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Intermittent Antegrade and Continuous Retrograde Coronary Sinus Cold Blood Cardioplegia to Prevent and Reverse Ischemic and Reperfusion Damage in Patients Undergoing Bentall's Procedure: A Clinical Report on 130 Patients

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ABSTRACT

Objective: This study was designed to ascertain the clinical outcome of intermittent anterograde and continuous retrograde cold blood cardioplegia in patients undergoing Bentall's procedure under hypothermia (28°C) with respect to survival, low-output syndrome, clinically significant supraventricular and ventricular arrhythmias, spontaneous return of rhythm and coronary sinus injuries.

Patients and methods: Between January 1998 and June 2018, 130 patients (70 males) aged between 22 and 66 years (mean ± SD 48.21 ± 13.6 years) undergoing Bentall's procedure had cardioprotection using an integrated management protocol as described above. The mean cross-clamp time was 114 ± 28.4 min (range, 91-184 min). Continuous cold blood cardioplegia was delivered at an average flow rate of 100 ml/min. The total administered volume of retrograde cardioplegia ranged from 3800 to 6000 ml and the total amount of cardioplegic solution delivered ranged from 5500 ml to 6500 ml.

Results: Six (4.6%) patients died of cardiac-related cause, 47% (n=61) had transient hemodynamic instability, 53% (n=69) had low cardiac output, 2.3% (n=3) required intra-aortic balloon counterpulsation, 11.5% (n=15) had supraventricular arrhythmias and 88.4% (n=120) had spontaneous return of sinus rhythm.

Conclusion: This integrated approach coordinates the myocardial protective strategies with an uninterrupted surgical procedure, provides unimpaired vision, avoid unnecessary ischemia, cardioplegic overdose, permits aortic unclamping and discontinuation of bypass shortly after completion of surgery.

Keywords: Bentall's procedure, Retrograde cold blood cardioplegia, Antegrade cold blood cardioplegia, Myocardial preservation

Abbreviations: ACE: Angiotensin-Converting Enzyme Inhibitor; CABG: Coronary Artery Bypass Grafting; CCF: Congestive Cardiac Failure; CK-MB: Creatine-Kinase-MB; CPB: Cardiopulmonary Bypass; IABC: Intra-Aortic Balloon Counterpulsation; LCOS: Low Cardiac Output Syndrome; LVEF: Left Ventricular Ejection Fraction

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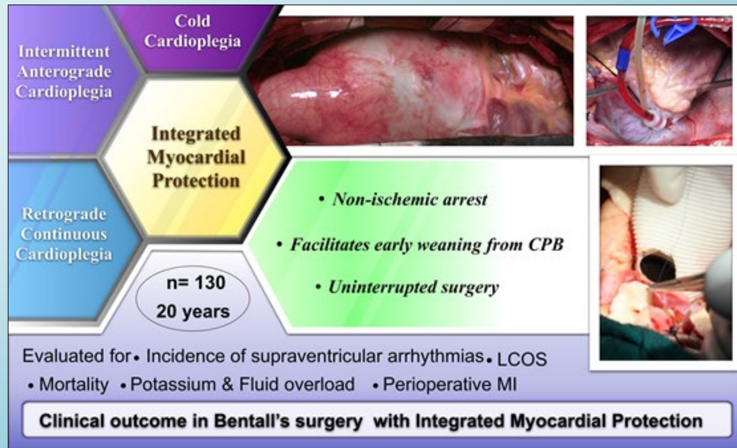
GRAPHICAL ABSTRACT



CENTRAL MESSAGE

Intermittent anterograde and continuous retrograde cold blood cardioplegia in Bentall's procedure compensates for their individual shortcomings in achieving optimal cardioprotection.

PERSPECTIVE STATEMENT

A combination of intermittent anterograde and continuous retrograde cold blood cardioplegia in patients undergoing Bentall's procedure is safe and effective, virtually eliminating the period of ischemia limiting reperfusion injury.

INTRODUCTION

Although there have been major advances in the methods of myocardial protection since the inception of open cardiac surgery, cardiac operations have nevertheless remained far from unhurried because of the anaerobic damage that can occur with all current methods of myocardial protection [1,2]. The current myocardial protection strategies provide excellent preservation with minimal attendant morbidity and mortality. The outcomes, however, are sub-optimal for urgent operations in high-risk subgroups with ventricular dysfunction and provide the impetus for investigating a finer technique for myocardial protection [1,2].

The efficacy of myocardial protection is gauged by the safe periods of aortic occlusion that it affords the surgeon [2]. Initially, cardiac operations with normothermic ischemic arrest by intermittent aortic occlusion were critically limited to a short duration, if prolonged beyond 45 min, not infrequently resulted in stone heart [3]. Griepp et al. [4] promoted topical hypothermia for profound cardiac cooling and were able to increase the time of safe aortic occlusion to 60 min. The introduction of cold potassium cardioplegia further prolonged the duration of safe ischemia time to 120 min [5]. Weisel et al. [6] have shown that despite the use of hypothermia and potassium cardioplegia, myocardial injury and worsening left ventricular function are directly related to aortic cross-clamp time. In patients with poor ventricular function, myocardial preservation strategies would be challenged at about 3 h of cardiac arrest [7,8].

Theoretically aerobic (continuous) cold cardioplegia could provide ideal myocardial protection even in prolonged high-risk procedures [9]. The arrested, normothermic heart requires 90% less oxygen than does the normal beating heart and the requirement further drops with hypothermia (1.1 vs. 0.135 mL O_2/min/100 g myocardium, at 37°C and 11°C, respectively) [9,10]. Therefore, we hypothesized that a combination of intermittent antegrade cold cardioplegia and continuous retrograde cold blood cardioplegia, drastically limiting the anoxic period, reperfusion injury and abolishing the detrimental effects of normothermia will be the best choice for high-risk patients requiring long aortic cross-clamp time. The purpose of this non-randomized study was to investigate the impact of integrated myocardial protection on survival, requirement for pharmacological and/or mechanical circulatory support, perioperative myocardial infarction, arrhythmias, volume overload, hyperkalemia and coronary sinus injury in patients undergoing Bentall's procedure in our institution over a period of 18 years.

PATIENTS AND METHODS

To test our postulates, we embarked on a program of "integrated myocardial protection" in patients undergoing Bentall's procedure in our institution. This study conforms to the principles outlined in the declaration of Helsinki. Between January 1998 and June 2018, 130 consecutive patients (70 males), aged 22-66 years (mean=48.21+13.6 years) underwent modified Bentall operation using the surgical techniques described after obtaining informed consent and institutional ethics committee approval. All operations were performed by a single surgeon (corresponding author), which ensured uniformity in the surgical protocol.

Nintey-two (70.7%) patients had annuloaortic ectasia and 38 (29.2%) patients had type A aortic dissection. One hundred and twenty-four (95.4%) patients had moderate-to-severe aortic regurgitation, 4 (4.2%) had grade II mitral regurgitation and 93 (71.5%) had left ventricular ejection fraction <0.40. Sixty-two (47.6%) patients underwent emergency operation, 66 (50.8%) patients had renal dysfunction, and 8 (6.1%) underwent concomitant coronary artery bypass grafting **(Table 1)**.

Table 1. Demographic and patient characteristics of the study group (n=130).

	Number (%)
Annuloaortic ectasia	92 (70.7%)
Stanford type A and B	38 (29.2%)
Moderate to severe aortic and mitral regurgitation	124 (95.4%)
Grade II mitral regurgitation	6 (4.6%)
Ejection fraction (<0.40)	93 (71.5%)
Emergency operation	62 (47.6%)
Renal dysfunction	66 (50.8%)
Concomitant coronary artery bypass grafting	8 (61.5%)

Surgical techniques

Standard anaesthetic and operative techniques were used throughout the study period. The operations were performed under moderately hypothermic cardiopulmonary bypass (CPB) through arterial cannulation (axillary artery n=28; femoral artery n=102) and bicaval venous cannulation through the femoral vein and superior vena cava. Antegrade and retrograde cold blood hyperkalemic cardioplegia were used in all patients for myocardial preservation.

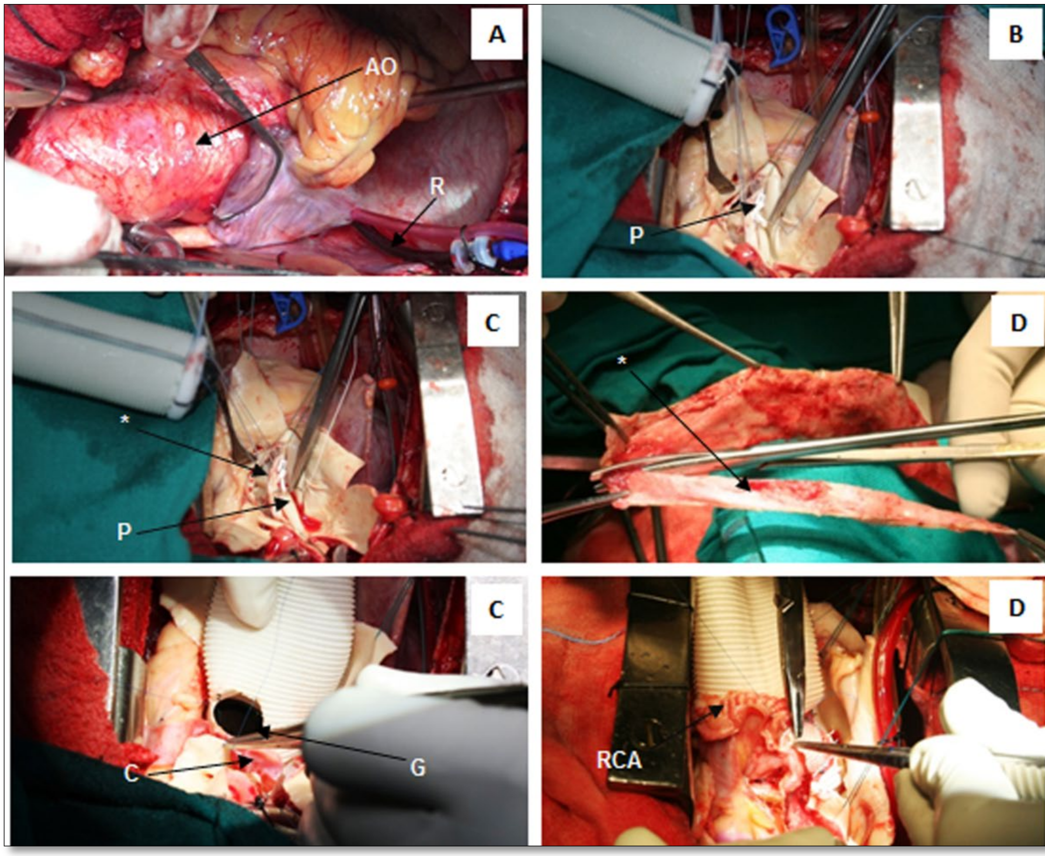
A retrograde coronary sinus cannula with self-inflatable balloon (RCO 14, Edwards Lifesciences, Irvine, CA, USA) was used in all patients. Transatrial blind cannulation of the coronary sinus was performed using a flexible introducer through a small stab wound within a purse string suture at the inferior vena cava-right atrial junction about 1 cm parallel to the atrioventricular groove on a partially filled right atrium. The introducer was shaped into a hockey-stick formation and then passed into the coronary sinus. In cases of difficult cannulation, the coronary sinus was cannulated through a short right atriotomy under direct vision. The proper placement was confirmed by observing distension of the posterior interventricular vein, maintenance of coronary sinus pressure, palpation of the coronary sinus cannula posteriorly at the base of the heart and transesophageal echocardiography. From this standpoint, it is noteworthy that, in adults, a single catheter size fits all coronary sinus orifices because of the compliance of the balloon.

Ultrafiltration was used in all patients during and after CPB to reduce the total body water, potassium overload and to remove the inflammatory mediators from the circulation, maintaining hematocrit >25% on CPB.

All patients were subjected to the same “integrated myocardial preservation management” strategy as was originally proposed by Buckberg [1]. Intermittent direct ostial, high potassium, cold blood cardioplegia (St Thomas II solution 4:1); containing 27 meq/L potassium at a dose of 150 ml/min/m2 along with topical cooling was used in all patients. After achieving cardiac arrest, the cardioplegia line was switched to the fluid-filled retroplegia cannula, and low potassium cold blood cardioplegia (containing 13 meq/L) was commenced via the autoinflating coronary sinus cannula at a flow rate of 100-150 ml/min. Coronary sinus pressure was maintained less than 40 mm Hg throughout the procedure. Antegrade direct ostial coronary cardioplegic infusions (500 ml through both the coronary ostia) were repeated intermittently every 20 min. Cardioplegic infusions by both routes were never given simultaneously.

A Dacron composite graft with a mechanical heart valve ((St. Jude Medical Inc.; Minn); (Conduit 25 mm, 55 patients; 27 mm, 52; 29 mm, 33)) was used in all patients. While creating the coronary buttons, the pericoronary diseased aortic tissue was excised leaving behind a cuff of 10-12 mm.

All patients in the study underwent “modified button technique” for reconstruction of the coronary arteries and proximal conduit suturing to obtain perfect hemostasis as developed by the corresponding author [11]. The composite graft was sutured to the annulus using averted, interrupted 2-0 mattress sutures over polytetrafluoro-ethlene pledgets. Each interrupted aortic supra-annular sutures were placed in such a fashion that successive sutures were made to pass through the previous pledget; thus ensuring perfect aortic annular hemostasis **(Figures 1A-1C)**. Using graft cautery, two side holes were created on the composite graft measuring around 10mm in diameter in the proposed area of coronary ostial implantation. The left and right coronary buttons were anastomosed in an end-to-side fashion with continuous 5-0 polypropylene suture to openings on the composite graft. While suturing, a long strip of glutaraldehde treated pericardium, about 1 cm wide was interposed circumferentially around each graft-coronary button anastomosis **(Figures 1D-1F**).



Figures 1. A) Surgical photograph of the surgical techniques used for coronary button implantation and proximal aortic conduit suturing in a patient undergoing modified Bentall procedure for annuloaortic ectasia using intermittent antegrade and continuous retrograde coronary sinus cold blood cardioplegia. **B&C)** Note the placement of interrupted pledgeted (P) mattress sutures for proximal aortic conduit suture line (*). Each interrupted pledgeted mattress suture is passed through the previous pledget (P), ensuring perfect hemostasis. **D&E)** Step-by-step demonstration of graft-coronary artery anastomosis. Note the circumferential placement of the pericardial patch (*) between the graft (G) and the native coronary ostium (C). **F)** Note the completed conduit-right coronary artery (RCA) anastomosis.
AO: Aortic Root; P: Pledgeted; G: Graft; C: Coronary Ostium; R: Retrograde Cardioplegia Cannula; RCA: Right Coronary Arter

We used topical thrombin (Tisseel, Baxter AG, Vienna) as an additional topical hemostatic agent on all patients. The anastomoses were checked for hemostasis by pressuring the graft with cardioplegia. The distal anastomosis was performed using a running 4-0 polypropylene suture in an end-to-end fashion, on a circumferential pericardial strip.

The left ventricle and main pulmonary artery were vented throughout the cross-clamp period and while performing the distal graft-aortic anastomosis, myocardial perfusion was restored with warm blood administered retrogradely through the coronary sinus catheter. Retrograde perfusion was assured by noting the engorged oxygenated cardiac veins as well as the return of dark blood through the vent in the aortic root.

Following removal of aortic cross-clamp, majority of the patients (96%) returned to normal sinus rhythm. Only 10 (7.6%) patients required antegrade administration of injection adenosine and 200-250 ml warm hotshot blood cardioplegia for spontaneous defibrillation. Direct current cardioversion was not used on any patient. We used atrioventricular sequential pacing for 24-48 h in patients with low heart rate.

Postoperative studies and follow-up

These included three-monthly clinical examinations, electrocardiograms, chest radiographs, cinefluoroscopy, echocardiography and computerized tomographic angiography as and when required. The functional class at follow-up was noted [12]. All patients received warfarin and aspirin (100 mg/day) for anticoagulation to maintain INR between 2.5 to 3.5.

All patients with normal renal function were administered oral angiotensin-converting enzyme inhibitor (ACE-I) (0.5-1.0 mg/kg; every 8 h) after extubation before weaning from inotropic agents. Digoxin, diuretics and ACE inhibitors were weaned at varying time intervals. Amiodarone was used for intractable atrial fibrillation.

STATISTICAL ANALYSIS

Statistical analysis was performed using Intercooled STATA 14.0 Software (College Station, Texas, USA). Interval related data were expressed as mean ± standard deviation (SD) or median (minimum-maximum) and categorical variables were expressed as percentages. The Kaplan-Meier curve was drawn to show the probability of survival over a period of follow-up time. The results were expressed as probability of survival (95% confidence interval) at various time intervals. Statistical significance was set at $p<0.05$).

RESULTS

Coronary sinus catheter placement and coronary sinus injury

The coronary sinus was easily cannulated by closed technique in 84 (64.6%) patients. Forty-six (35.4%) patients required insertion of the retroplegia cannula under direct vision. No anomalies of coronary sinus or coronary sinus injuries were confronted.

Operative mortality

There were six (4.6%) early deaths due to LCOS with multiorgan failure and superimposed sepsis between 10th and 18th postoperative days. These patients had acute type A aortic dissection and were in congestive cardiac failure (CCF) preoperatively.

Postoperative pharmacological and mechanical circulatory support

Patients who needed moderate amounts of inotropic drugs (usually dopamine and/or dobutamine hydrochloride, 5 µg/kg/min) for less than 24 h postoperatively were considered as having transient postbypass hemodynamic instability (n=61). In contrast, patients who required inotropic agents, vasopressors and/or intra-aortic balloon counterpulsation (IABC) for more than 24 h postoperatively were categorized as having a true LCOS (n=69).

Patients considered to have LCOS (n=69) required dopamine (4-10 $\mu g.kg^{-1}.min^{-}1$), epinephrine (0.01-0.1 $\mu g.kg^{-1}.min^{-1}$) and milrinone (50 µg/kg IV bolus followed by 0.375-0.75 $\mu g.kg^{-1}.min^{-1}$) either isolated or in combination. Five patients required intraoartic balloon counterpulsation as an additional support. Overall, 30% (n=39) of the 130 patients required pharmacological support in varying combinations postoperatively. Three patients who required IABC survived. The incidence of LCOS remained fairly constant over the course of the study.

Postoperative hyperkalemia and volume overload

Mean cross-clamp time was 114.6 ± 28.4 min (range, 91-184 min) and mean CPB time was 152.6 ± 28.6 min (range, 124-210 min). The mean flow of cardioplegia in the coronary sinus was 100 ml/min (range, 80 to 180 ml/min). Cardioplegic flow rates varied and the total administered volume of retrograde cardioplegia ranged from 3800 ml to 4500 ml. The total amount of cardioplegic solution delivered ranged from 5500 ml to 6500 ml. The total amount of potassium delivered ranged from 86 to 190 meq with a mean of 98 meq. Hyperkalemia was not a clinically significant problem in any patient **(Appendix)**.

Perioperative myocardial infarction and arrhythmias

No patients sustained a perioperative myocardial infarction. Fifteen (11.5%) patients experienced postoperative supraventricular arrhythmias. Ventricular arrhythmias developed in 10 (7.6%) patients (premature ventricular contraction (n=8) and ventricular tachycardia, n=2). Overall, 14 (10.7%) patients had bundle branch block postoperatively and 10 (7.7%) had junctional rhythm. No patient had complete heart block **(Appendix)**.

Postoperative ventricular function

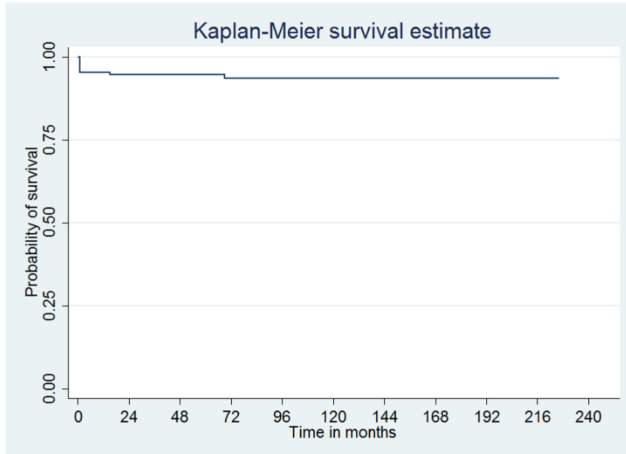
Preoperatively, the mean LVEF was 48 ± 8.8% (range, 15% to 60%). Forty-two (32.3%) patients had LVEF between 15% to 25%. The mean LVEF was 55 ± 7.0% (range, 15% to 70%) in the postoperative period. Thirty-nine (30%) patients had LVEF between 15% to 25%.

Morbidity

Hospital morbidity included re-exploration for excessive bleeding from non-anastomotic sites within 12 h in 8 patients with acute type A aortic dissection. The average 12 h postoperative drainage was 245 ± 70 ml. Twelve (9.2%) patients required tracheostomy and long-term ventilator support. Hospital stay ranged from 5 to 52 days (median, 8.8 days; mean, 18 ± 8 days). Three patients required hospital readmission on 18^{th}, 21^{st} and 22^{nd} days postoperatively because of deranged prothrombin time requiring pericardiocentesis.

Late results

There were 2 (1.6%) late deaths 15 and 69 months after surgery due to intractable ventricular arrhythmias and anticoagulant-related intracranial bleed respectively. Follow-up was 100% complete (1-226 months) and yielded 1218 patient-years of data. At a mean follow-up of 119.8 (SD ± 67.13) months, the actuarial survival was 93.6 ± 0.02% (95% CI: 87.5-96.7; **Figure 2**). All survivors were in New York Heart Association I or II at their last follow-up. Two patients required thoraco-abdominal aortic graft replacement with re-implantation of celiac, superior mesenteric and right renal arteries 3 years following Bentall's procedure. No survivors had structural deteriorations, pseudoaneurysm formations or thromboembolic complications.



Follow up (months)	0	24	48	72	96	120	144	168	192	216	240
Number at risk	130	118	107	91	78	67	56	41	23	6	2

Figure 2. Actuarial event free (Kaplan-Meier) survival of patients undergoing Bentalls procedure using a Dacron composite graft with a St. Jude Medical Mechanical heart valve in the study group.

DISCUSSION

In this study, we selected the patients with annuloaortic ectasia with or without acute aortic dissection undergoing Bentall's procedure, since they typify the high-risk group who present with acutely decompensated cardiac function, requirement of urgent surgery and longer aortic cross-clamp time. This subset of patients poses particular challenges to the existing hypothermic intermittent cardioplegic arrest techniques [5,6]. Aerobic/continuous blood cardioplegia was contemplated as a superior method of achieving myocardial protection in high-risk patients who require longer cross clamp time [4-6,10-20]. Menasche has defined the technique of aerobic arrest as a simultaneous combination of continuous or almost continuous delivery of cardioplegia with high haematocrit and high flow rate through retrograde or a combined route of delivery [19]. Aerobic cardioplegia could be warm, tepid or cold [19].

Warm heart continuous blood cardioplegia/tepid blood cardioplegia/continuous cold blood cardioplegia

Warm/normothermic aerobic perfusion of the arrested heart produces a large increase in the ratio of aerobic energy production to cellular energy utilization provided the aortic root flow exceeds 80 ml/min with a haemoglobin concentration >80 g/L [21]. This process seemed particularly suited for the setting of metabolically compromised myocardium [4-6,10-20]. But the theoretical advantages of warm cardioplegia are minimized by inhomogeneous cardioplegic distribution, increased endothelial dysfunction, increased incidence of adverse neurologic events and greater hemolysis due to increased perfusion flow requirement [9,14-18].

The Emory University trial that enrolled 1001 patients for randomized control study between warm and cold aerobic cardioplegia had to be stopped prematurely as the result of increased incidence of adverse neurologic events (new stroke or encephalopathy) in the warm cardioplegia group, 4.5% vs. 1.4% in the cold cardioplegia group [9]. The etiology of neurological injury during CPB is multifactorial. In our previous investigation on 172 patients undergoing normothermic CPB, using jugular blood desaturation as a marker for cerebral oxygen demand, we demonstrated that patients undergoing normothermic CPB are at greater risk of cerebral desaturation [22]. Also, it has been demonstrated air embolism if occurred can cause more damage in the warm brain through the formation of energy dependent pinocytic vesicles and transendothelial channels involving mainly the neocortex, perivascular white matter and basal ganglia [23,24]. These technical problems and concerns have slowed the adoption of warm cardioplegia in many centers.

In 1999 Elwatidy and associates introduced tepid "lukewarm" (28-32°C) cardioplegia in order to overcome the potential hazards associated with normothermic "warm" cardioplegia [25]. However, several investigators have shown insignificant difference in hospital mortality and morbidity between warm and tepid cardioplegia [25,26].

Continuous cold blood cardioplegia has never been widely used because of the inconvenience of a continuous perfusion without any evident advantages over intermittent cold techniques. In 1981, Bonfim et al. [27] compared continuous cold antegrade and single dose blood cardioplegia during aortic surgery. They demonstrated a decrease in lactate release; creatine-kinase (CK)-MB, myoglobin, myocardial adenosine triphosphate and normal lactate extraction 30 min after declamping with continuous cold cardioplegia [27]. Khuri et al. [28] reported no change in myocardial pH during aortic clamping with continuous cold blood cardioplegia, but a decline with multidose perfusion. Recently, Louagie and associates reported better left and right ventricular stroke work index with continuous retrograde cold blood cardioplegia after CABG [28]. Moreover, hypothermia enhances myocardial protection, reduces adverse neurologic events, and provides a wider safety margin in the event of accidental interruption of CPB [4,5,10,20,28].

Combination of anterograde and retrograde cardioplegia

Retrograde coronary sinus cardioplegia has been proposed as a superior method to deliver cardioplegia to the myocardium distal to an occluded coronary artery [13,29,30]. However, venovenous shunting through arteriosinusoidal and thebesian communications may limit the nutritive retrograde cardioplegic flow to the right ventricular free wall and posterior ventricular septum. Warm retrograde cardioplegia decreased anaerobic lactate production when flow rates were increased from 50 to 200 mL/min. However, further increases to 300 or 500 mL/min increased the shunt flow without reducing anaerobic lactate production [14,16,21].

The concept of "integrated myocardial protection" with a combined antegrade and retrograde cold blood cardioplegic infusions was proposed to utilize the benefits of both techniques [1,30,31]. Intermittent infusions of antegrade and then continuous retrograde cold blood cardioplegia provided more homogenous myocardial cooling, complete recovery of left and right ventricular function and excellent clinical outcomes in patients. However, this cardioplegic technique cannot be employed for warm heart operations [26]. In this study, following the suggestion of Bonfim et al. [27], we have used intermittent antegrade cold blood cardioplegia every 20 min and continuous retrograde cold (15-20°C) blood cardioplegia.

The common reasons for retrograde cardioplegic delivery failure are smaller size coronary sinus opening, common orifice of the coronary sinus and middle cardiac vein, catheter displacement/misplacement, direction of the catheter tip into one of the venous tributaries, extreme advancement of the catheter tip beyond the base of the left atrial appendage and occasionally an overdeveloped thebesian valve obstructing the access to the coronary sinus ostium [29,32]. Pressure monitoring of the side port of the cannula remains the most reliable method of surveillance for catheter position. An abrupt change in pressure from 30 and 40 mm Hg to between 1 and 4 mm Hg or negative pressures indicates catheter displacement. Additionally, desaturated blood emanating from the coronary ostia and distension and filling of the great cardiac veins with pink blood implies good catheter position. Careful insertion, confirmation of position, continuous monitoring of perfusion pressure limited to less than 40 mm Hg and avoidance of excessive traction especially in hypertrophied hearts avert the dreaded complication of traumatic coronary sinus injury. In this study, absence of retroperfusion-related traumatic coronary sinus injuries compares favourably with the 0.6% to 5% incidence of complications reported after the use of direct ostial cannulation [29-33].

The overall mortality for patients undergoing Bentall's procedure in our study was 4.6%. These figures are comparable with the published figures by other investigators. Our findings that advanced age, urgent operation, aortic dissection, renal failure and concomitant CABG increased operative mortality are also consistent with the results of other clinical series [34,35]. In a systematic review and meta-analysis of 46 studies with 7629 patients, pooled operative mortality was 6% (422 patients) and at a mean follow-up of 6 years (49175 patient-years), the annual linearized late mortality was 2.02% [35].

Data on the postoperative LCOS are scarce, and comparison between series is made difficult by the wide diversity in postoperative care protocols among institutions. The incidence of LCOS in our study was 15% compared to 29.4% reported by Mookhoek et al. [35] in a systematic review of 46 studies with 7629 patients. As far as 11.5% incidence of supraventricular arrhythmias is considered, it is in the low range compared with that in previously published reports. It can be concluded that use of "integrated myocardial management" resulted in outcomes comparable with those reported by other investigators [35].

The question is, why use a technique that appears more cumbersome than the traditional anterograde cardioplegia delivery techniques if it does not provide better protection? The reason is related to some specific advantages of the coronary sinus approach. Adequate, immediate delivery of the cardioplegic solution is achieved, especially in the setting of type-A aortic dissection, thus minimizing the ischemic time. Homogenous distribution of cardioplegia and cooling is attained with coronary sinus perfusion even in critically obstructive coronary artery disease and grossly hypertrophied heart [28,29,31]. It reduces the occurrence of supraventricular arrhythmias by retarding atrial rewarming during aortic cross-clamp by topical endocardial cooling by the egressed cold cardioplegic solution [19]. Coronary sinus cardioplegia is able to retrogradely flush air and atheromatous debris from the coronary arteries [29-33].

The main concerns regarding retrograde cardioplegia are inadequate protection of right ventricle, occasional need for bicaval cannulation, iatrogenic coronary sinus injury and longer time to induce cardiac arrest. The experience derived from the present study suggests, however, that some of them have probably been over-estimated and "integrated myocardial preservation strategies" combines the advantages of various techniques to compensate for their individual shortcomings. While conventional methods of cardioplegia rely on intermittent anoxic arrest and topical cooling, this method relies on continuous perfusion, hypothermia and chemical arrest [17].

Issues of hemodilution, hyperkalemia, flooding of blood and right ventricular preservation

Some queries regarding the described integrated myocardial protection are the concern about systemic potassium and volume overload, blood flooding the operative field, amount of cardioplegia required and adequacy of right ventricular preservation. Despite administering 3000-4500 ml of cardioplegia, we have not encountered volume overload or hyperkalemia in any patients because of routine use of ultrafiltration during and after CPB. The warm heart investigators have also demonstrated similar findings [16,17]. Venous effluent through the ostia does not seem to impair the technical aspects of conduit placement including the coronary button implantation, as the volume of blood emanating from the coronary ostia is small. Indeed, the adequacy of left and right ventricular perfusion by the coronary sinus is constantly assured by the return of desaturated blood. Published literature does not provide any conclusive answer on the permissible flow rates and total cardioplegia dose to the chemically arrested heart. In our clinical practice it ranged from 40 to 100 ml/min. In this study group, we have administered more than what we think is needed, especially in hypertrophied hearts, to have a large safety margin.

The extent of right ventricular preservation during retrograde continuous cardioplegia has never been conclusively established. In this study, irrespective of the degree of cardiomegaly and/or myocardial hypertrophy, elevated pulmonary artery pressures, we have maintained a uniform myocardial preservation protocol. There was not a single case of isolated right ventricular failure in our study group. After removal of aortic cross-clamp approximately 96% of heart reverted to normal sinus rhythm. We used atrioventricular sequential pacing for 24-48 h in patients with low heart rate. No patients required direct current cardioversion for ventricular fibrillation. Further basic research is underway using models of left and right ventricular hypertrophy to answer these important questions.

STUDY LIMITATIONS

Statistical heterogeneity limits application of our findings for use in individual patients. Heterogeneity is likely the result of large diversity in patient characteristics as well as long study period. Acquiring the information that documents superior postoperative outcome following Bentall's procedure utilizing an "integrated myocardial management" would require pooling of data from individual centers or surgeons to benchmark their experiences.

To properly test the hypothesis that "integrated myocardial management as above results in superior clinical outcome" compared with conventional management in high-risk patients requiring longer clamp time like Bentall's procedure, a multi-institutional, prospective randomized trial would be necessary and would be the last refuge who cannot accept the conflicting complex findings of the published literature.

EXPLORING THE UNKNOWNS: FUTURE DIRECTIONS

This communication is not meant in any way to convince those surgeons satisfied with their own methods of myocardial protection in high-risk patients requiring prolonged aortic cross-clamp times like Bentall's procedure. Rather it hopes to point out that an "integrated myocardial preservation strategy" as enunciated above is beneficial in the setting of Bentall's procedure with or without aortic dissection.

CONCLUSION

We conclude that intermittent anterograde and continuous retrograde coronary sinus cold cardioplegia is a safe and effective means of cardioplegia delivery in patients undergoing Bentalls procedure. It is associated with a significant reduction of postoperative adverse cardiac events and a trend towards better biventricular performance.

Our study further demonstrates that the pre-requisites for retrograde continuous cold cardioplegia to be safe and effective are avoidance of hemodilution, hyperkalemia and maintenance of appropriate retrograde flow rates.

We submit that in increased appreciation of "integrated myocardial management", will stimulate clinical trials in these high-risk patients to better define its place in the armamentarium of cardioplegia delivery techniques.

DEFINITIONS (APPENDIX)

Low cardiac output syndrome (LCOS)

Low cardiac output syndrome following Bentall's procedure was diagnosed if the patient required inotropic support (dopamine at 4-10 $\mu g.kg^{-1}.min^{-1}$), dobutamine at 5-10 $\mu g.kg^{-1}.min^{-1}$, epinephrine at 0.01-0.1 $\mu g.kg^{-1}.min^{-1}$ either isolated or in combination in the operating room or in the intensive care unit, to maintain stable hemodynamics (systolic blood pressure at greater than 90 mm Hg and cardiac output greater than 2.2 $L.min^{-1}.m^{-2}$) in the absence of residual structural lesions and mechanical external compression after correction of all electrolytes or blood gas abnormalities and after adjustment of the preload to its optimal value. Low-output syndrome was also diagnosed if there was an increasing requirement of the above-mentioned inotropes with or without intra-aortic balloon counterpulsation along with afterload reduction with sodium nitroprusside. Patients who received less than 4 $\mu g.kg^{-1}.min^{-1}$) dopamine to increase renal perfusion were not considered to have low output syndrome. 13 Patients who received vasoconstricting medications because of high cardiac output (>2.5 $L.min^{-1}.m^{-2}$) and low systemic vascular resistance were also not considered to have low cardiac output syndrome.

Perioperative-myocardial infarction and arrhythmias

A postoperative myocardial infarction was diagnosed by the appearance of new Q waves associated with an increase in the levels of the myocardial-specific creatine kinase. Postoperative arrhythmias were classified into three categories: (1) sustained new onset supraventricular tachyarrhythmias of new onset necessitating antiarrhythmic therapy, with or without the need for direct-current cardioversion; (2) multifocal or coupled premature ventricular beats with a normal concentration of serum potassium necessitating antiarrhythmic drugs; and (3) ventricular tachycardia or fibrillation. Conduction defects were classified as (1) junctional rhythm, (2) bundle-branch block of new onset, and (3) complete heart block.

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