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Can heartbeat recovery be improved with terminal non-cardioplegic warm blood perfusion prior to aortic unclamping in single-clamp technique coronary artery bypass surgery? A randomized controlled trial

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Abstract

Background The objective of this study is to investigate whether the use of antegrade perfusion with terminal non-cardioplegic warm blood (TNWB) before aortic unclamping in single-clamp technique coronary artery bypass has a positive impact on intraoperative heartbeat recovery.

Methods Between December 2022 and May 2023, 40 consecutive patients undergoing coronary artery bypass using single-clamp technique were randomized into one of two groups: the TNWB group received an antegrade perfusion with TNWB before removing the aortic cross-clamp ($n = 20$), while the control group did not receive ($n = 20$). The time intervals between coronary perfusion and the onset of the first heartbeats and sinus rhythms, occurrences of spontaneous sinus rhythm, intraoperative defibrillation requirements, as well as postoperative CK-MB and troponin T levels were recorded and subjected to analysis.

Results In the TNWB group, the median onset of the first heartbeats after the initiation of coronary perfusion was 34 s (4-100), while in the control group, it was 90 s (15–340) ($p < 0.001$). The median onset of the sinus rhythms was 100 s (28–290) in the TNWB group and was 132 s (45–350) in the control group ($p = 0.023$). The occurrence of intraoperative arrhythmias was 15% in the TNWB group compared to 50% in the control group ($p = 0.018$), and the incidence for internal defibrillation was 5% in the TNWB group and was 30% in the control group ($p = 0.037$). The TNWB group showed the median CK-MB levels at 6 h postoperative was 14.10 ng/mL (9.78–19.26), compared to 18.31 ng/mL (13.98–23.80) in the control group ($p = 0.045$).

Conclusions During single clamp coronary artery bypass, administration TNWB into the aortic root before aortic unclamping has the potential to enhance heartbeat recovery, as evidenced by the shortened time to the initial heartbeat and the establishment of sinus beats following coronary perfusion.

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Background

A comprehensive myocardial preservation strategy is a tailored approach used by cardiac surgeons to protect the heart muscle during surgery, aiming to improve patient outcomes and minimize complications [1, 2]. Reperfusion with warm blood before aortic unclamping is crucial for minimizing ischemia-reperfusion injury and promoting recovery post-cardiac surgery, warranting careful consideration and ongoing research [3].

The single-clamp technique coronary artery bypass grafting (CABG) is a particular cardiac procedure, first described by Salerno in 1982, where gradual coronary reperfusion is achieved for each grafted coronary vessel throughout aortic cross-clamping [4, 5]. Following aortic unclamping and during cardiopulmonary bypass, the perfusion pressure tends to be lower than normal and lacks pulsatility during the initial phase. Heart distention, vasoconstriction, and vasodilatation result in uncontrolled coronary autoregulation. In the single-clamp technique coronary artery bypass, once all the anastomoses are completed, the opportunity to regulate and ensure sufficient coronary blood flow occurs solely before the aortic unclamping. While non-cardioplegic warm blood seems to enhance the energy charge for heartbeat recovery and washout of the waste products, there is a shortage of reports assessing the effectiveness of TNWB in the single-clamp technique for coronary artery bypass. We postulated that addition of TNWB before aortic unclamping might improve heartbeat recovery and provide smooth weaning from cardiopulmonary bypass.

Methods

Between December 2022 and May 2023, 40 consecutive patients undergoing coronary artery bypass using the single-clamp technique were randomized into two groups: the TNWB group, which received antegrade perfusion with TNWB before removing the aortic cross-clamp ($n=20$), and the control group, which did not receive this perfusion ($n=20$). We recorded and analyzed the time intervals between coronary perfusion and the onset of the first heartbeats and sinus rhythms, occurrences of spontaneous sinus rhythm, intraoperative defibrillation requirements, and perioperative CK-MB and troponin T levels.

This study has been approved by Human Ethics Committee of Thammasat University (MTU-EC-SU-1-051/66).

Patient selection

Patients with significant left anterior descending (LAD) artery stenosis and at least another major coronary artery stenosis planned for coronary artery bypass were included in the study. The exclusion criteria comprised (1) emergency surgery, (2) ejection fraction lower than 30%, (3) combined cardiac-associated operative procedure, (4) recent myocardial infarction (within the last 4 weeks), and (5) age exceeding 80 years. Randomization was performed by opening a sealed envelope at the time of incision. Patients whose left internal mammary artery (LIMA) to LAD anastomosis could not be achieved or who had an aortic clamp time exceeded 120 min were omitted from the study.

Sample size calculation

The sample size for this study was calculated to ensure sufficient statistical power to detect significant differences in heartbeat recovery outcomes between the TNWB and control groups. Using data from a previous study by Susumu et al. (2006) [12], the sample size was determined based on a standardized effect size, with an α of 0.05 and a β of 0.20. The estimated minimum sample size was 17 patients per group. To account for potential dropouts, an additional 10% was added, resulting in a target of 20 patients per group for the primary outcome analysis. Consequently, the research team estimates a total of 40 participants will be required for the study.

Randomization

Patients were block randomized according to a computer-generated list. The allocations were concealed until the date of the operation. Participants were recruited by the surgical team, and the allocation of groups was disclosed to the perfusionist at the beginning of the operation and to the surgeon after the proximal anastomosis was completed.

Operative technique

All patients received standard anesthesia. A median sternotomy was performed. Both the left internal mammary artery (LIMA) and arterial or venous grafts were prepared. Routine cardiopulmonary bypass (CPB) was carried out under mild hypothermia (32ºC). Myocardial preservation was achieved using antegrade whole blood cardioplegia administered at a cold temperature. Distal and proximal anastomoses were consequently constructed during a single period of aortic cross-clamp. Additional cardioplegia was delivered upon completion of each proximal anastomosis or after 20 min. Finally,

grafting of the left anterior descending artery with the left internal thoracic artery was performed following the sequential completion of arterial graft or saphenous vein graft anastomoses. The patient's body temperature was maintained at 32 °C during cardiopulmonary bypass. Systemic rewarming commenced during the final construction of the proximal anastomosis and prior to grafting of the left anterior descending artery.

After completion of the procedure and adequate rewarming, weaning from cardiopulmonary bypass was conducted according to the established protocol. During this period, occurrences of arrhythmia, the need for defibrillation, and pacing requirements were recorded. The inotropic agent for the weaning-off process was primarily dobutamine at a dosage of 5 mcg/kg/min. Decannulation took place upon achieving hemodynamic stability.

Myocardial protection

Patient blood was obtained from the oxygenator and combined with a prepared cardioplegic solution (containing 16 mEq of potassium in 20 mL) to provide whole blood cardioplegia with a potassium concentration of 16 mEq/L. This mixture was delivered at a cold temperature (14–16 °C) through the antegrade route. The infusion protocol involved administering the initial dose of 20 mL/kg within 3 min, with subsequent doses administered following the completion of each proximal anastomosis or after 15–20 min, as needed.

Technique of TNWB

In the TNWB group, warm blood at 36 °C was infused into the aortic root via the antegrade cardioplegia cannula before aortic unclamping. This was maintained at a targeted flow rate of 250 ml/min for 3 min, which

Table 1 Patient characteristics

	TNWB (n = 20)	Control (n = 20)	*p*
Age (years old)	65.2 ± 7.75	65.05 ± 8.78	0.955
Male	16 (80%)	15 (75%)	0.705
Weight (kg)	65.90 ± 14.07	64.95 ± 14.21	0.833
Height (cm)	161.65 ± 7.04	164.30 ± 10.70	0.361
Body surface area (m²)	1.71 ± 0.20	1.71 ± 0.23	0.966
Body mass index (kg/m²)	25.16 ± 4.86	23.86 ± 3.56	0.340
Left ventricular ejection fraction (%)	49.10 ± 14.93	49.37 ± 14.81	0.954
Triple vessels disease	19 (95%)	17 (85%)	0.549
Left main coronary disease	11 (55%)	12 (60%)	0.749
Diabetes	11 (55%)	11 (55%)	1.000
Hypertension	19 (95%)	20 (100%)	0.311
Hyperlipidemia	20 (100%)	20 (100%)	n/a
Chronic obstructive pulmonary disease	0 (0%)	1 (5%)	0.269

Normal distributed continuous data are presented as the mean ± SD. Nominal data are presented as number (percentage)

corresponds to normal resting coronary blood flow. For the safety reason, the pressure is limited at 150 mmHg to commence coronary perfusion. In the control group, coronary perfusion begins after aortic unclamping.

Endpoints

The primary endpoint for this study is heartbeat recovery, specifically the duration to the first heartbeat and sinus beat following coronary perfusion. First heartbeat referred to the first observable heart contraction following coronary perfusion. A sinus beat could describe based on the electrocardiogram (ECG), in which the P-wave was upright and preceded each QRS complex. Coronary perfusion began in the TNWB group with the initiation of TNWB, whereas in the control group, it commenced upon aortic unclamping. Spontaneous heartbeat recovery is evidenced when electrical activity in the monitor was observed, and the patient could wean off from cardiopulmonary bypass without the need for electrical defibrillation or pacing.

The secondary endpoint is the safety analysis of TNWB. The decision to use temporary pacing before discontinuing cardiopulmonary bypass depended on the patient's condition, ensuring optimal cardiac function during the transition, particularly in bradyarrhythmias and atrioventricular block. The decision to use defibrillation was considered in the event of ventricular fibrillation or ventricular tachycardia. CK-MB and troponin T levels were evaluated at two time points: prior to aortic cross-clamp and 6 h post-operation upon arrival in the ICU.

Statistics

STATA 16.0 was utilized for data analysis. Normal distributed continuous data were expressed as the mean ± SD, and Student's t-test was used to compare the two groups. Non-normal distributed continuous data were expressed as a median with the interquartile range (25th to 75th percentiles), and the Mann-Whitney test was used to compared the two groups. Nominal data were expressed as number and percentage, and the two-tailed Fisher's test was used for analyses. The normality of the data was assessed using both the Shapiro-Wilk test and histograms. Statistical significance was considered at a $p < 0.05$.

Results

The patient characteristics data showed no significant differences between the two groups, as summarized in Table 1.

Intraoperative data is shown in Table 2. There were no significant differences among the two groups in terms of cardiopulmonary bypass time, aortic clamping time, number of vessels grafted. The time interval from coronary perfusion to the first heartbeat was shorter in the

Table 2 Intraoperative and postoperative data

	TNWB (n = 20)	Control (n = 20)	p
Cardiopulmonary bypass time (min)	92.65 ± 26.48	95.40 ± 25.09	0.738
Aortic clamp time (min)	70.45 ± 21.31	72.30 ± 23.31	0.795
Number of vessels grafted 5	1 (5%)	0 (0%)	0.524
4	5 (25%)	6 (30%)	
3	13 (65%)	11 (55%)	
2	1 (5%)	3 (15%)	
Duration from coronary perfusion to the first heartbeat (sec)	34 (4-100)	90 (15–340)	< 0.001*
Duration from coronary perfusion to sinus beat (sec)	100 (28–290)	132 (45–350)	0.023*
Spontaneous heartbeat recovery	17 (85%)	13 (65%)	0.144
Intraoperative arrythmia	3 (15%)	10 (50%)	0.018
Intraoperative defibrillation	1 (5%)	6 (30%)	0.037
Temporary pacing	3 (15%)	5 (25%)	0.429
Mechanical support	0 (0%)	0 (0%)	n/a
Time to extubation (hours)	8 (6–10)	8 (6–9)	0.978*
Postoperative atrial fibrillation	2 (10%)	3 (15%)	0.633
Reoperation	0 (0%)	1 (5%)	0.311
ICU stay (hours)	32.00 ± 11.58	34.20 ± 16.18	0.624

Normal distributed continuous data are presented as the mean±SD. Non-normal distributed continuous data are presented as a median (IQR). Nominal data are presented as number (percentage)

*Non-normal distribution analyzed by Mann-Whitney U test

TNWB group compared to the control group (TNWB: 34 s (4-100) vs. control: 90 s (15–340), $p<0.001$). Similarly, the time interval from coronary perfusion to sinus beat was also shorter in the TNWB group compared to the control group (TNWB: 100 s (28–290) vs. control: 132 s (45–350), $p=0.023$). The incidence of intraoperative arrhythmia was lower in the TNWB group compared to the control group (15% vs. 50%, $p=0.018$). Additionally, the defibrillation rate was 5% in the TNWB group and 15% in the control group ($p=0.037$). Spontaneous heartbeat recovery was more evident in the TNWB group than in the control group (85% vs. 65%, $p=0.144$), although the difference did not reach statistical significance. There were no differences in the need for temporary pacing, or mechanical support between both groups.

The postoperative course, as shown in Table 2, revealed no significant differences in time to extubation, occurrence of atrial fibrillation, need for reoperation, and length of ICU stay between the groups.

The concentrations of perioperative cardiac markers are displayed in Figs. 1 and 2. Initial measurements of both CK-MB and troponin T before aortic clamping showed no significant differences between the TNWB and control groups. Importantly, CK-MB at 6 h postoperatively was significantly lower in the TNWB group compared to the control group (TNWB: 14.10 ng/mL (9.78–19.26) vs. control: 18.31 ng/mL (13.98–23.80), $p=0.045$). However, serum cardiac troponin T levels at 6 h postoperatively did not differ significantly between the two groups.

Discussion
The primary finding of our experiment is that the TNWB group demonstrated a shorter time to the first heartbeat and initial sinus rhythm after coronary perfusion, indicating improved myocardial recovery. This is a significant indicator of effective myocardial protection, as the recovery of the heartbeat is regarded as a key metric [12].
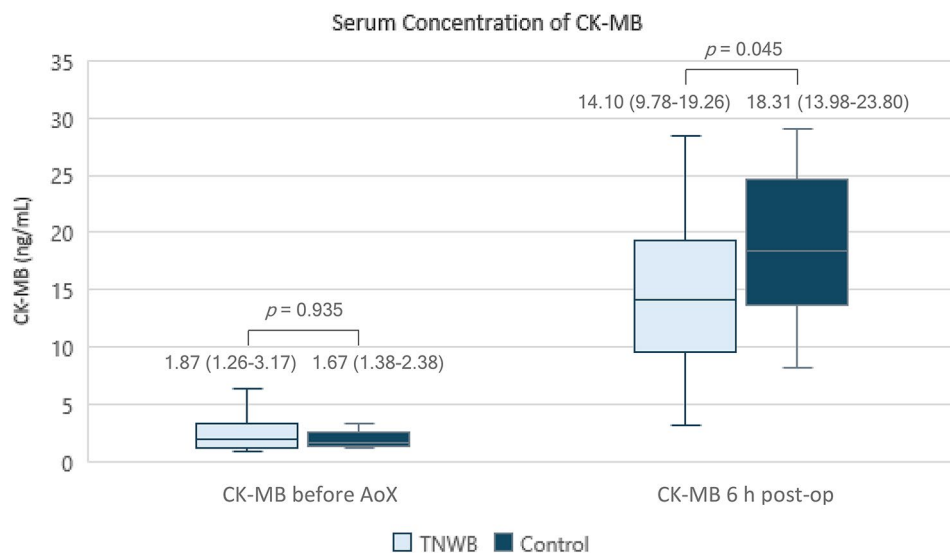

Fig. 1 Serum concentration of CK-MB (ng/mL) before aortic cross-clamp, and 6 h post-op. Data are presented as median (IQR). The upper and lower borders of the box represent the upper and lower quartiles. The middle horizontal line represents the median. The upper and lower whiskers represent the maximum and minimum values of nonoutliers
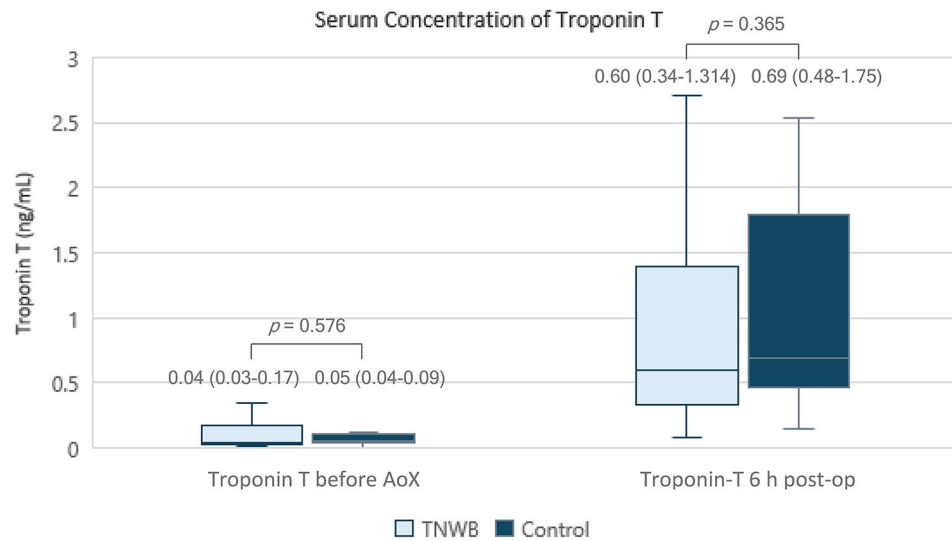
Fig. 2 Serum concentration of Trop T (ng/mL) before aortic cross-clamp, and 6 h post-op. Data are presented as median (IQR). The upper and lower borders of the box represent the upper and lower quartiles. The middle horizontal line represents the median. The upper and lower whiskers represent the maximum and minimum values of nonoutliers

Furthermore, no significant differences were observed between the TNWB and control groups in the early postoperative course regarding time to extubation, arrhythmia, reoperation, or length of ICU stay, indicating that TNWB is safe and does not adversely affect these outcomes.

These results highlight the potential benefits of TNWB in enhancing myocardial recovery without compromising patient safety in the early postoperative period. Future studies should continue to explore the long-term outcomes and mechanisms underlying these benefits to further validate the efficacy and safety of TNWB in coronary artery bypass surgery.

Rationale behind TNWB

The rationale for using TNWB in our study is grounded on scientific principles including: (1) the single clamp technique in CABG already achieves a gradual revascularization of the ischemic myocardium for each grafted coronary vessel, (2) by administering cardioplegia through blood mixtures and repeating it after each set of coronary grafting, a gradual reperfusion of the ischemic myocardium seemed to occur, (3) once all the anastomoses were completed, the opportunity to regulate and ensure sufficient coronary blood flow occurs solely before the aortic unclamping, and (4) a non-cardioplegic warm blood may be a more optimal choice than using a high-potassium solution, which has potential adverse effects, to enhance the energy charge for heartbeat recovery and washout of the waste products in the brief period before aortic unclamp.

The 'single-clamp technique' in coronary artery bypass surgery involves creating both distal and proximal anastomoses during a single period of aortic cross-clamping. This method allows for gradual coronary reperfusion with each grafted vessel and enhances myocardial protection through the administration and repetition of blood cardioplegia after each proximal anastomosis [5]. At our institute, intermittent antegrade whole blood cardioplegia, which reduces the use of crystalloid solutions, has been routinely used in coronary bypass procedures for the past decade. Literature supports its benefits, maintaining myocardial protection, mortality, and morbidity without compromise [6, 7]. We observe similar advantages at our institution.

Following aortic unclamping, the flow and pressure decreased, heart distended, presence of vasoconstrictors or vasodilators influence the range of coronary autoregulation uncontrolled. In the single-clamp technique coronary artery bypass, once all the anastomoses are completed, the opportunity to regulate and ensure sufficient coronary blood flow occurs solely before the aortic unclamping. TNWB technique, the infusion is carried out at a flow rate of 250 ml/min, mimicking normal resting coronary blood flow. The perfusion is maintained at a pressure of 100–150 mmHg, and the perfusion time is set at 3 min, mirroring the conditions of the initial antegrade cardioplegic perfusion.

Elevated potassium level associated with potential adverse effects [8], which further enhances myocardial damage, by limiting myocardial perfusion [9]. Another significant aspect of high K^+ levels is the differential sensitivity of the atria and ventricles to high potassium. This discrepancy can contribute to an arrhythmogenic substrate between the chambers during reanimation after cold-diastolic arrest [10]. Considering that blood

possesses inherent properties as a potent buffering effect of oxygen-derived free radicals, which may be released during reperfusion, opting for a non-cardioplegic warm blood could be considered a more optimal choice compared to using a high-potassium solution in the brief period before aortic unclamp.

Although there have been several randomized controlled trials exploring the benefits of warm blood hyperkalemic perfusion (Hot shot) in various settings, often administered retrogradely, studies focusing on antegrade non-cardioplegic warm blood perfusion before aortic unclamping are rare [11–13]. Further validation of this strategy is necessary.

Cardiac markers
Elevated levels of CK-MB and troponin T in the blood are indicators of myocardial damage, often correlating with the extent of injury. The release of CK-MB into the bloodstream typically occurs within 4–6 h after the onset of myocardial injury, peaking around 18–24 h, and returning to normal levels within 48–72 h. Troponin T levels rise within 3–4 h after the onset of myocardial injury, peak at around 12–48 h, and can remain elevated for several days [14, 15]. Our data show a significant difference in CK-MB levels at 6 h postoperatively between the groups, while troponin T levels did not differ significantly. This discrepancy may be attributed to the limited 6-hour window for collecting enzyme levels. However, these cardiac markers were secondary endpoints for assessing the safety of TNWB. Extending the sample collection time to 12–48 h would provide a clearer conclusion on this matter.

Conclusion
Administering TNWB into the aortic root before aortic unclamping is a simple and efficient procedure that can be performed at the operating table. Our study suggests that incorporating TNWB before aortic unclamping in single-clamp technique coronary artery bypass surgery can enhance myocardial protection. This method has the potential to improve heartbeat recovery, as shown by the shortened time to the initial heartbeat and the establishment of sinus rhythm following coronary perfusion. While TNWB may not significantly impact clinical outcomes, it could serve as an adjunct in a multimodal myocardial protection strategy for single-clamp technique coronary artery bypass surgery.

Limitations
This was a small randomized controlled trial (RCT) focusing on the single-clamp technique for coronary artery bypass grafting (CABG). The findings of this study should be considered applicable to a similar set of myocardial protection protocols.

Abbreviations
TNWB	terminal non-cardioplegic warm blood
CABG	coronary artery bypass graft
CPB	cardiopulmonary bypass
LAD	left anterior ascending artery
LIMA	left internal mammary artery
LVEF	left ventricular ejection fraction
LM	left main coronary artery
COPD	chronic obstructive pulmonary disease

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study has been approved by Human Ethics Committee of Thammasat University (MTU-EC-SU-1-051/66).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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