

Management of the Heart Rate during Coronary Artery Bypass Grafting on the Beating Heart: Newly Devised Methods of Decreasing Heart Rate —A Preliminary Report—

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Background: To develop new methods for achieving bradycardia, we studied the feasibility of producing transient, reversible bradycardia with atrial stimulation and cooling of the sinoatrial node.

Methods: In an animal study, the atrium was stimulated electrically during the refractory period of the atrioventricular node. Alternatively, an area of the sinoatrial node was cooled regionally. The two methods were also performed in combination. In a clinical study, atrial stimulation was applied in seven consecutive patients who underwent coronary artery bypass grafting (CABG).

Results: In the animal study, atrial stimulation was effective only when 2 mg/kg of diltiazem was administered. Such atrial stimulation decreased heart rate (beats/minute) from 95.8 ± 16.9 to 64.2 ± 20.0 (the average reduction from the control value $66.1 \pm 10.3\%$). Cooling the sinoatrial node decreased heart rate, and was effective with or without administration of diltiazem. Heart rate was decreased from 156.6 ± 31.7 to 110.7 ± 21.7 (average reduction from control value $71.3 \pm 9.2\%$) before using diltiazem and from 102.0 ± 11.9 to 63.5 ± 13.9 (average reduction from control value $62.0 \pm 10.4\%$) after administration of diltiazem. By combining the two methods, heart rate was decreased from 102.0 ± 12.3 to 44.6 ± 9.1 (average reduction from control value $43.5 \pm 6.3\%$). In our clinical study, the atrial stimulation method was effective.

Conclusion: Atrial stimulation or regional cooling of the sinoatrial node slowed the heart rate. By combining the two methods, the heart rate was slowed to 40. Clinically, atrial stimulation was effective in CABG patients. (*Ann Thorac Cardiovasc Surg* 2001; 7: 358–67)

Key words: bradycardia, off pump coronary artery bypass grafting (CABG), atrial electrical stimulation, sinoatrial node cooling

Introduction

Reintroduction of coronary artery bypass grafting (CABG) on the beating heart, which includes minimally invasive direct coronary artery bypass grafting

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(MIDCAB),¹⁻⁶⁾ has broadened the surgical indication for CABG to patients with porcelain ascending aorta or low left ventricle ejection fraction (LVEF).⁷⁾ Both have been traditional contraindications for extracorporeal circulation (ECC).⁸⁾ However, the graft failure rates reported for minimally invasive direct CABG were higher²⁻⁴⁾ than those for CABG with ECC.⁹⁾ Many cardiac surgeons are still concerned about the quality of surgical anastomosis performed on the beating heart.^{10,11)} A key difference between conventional CABG and CABG on the beating heart is related to achieving elective asystole during construction of the distal anastomosis. There is significant

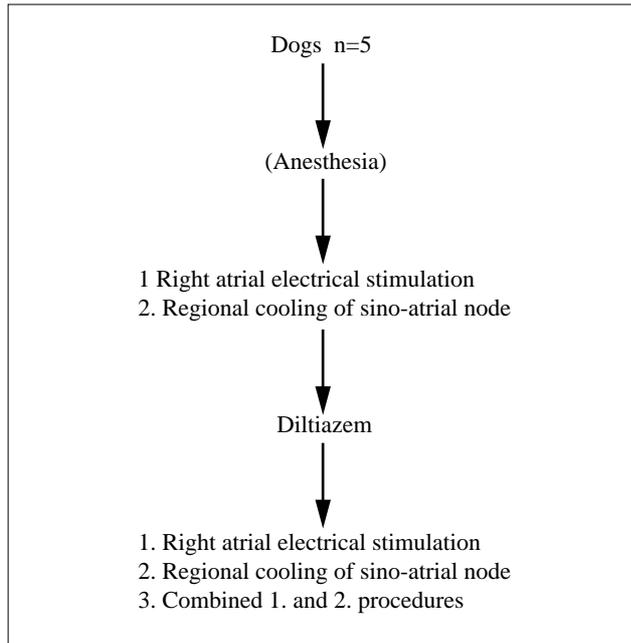


Fig. 1. Experimental protocol.

anastomosis site motion in the beating heart. Cardiac motion can be minimized during CABG on the beating heart with pharmacologically-induced bradycardia and mechanical stabilization. Pharmacologically-induced bradycardia is simple but can suppress heart function, which may cause postoperative low output syndrome. We developed two new methods to achieve bradycardia without heart suppression. One is an electrical atrial stimulation method. In this method, artificial electrical stimulation of the right atrium (RA) during the refractory period of the atrioventricular (A-V) node, is conducted to the ventricle and repolarizes the sino-atrial (S-A) cells, prolonging the interval between electrocardiographic (ECG) P waves. The other approach is to use regional cooling of the S-A node area. We report here our new methods and their clinical applications.

Material and Methods

Five mongrel dogs weighing 15 to 22 kg underwent atrial stimulation and S-A node cooling. General anesthesia was induced with ketamine hydrochloride (20 mg/kg intramuscularly). The animals were intubated endotracheally and connected to a volume ventilator with a tidal volume of 10 ml/kg and respiratory rate of 20 to 30 breaths/minute to maintain normal arterial blood gas and pH value with pH; 7.401 ± 0.08 , PCO_2 ; 38.7 ± 3.48 , and PO_2 ; 95.8 ± 3.4 . Anesthesia was maintained with additional sodium pentobarbital (1 to 2 mg/kg intravenously). A

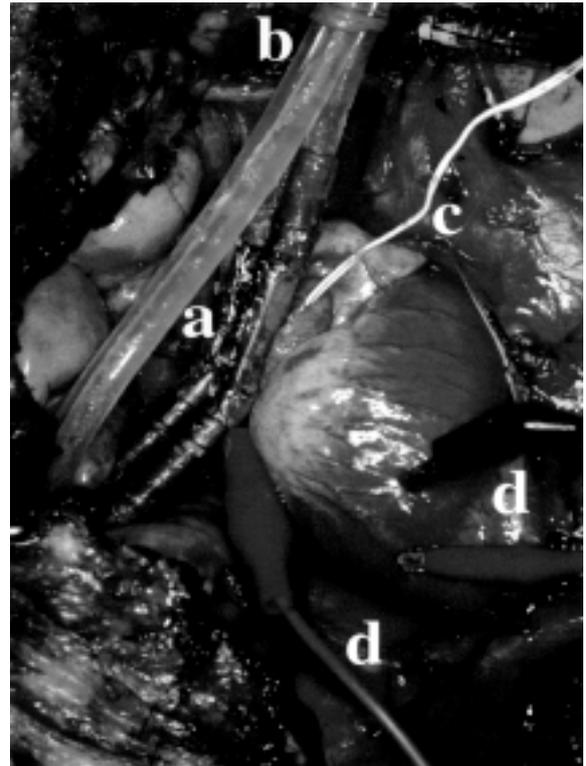


Fig. 2. Intraexperimental photo. The cooling device ($30 \times 50 \times 5$ mm³) (a) is made of copper and is connected to the heart exchanger (b) to keep the head of the device at approximately 0°C. The myocardial temperature is monitored (c), and the RA is cooled and stimulated electrically (d). RA: right atrium.

median sternotomy was made to expose the heart, and the left internal thoracic artery (LITA) was prepared for monitoring systemic blood pressure. Limb leads were placed for ECG monitoring (Life scope 9 BSM-8302 Nihon Kohden Co, Tokyo, Japan). All dogs in this study received human care in compliance with the "Guides for the Care and Use of Laboratory Animals" published by the National Institute of Health (NIH Publication No. 85-23, revised 1985).

As shown in Fig. 1, each animal underwent stimulation of the RA and cooling of the S-A node before and after administration of the calcium channel blocker; diltiazem (2 mg/kg). RA stimulation was performed using a SEC-3102 Cardiac Stimulator (Nihon Kohden Co, Tokyo, Japan) in the bipolar mode at a frequency of 50 Hz, an impulse duration of 0.4 msec, and an amplitude of 2 to 6 mv. The atrium was stimulated based on the timing of the QRS wave. Just before the end of the A-V node refractory period, atrial stimulation was delivered so as to obtain the longest interval between P waves. The sites for atrial stimulation were not limited (Fig. 2).

Table 1. Patients profiles and indication for CABG on the beating heart

No.	Age	Diagnosis	Indications for CABG on the beating heart
1	73	AP (OMI), AAA	1) Calcification of ascending aorta
2	87	AP (LMT)	1) Calcification of ascending aorta 2) Poor LVEF
3	69	AP (OMI)	1) Calcification of ascending aorta 2) Poor LVEF
4	71	AP (OMI), aortic arch aneurysm	1) To shorten cardiac arrest time
5	73	AP (OMI)	1) Calcification of ascending aorta
6	68	AP	1) Calcification of ascending aorta 2) Poor LVEF
7	73	AP (OMI), AAA	1) Poor LVEF
Average	73.4		
S.D.	6.32		

AAA: abdominal aortic aneurysm, AP: angina pectoris, CABG: coronary artery bypass grafting, LMT: left main trunk lesion, LVEF: left ventricular ejection fraction, OMI: old myocardial infarction.

We developed a device to cool the S-A node. It is a hollow copper box that measures $30 \times 50 \times 50 \text{ mm}^3$ and is connected to a heat exchanger in order to maintain the temperature of the cooling device at approximately 0°C (Fig. 2). The area cooled by the device comprised the area from the junction of the RA-superior vena cava to the midpoint of the right surface of the RA along the terminal sulcus. Myocardial temperature was monitored in this area (NT-14 Thermister Senko Medical Instrument MfgCo, Tokyo, Japan). Rectal temperature was also monitored. To elucidate the mechanisms of decreased heart rate by cooling the S-A node, electrical mapping of the RA was performed before and after bradycardia induced by cooling. For each method, changes in heart rate were observed before and after administration of diltiazem. Simultaneously, the change of the blood pressure was also recorded.

Both methods were performed together, and changes in heart rate were observed. From November 1999 to January 2000, the atrial stimulation method was used during the creation of distal anastomoses in the beating hearts of seven patients who demonstrated absolute or relative contraindications for ECC. All patients provided informed consent as part of their preoperative orientation. The age of the patients ranged from 68 to 87 years (73.4 ± 6.3 years). The patients included one woman and six men. Preoperative diagnoses were angina pectoris in all patients, abdominal aortic aneurysm (AAA) in two patients, and aortic arch aneurysm in one patient. The indications for CABG on the beating heart were calcification of the ascending aorta in five patients, poor LVEF in four patients, and to shorten the cardiac arrest time

during total arch graft replacement surgery in one patient (Table 1). The cooling method was not used because the safety of cooling the right atrium has not been established. After the induction of anesthesia, diltiazem was infused continuously at concentrations of 1.25-2.75 $\mu\text{g}/\text{kg}/\text{min}$, which resulted in bradycardia at 50 to 70 beats/min (average 64.0 ± 4.6 beats/min) by the beginning of the distal anastomoses. Thereafter, atrial stimulation was carried out.

Statistical analysis

The data in this study are expressed as the mean \pm standard deviation (SD). The difference among the groups was determined by the paired t-test, which was performed by StatView 5.0 (SAS institute, Cary, NC) statistical software packages.

Results

Before administration of diltiazem, the heart rate of animals was maintained at approximately 150 beats/min with a maximum of 200 beats/min. Under this condition, atrial stimulation had no effect. All atrial stimuli were conducted through the A-V node to the ventricle. When the heart rate was decreased by the administration of diltiazem, atrial stimulation was effective in prolonging the P-P interval (Fig. 3). The intervals of the atrial stimuli from the QRS wave varied from 50 to 280 msec. With atrial stimulation, the average heart rate (HR) slowed from 95.8 ± 17.0 beats/min to 64.2 ± 20.0 beats/min ($p < 0.0001$) (the average reduction rate was $66.1 \pm 10.3\%$ of the control HR) (Fig. 4). The blood pressure changed from

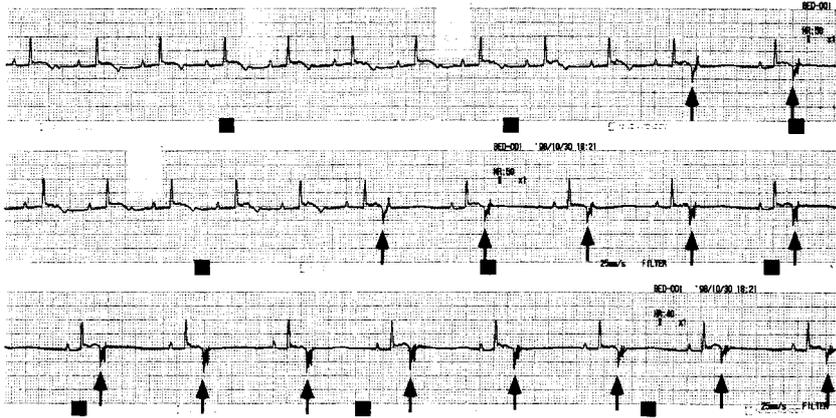


Fig. 3. Under administration of diltiazem (2 mg/kg), which reduced the heart rate to 65 beats/min, RA stimulation during the refractory period of the QRS wave was effective in slowing the heart rate to 41 beats/min. The arrows indicate the stimulation impulses of the cardiac stimulator.

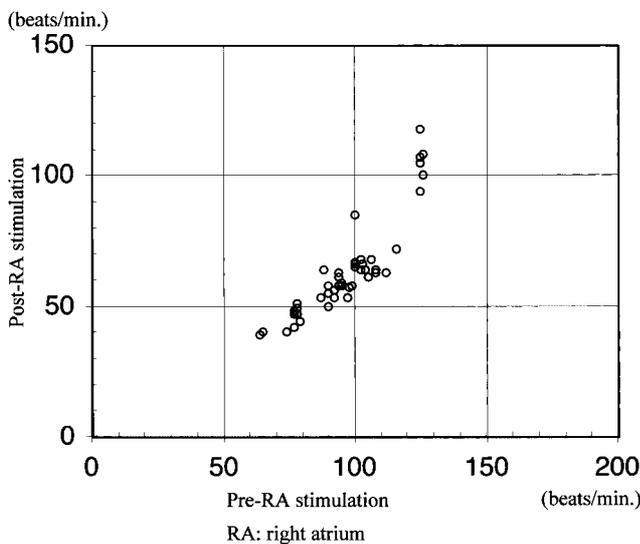


Fig. 4. Diagram shows the change in HR between the pre- and post-RA stimulation periods. RA stimulation was not effective when HR was greater than 130 beats/min. RA: right atrium.

114.7±8.2 mmHg to 112.8±7.5 mmHg without significant difference.

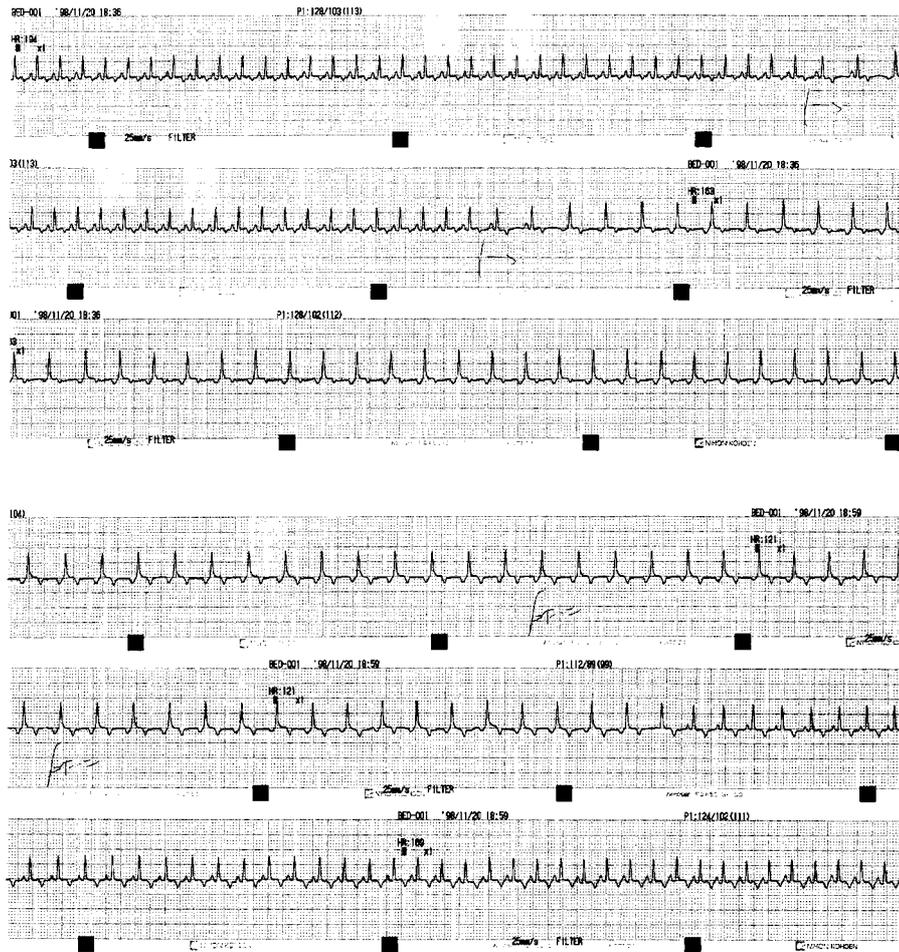
Cooling of the S-A node resulted in sudden slowing of the heart rate when the myocardial temperature dropped below 15°C and was accompanied by a disappearance or change in the ECG configuration of the P waves (Fig. 5). Myocardial temperature near the S-A node was maintained at approximately 10°C during attachment of the cooling device. The average HR slowed from 156.6±31.7 beats/min to 110.7±21.7 beats/min ($p<0.0001$), and the average reduction rate was 70.2±7.0% of the control HR (Fig. 6). The blood pressure changed from 142.7±4.1 mmHg to 142.6±4.0 mmHg without significant difference. With diltiazem administration, the average HR slowed from 102.0±11.9 beats/

min to 63.5±13.9 beats/min significantly ($p<0.0001$) (the average reduction was 62.0±10.4% of the control HR) (Fig. 7). The blood pressure changed from 104.0±11.9 mmHg to 103.3±11.5 mmHg without significant difference.

Cooling of the S-A node effectively decreased the HR and did not depend on the precooled heart rate. When the cooling device was detached from the S-A node area, the control P wave reappeared when the myocardial temperature reached 25°C. HR returned to the control rate, and the P wave configuration returned to that of the precooled P wave. Electrical mapping of the RA after cooling demonstrated that during bradycardia the atrial pacemaker focus transferred near to the A-V junction with configuration change or disappearance of the P waves (Fig. 8).

When both methods were applied together, the HR decreased from 102.2±12.3 beats/min to 44.6±9.1 beats/min ($p<0.0001$). The average reduction was 43.5±6.3% of the control HR (Figs. 9, 10). The blood pressure changed from 100.2±12.3 mmHg to 103.3±11.5 mmHg without significance.

In our clinical study, atrial stimulation was effective for slowing the HR in 4 out of the 7 patients (Table 2). The longest interval of atrial stimulation from the QRS wave in these patients ranged from 150 to 200 msec (average 180 msec). Based on these atrial stimuli timings, the HR decreased from 59, 64, 63, and 70 beats/min (average 64.0±4.5 beats/min) to 37, 39, 38, and 40 beats/min (average 38.5±1.3 beats/min) in respective patients during distal coronary anastomoses on the beating hearts. The bypass grafts used in the operations were LITA, right internal thoracic artery (RITA), right gastroepiploic artery (RGEA) and radial artery for branching or elongating. Segments of the target coronary vessels were exposed and isolated by encircling the segment with silicone elas-



a

b

Fig. 5. a: The P wave disappeared by cooling the area of the sinus node, and the HR was decreased from 187 beats/min to 125 beats/min. The cooling of the area of the sinus node effectively slowed HR, even with tachycardia over 140 beats/min. **b:** By detaching the cooling device, the P wave soon reappeared and the HR returned to baseline.

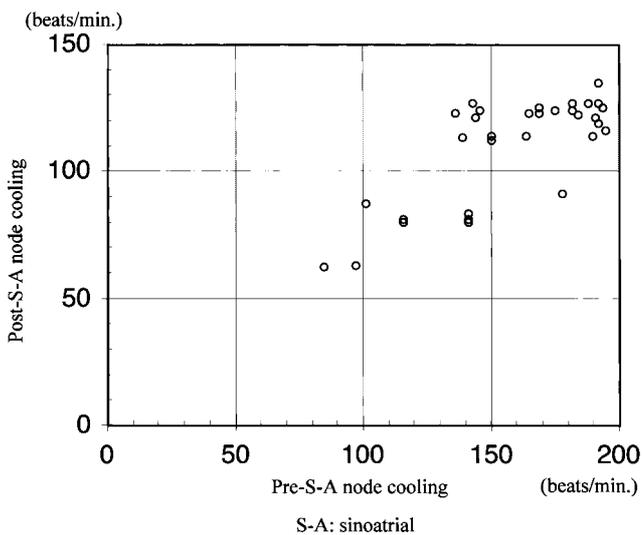


Fig. 6. Diagram shows the change in HR between the pre- and the post-S-A node cooling. When HR ranged from 140 beats/min to 190 beats/min, it decreased to approximately 120 beats/min, which may indicate the decreased automaticity. S-A node: sino-atrial node.

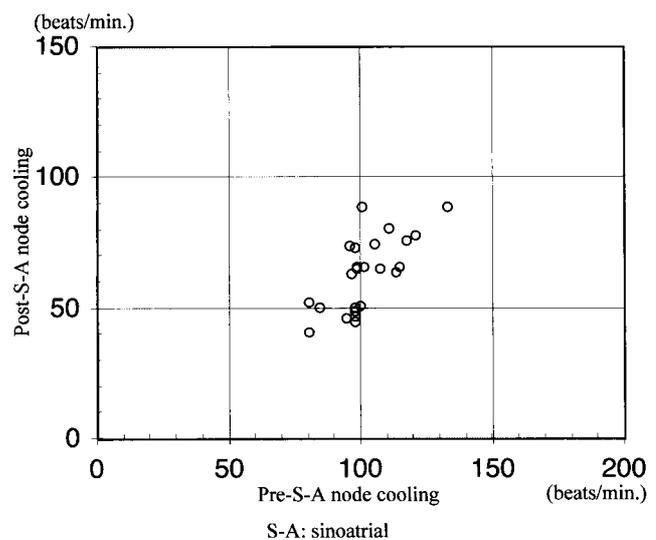


Fig. 7. Diagram shows the change in HR between the pre- and the post-S-A node cooling after administrating diltiazem.

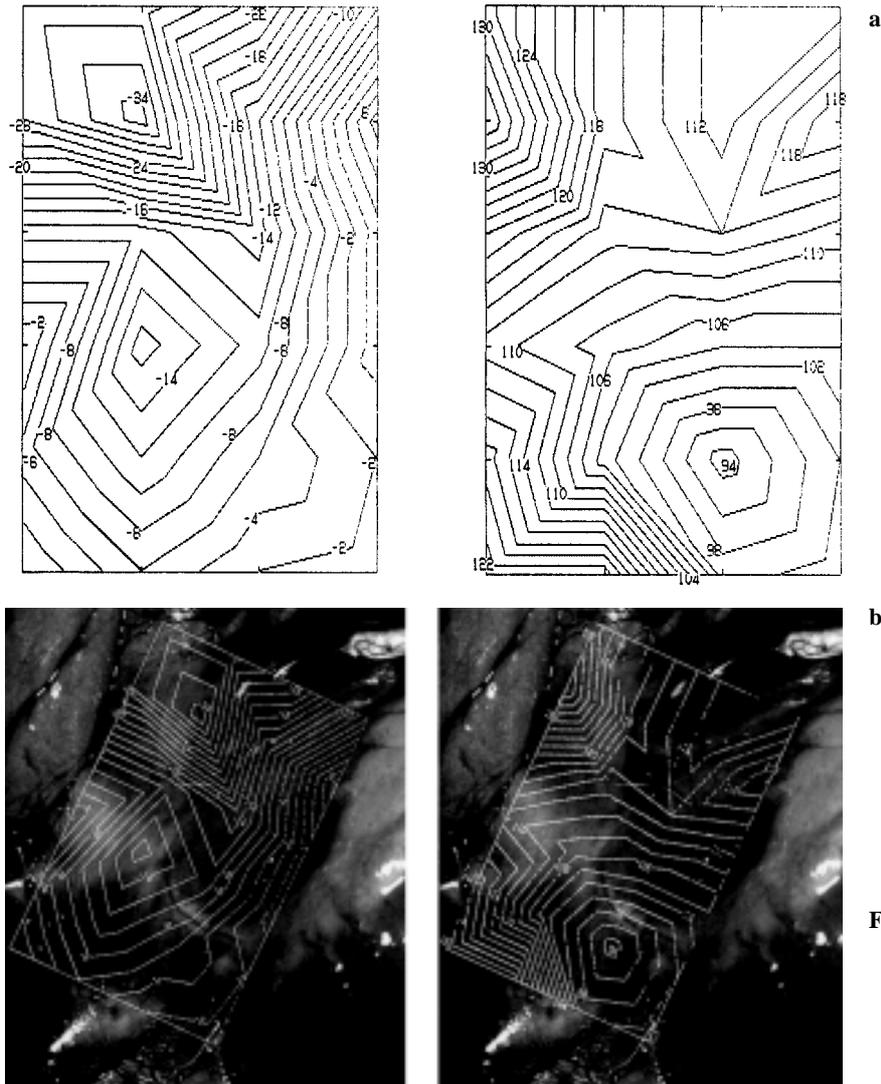


Fig. 8. a: Electrical mapping of the RA before (left) and after (right) cooling of the area of the sinus node. b: The projection of the mapping to the RA shows the shift of the atrial pacemaker from the sinus node to the area around the atrioventricular junction.

toomer surgical tapes (Quest Medical Inc., Dallas, TX) proximal and distal to the proposed arteriotomy site. In this series, a mechanical cardiac stabilizer was not used. Coronary anastomoses were performed using either 7-0 or 8-0 continuous polypropylene sutures. The number of bypassed coronary arteries ranged from 1 to 3, with an average of 2.1 ± 0.9 /patient.

CABG and AAA resection were performed concomitantly in a 73-year-old patient (No. 1 in Table 1). At first, CABG was performed by anastomosing the LITA to the LAD and the RGEA to the right coronary artery (RCA). During these coronary anastomoses, atrial stimulation was performed and the HR reduced from 59 beats/min to 37 beats/min. There was no need for catecholamine support for hypotension. After complete hemostasis neutralized by protamine, the AAA was resected and replaced with a Y graft.

Another patient, aged 69 years, had three vessel disease with a severely calcified ascending aorta. CABG was performed on the beating heart to anastomose the LITA to the left anterior descending artery (LAD) and a composite graft of the RITA with an radial artery sequentially to the posterior descending artery (PDA) and left circumflex artery (LCX). During these graft anastomoses, atrial stimulation for bradycardia was performed and was effective (Fig. 11). One patient with an arch aneurysm and associated stenosis of the RCA underwent CABG on the beating heart to anastomose the RGEA to the RCA prior to graft replacement of the aortic arch aneurysm. This was done to reduce the cardiac arrest time for this operation. Postoperative angiography demonstrated coronary bypass anastomosis patency without significant stenoses in these patients.

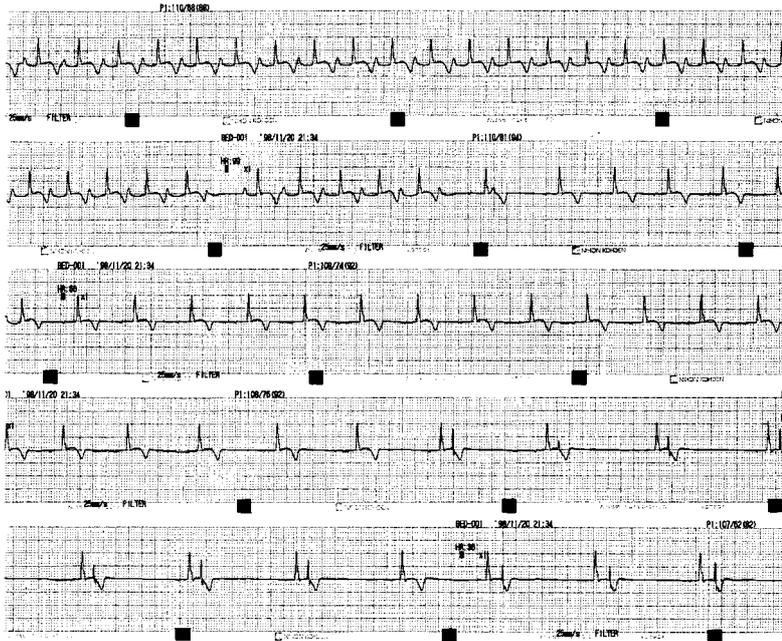


Fig. 9. The two methods were performed together. HR decreased from 99 beats/min to 68 beats/min by cooling the sinus node and then further from 66 beats/min to 37 beats/min by RA stimulation. RA: right atrium.

Discussion

CABG on the beating heart, including MIDCAB, has had a resurgence throughout the world because it is less invasive than conventional CABG. However, the early post-operative graft patency rate is reported to be lower than that of conventional CABG due to technical problems during surgery, instability of the coronary anastomosis field and difficulty in achieving a precise anastomosis with the moving of the epicardial surface. Successful anastomosis on the beating heart requires technical skills that are limited to a small number of cardiac surgeons. Drugs such as β -blockers can decrease heart motion. Drugs used in CABG on the beating heart are mainly heart rate suppressors. With other drugs, such as adenosine triphosphate, it is necessary to administer them whenever performing an anastomosis stitch.¹²⁾

Another approach is local coronary stabilization using mechanical immobilization devices.¹³⁾ Subramanian et al.¹⁴⁾ reported the utility of such devices for stabilizing the anastomotic field; patency of the LITA to the LAD was improved from 92% to 96.2% using the mechanical regional cardiac wall immobilization platform. Poirier et al.¹⁰⁾ reported the availability of a stabilizer of CABG on the beating heart. However, the stabilizer may not always be effective for anastomosis on the LCX region. In this situation, various devices have been made. Induced bradycardia may be one of the most useful approaches for successful CABG of the LCX on the beating heart.

There are a few reports concerning non-drug-induced bradycardia for CABG on the beating heart. Matherny and Shaar¹⁵⁾ described electrical stimulation of the vagus nerve to temporarily slow or arrest the heart, and this technique was applied clinically for satisfactory LITA-LAD anastomosis. With the patient fully supported by ECC, a maximum 30-second cessation of heart beat was achieved. Budkin et al.¹⁶⁾ clearly demonstrated the effectiveness of vagal stimulation for achieving asystole ex-

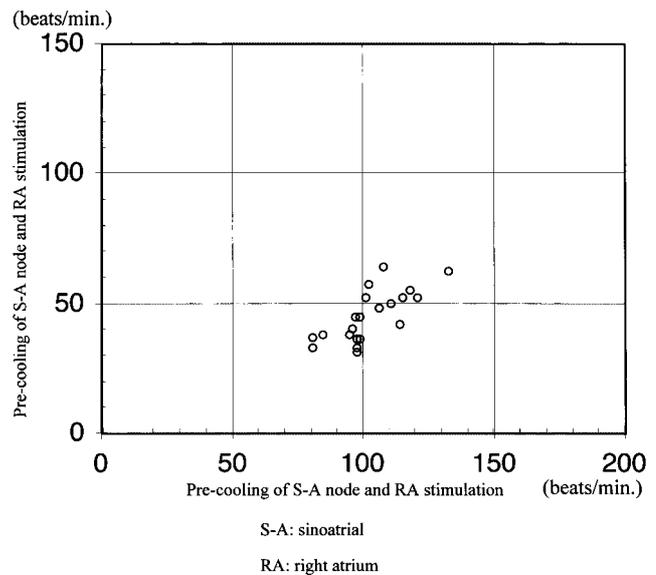


Fig. 10. Diagram shows the effects of the two methods combined. The average HR was decreased from 102.2 beats/min to 43.5 beats/min.

Table 2. Clinical cases and results of RA stimulation

No.	Operative procedure	No. of bypassed coronary arteries	HR before atrial stimulation (beats/min)	HR during atrial stimulation (beats/min)	Result
1	LITA-LAD, RGEA-RCA (3), LITA-D1	2	59	37	effective
2	RGEA-LAD, LITA-D1	2	64	39	effective
3	LITA-LCX (12) RITA-(RA)*-4PD, LCX (13)	3	63	38	effective
4	Total arch graft replacement, RGEA-RCA (3)	1			not effective
5	LITA- LAD	1			not effective
6	LTA- LAD, RITA-(RA)**-LCX (13), RGEA-LCX (13)	3	70	40	effective
7	Aorta-RA-D2, LIRA-LAD, RGEA-4PD	3			not effective
Average		2.1	64.0	38.5	
S.D.		0.9	4.5	1.3	

AAA: abdominal aortic aneurysm, D1: first diagonal artery, D2: second diagonal artery, LAD: left anterior descending artery, LCX: left circumflex artery, LITA: left internal thoracic artery, 4PD: posterior descending artery, (RA)**: elongation by radial artery, (RA)*: branching by radial artery, RA: radial artery, RCA: right coronary artery, RGEA: right coronary artery, RITA: right internal thoracic artery.

perimentally. However, exposure of the vagus nerve is complicated, although the surgical invasiveness should be minimal.

Our new method of atrial stimulation for bradycardia is based on the principle of nonconductive supraventricular extrasystole, which repolarizes the S-A node and extends the time to the next P wave. By artificially stimulating the atrium electrically, the P-P interval is prolonged. This prolongs the Q wave interval and reduces the HR. The longer the period between the original P wave and the artificial electrical stimulation, the longer the Q wave interval. Therefore, prolongation of the Q wave interval depends on the duration of the refractory period of the

A-V node. The length of the A-V node refractory period is the key to producing an appropriate bradycardia; the longer the refractory period of the AV node, the longer the P-P interval that can be obtained. In patients undergoing CABG on the beating heart and AAA resection concomitantly, the timing of atrial stimulation based on the QRS wave on the ECG was 200 mseconds which resulted in a HR of 37 beats/min. To potentiate electrical stimulation of the atrium for bradycardia, the refractory period should be prolonged, and further research into prolongation of the A-V node refractory period is needed.

The duration of the refractory period is determined by factors such as sympathetic tone, HR and the use of



Fig. 11. A 73-year-old man underwent CABG on the beating heart and concomitant AAA resection. During the CABG, atrial stimulation was applied, reducing the heart rate from 58 beats/min to a minimum 36.5 beats/min, which facilitated the distal coronary anastomoses. Arrows indicate electrical RA stimulation by the cardiac stimulator.

CABG: coronary artery bypass grafting, AAA: abdominal aortic aneurysm, RA: right atrium.

inotropes. Inotropic agents usually accelerate A-V conduction, and calcium antagonists and β -blockers usually inhibit A-V conduction. The feasibility of using digitalis, which has an inotropic action and prolongs A-V node conduction, should be investigated. In 3 out of our 7 study patients, atrial stimulation was not completely effective even though stimulation conditions were the same in all patients. For establishing atrial stimulation, it is necessary that the atrium is non-refractory during the atrial stimulation. In cases when this method was effective, the atrium contracted twice during a single contraction of the ventricle, which indicates that the atrium was in a conditioned non-refractory period of the S-A node and a refractory period of the A-V node. Our success rate was 5 of 7 (57%). Two of 7 patients had no contraction of the atrium after atrial stimulation, which indicates that the refractory period of the atrium was longer than that of the A-V node.

Establishing bradycardia before atrial stimulation is necessary to achieve the required slowed heart rate. For satisfactory bradycardia for CABG on the beating heart, atrial stimulation alone is of limited utility. We attempted to suppress the activity of the S-A node without using heart suppressing drugs by cooling the S-A nodes in dogs. To suppress activity of the S-A node, we cooled regions of the S-A node using our device. There are a few reports of bradycardia created by cooling the S-A node or conduction system,¹⁷⁻¹⁹⁾ but there is no description of the temperature that affects the pacemaker cell. In our study, myocardial temperature around the S-A node was monitored with a needle electrode. When the temperature decreased to below 15°C, the heart rate slowed suddenly, and the ECG P wave disappeared or changed configuration. Cooling of the S-A node decreased the heart rate presumably by shifting the pacemaker site to a site of lower automaticity. According to electrical mapping of the RA before and after cooling, the pacemaker had shifted to near the A-V junction. The change in P wave configuration on the ECG of cooling-induced bradycardia also suggested that the pacemaker shifted to a lower automaticity site. Although the theory behind inhibited activity of the S-A node via cooling has not been detailed, we did identify the temperature at which cessation of S-A node activity takes place. Compared with drugs, physical cooling of the S-A node is advantageous because there is not the complication of heart suppression, and the heart can be returned to its normal rate quickly by detaching the cooling device from the area of the S-A node. Although this cooling method appears to

be without side effects, there is the potential for lowering the body temperature and for cold injury to the atrial myocardium around the S-A node. In this study, the average rectal temperature of the mongrel dogs was decreased from 37°C early in the procedure to 35°C by the end of the experiment.

Our approaches reduced numbers and amounts of drugs used; only diltiazem at a low concentration was used. Finally, the precision of the distal anastomoses revealed by angiography conclusively established the utility of our new methods. However, bradycardia may reduce cardiac output, and there is a risk of decreased cerebral circulation. Therefore, it is necessary to evaluate further the relation between heart rate and cardiac output.

In summary, atrial electrical stimulation during the refractory period of the A-V node prolongs the R-R interval, which may be effective only when calcium channel blockers are administered. Cooling of the S-A node area slows the heart rate when the myocardial temperature drops below 15°C, and the P waves disappears or changes in configuration. The heart pacemaker shifts to a lower automaticity site when cooled to below 15°C, and it is reversible by rewarming the myocardium to 25°C. By combining the two methods, the heart rate is decreased to a maximum of 30 beats/minute. In clinical applications, variations in the effects of atrial stimulation were observed. Further investigation is necessary to determine the source of this variation.

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