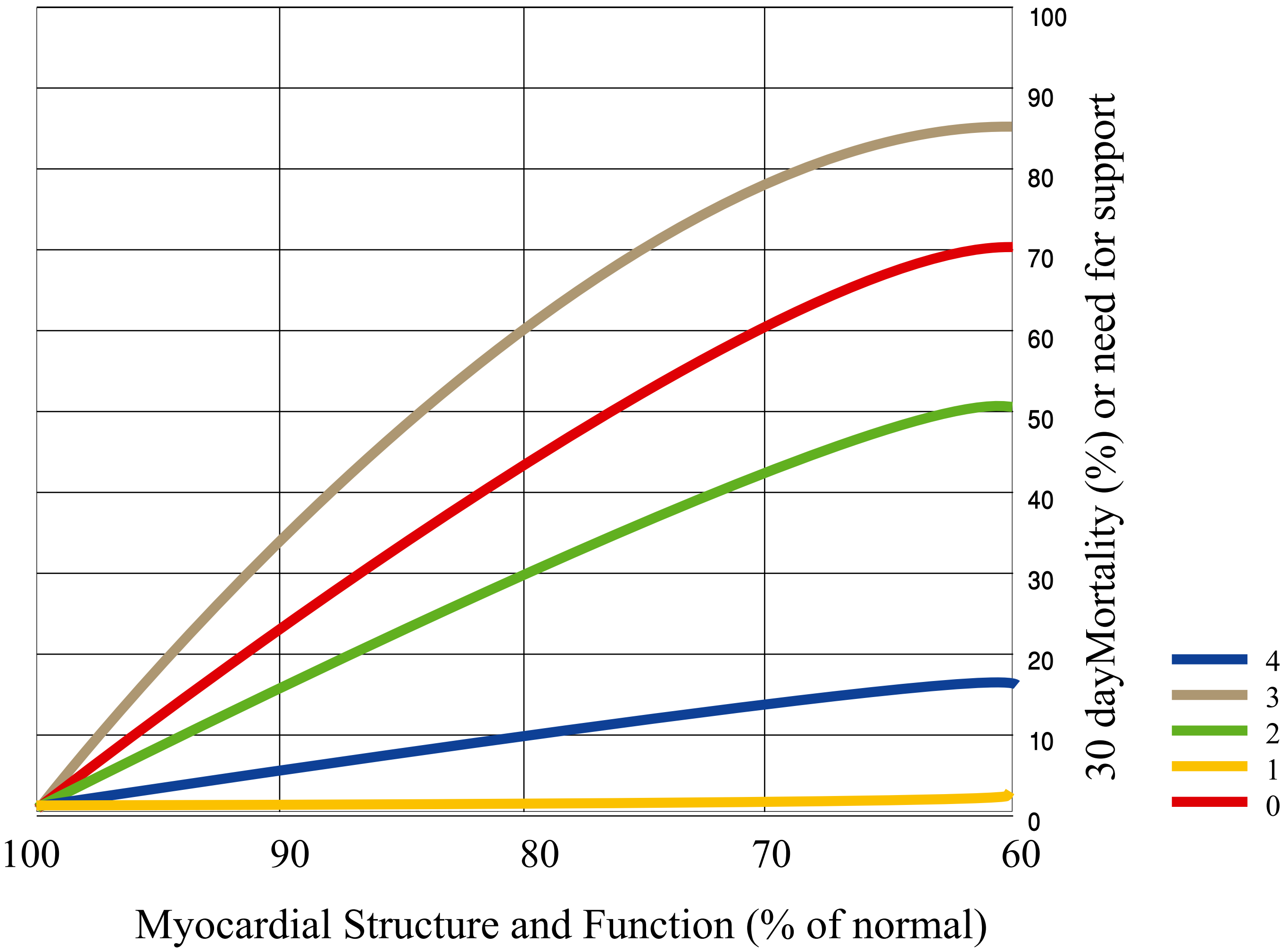


Figure 2 Horizontal axis represents preoperative state of heart (as percent of normal function; e.g. more right on the axis, more reduced function), vertical axis represents either mortality or important catecholamine or mechanical support. There is five groups of patients (from 0 to 4); 4 is for most complete myocardial management available (warm induction of cardioplegia), controlled aortic root reperfusion; the other end of spectrum is 0 that means no special management. As it is seen, differences in outcome in low risk patients (on the left side of curve) are small; in contrast in high risk patients (at the right) these differences are high.

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