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Orthotopic Heart Transplantation: Bicaval Versus Biatrial Surgical Technique

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Abstract

In 1967, the first cardiac transplantation was performed in South Africa by Christiaan Barnard, becoming one of the most pioneering events of the human history, comparable to the first step on the moon, 2 years later. Even if Barnard became extremely famous because of this outstanding operation, behind this event there were years and years of studies, experimentations and hard work done by others, in particular by Lower and Shumway. The initial technique, still called 'standard technique' is the biatrial one. In the late 1980s, alternatives like the 'bicaval technique' were developed in order to get a more anatomical result. In the present chapter, we will throw the reader into the early years of the cardiac transplantation era, describing all the efforts made by the "fathers" of the cardiac surgery in order to standardize techniques inherited by the modern surgeons. Afterwards, we will present a review of the literature to answer the question if the biatrial technique should still be called "standard technique".

Keywords: Yacoub, Shumway, tricuspid regurgitation, technical issues

1. Historic background of cardiac transplantation surgical techniques

On December 3, 1967 in Cape Town, Christiaan Barnard performed the first human heart transplant. This was one of the most significant accomplishments in history, allowing to save the life of several patients with end-stage heart disease in the last 50 years. This remarkable

surgical innovation was the result of constant work, diligent research, creativity and innovative perception. During the early 1900s, Alexis Carrel, the father of vascular and transplant surgery who was awarded the Nobel Prize in Physiology or Medicine in 1912, and Charles Guthrie, professor of Physiology and Pharmacology at Washington University, performed the first heterotopic heart transplant [1]. Subsequently, other American surgeons, including Mann [2] at Mayo Clinic in 1933 and Marcus [3] at Chicago Medical School two decades later, pursued the experimentation and proposed new techniques for heterotopic heart transplantation. At the same time, on the other side of the world, Vladimir Demikhov at M.V. Lomonosov Moscow State University gave a considerable contribution to this experimental specialty, performing the first combined heart-lung transplant and also the first orthotopic transplant in dogs without the use of hypothermia and pump-oxygenator support. His technique consisted of end-to-side anastomoses between the corresponding thoracic *aortae*, superior *venae cavae*, inferior *venae cavae*, and pulmonary arteries. The donor's inferior pulmonary veins were joined together and connected to the recipient's left atrial appendage. Then, the portion of recipient's heart excluded from circulation was ligated and excised [4]. Unfortunately, Demikhov's research remained unknown for a long time and it was published in English only in 1962.

The introduction of hypothermia and cardiopulmonary bypass in the early 1950s had a decisive impact on heart transplantation research.

In the late 1950s, Shumway and Lower at Stanford University achieved brilliant results experimenting on dogs [5]. They used a simple and effective surgical technique, called "Shumway" or biatrial technique (BA), where the anterior part of donor's left and right atria was incised and anastomosed to the posterior wall of the recipient's atria. This became the standard heart transplant surgical technique until the 1990s. These two pioneers also introduced two innovative methods that allowed to prolong survival times: the use of isotonic saline solution at 4°C to preserve the donor's heart and the use of cardiopulmonary bypass to support the transplanted heart [6].

Based on these promising premises, Shumway began to think about human heart transplant.

This research recalled the attention of the international scientific community, in particular of Christiaan Barnard, a young South African surgeon with a good reputation in open heart surgery who developed almost an obsession for heart transplantation. In August 1966, he spent 4 months in Lower's laboratory learning the principles of Shumway's research.

At his return to South Africa, on December 3, 1967, he performed the first heart transplant [7]. The donor was Denise Darvall, a 25-year-old woman who had a severe brain injury and was certified brain dead by the neurosurgeons. The recipient was Luois Washkansky, a 53-year-old man with severe heart failure; he died 17 days later due to pneumonia [8].

On December 6, 1967, Adrian Kantrowitz, another pioneer in this field, performed the first pediatric heart transplantation at Maimonides Hospital of New York. The donor was an anencephalic baby and the recipient was an 18-day-old child with Ebstein anomaly. Unfortunately, the young patient died after 6 hours [9].

One month later, on January 6, 1968, Shumway and his team performed the first human heart transplant in the United States. The patient died of gastrointestinal bleeding on the 15th postoperative day.

During the next year, 102 heart transplants were performed around the world, with only 40% survival at 1 year [7]. These poor results were the reason why the most important cardiovascular surgery centers abandoned the procedure.

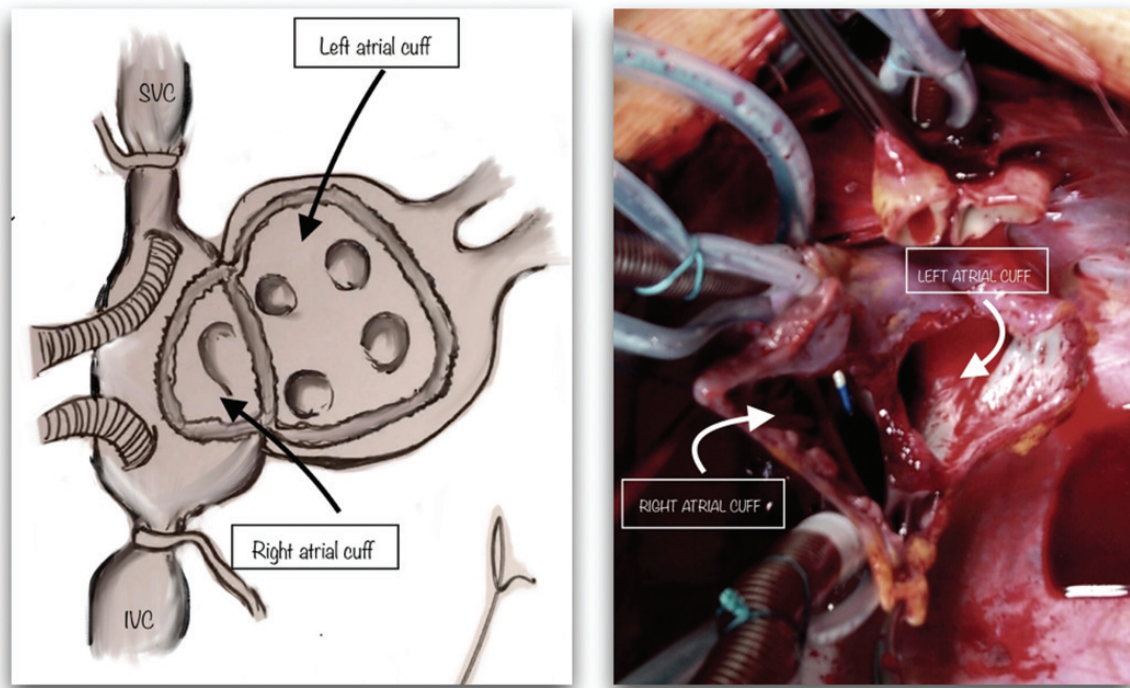
After these first attempts, heart surgeons realized that specific suppression of the recipient's immune system was required for long-term graft survival. After the introduction of percutaneous transvenous endomyocardial biopsy in 1973, that improved the diagnosis of acute and chronic rejection, and the discovery of cyclosporine A in 1976, a powerful immunosuppressor, better results in terms of survival were achieved, therefore a greater number of procedures was performed [6].

While the "Shumway technique" remained the standard for more than 20 years worldwide, in the early 1990s, some surgeons proposed new effective surgical techniques trying to improve hemodynamic results and late survival [10]. Despite the technical evolution, in the last 50 years, despite the improvement in pharmacological treatment of end-stage heart failure, cardiac transplantation has remained the only treatment (along with left ventricle assistance devices (LVAD) implantation as destination therapy) capable of improving the long-term survival [11, 12]. The standard BA technique, based on the description of Cass and Brock [13] and Lower and Shumway [5] for orthotopic heart transplantation (OHT), was adopted worldwide for many years due to its simplicity and reproducibility. This technique requires, to some extent, the excision of the posterior part of the donor's left atrium and the incision of the right atrium from the inferior vena cava toward the right atrial appendage to avoid injuries to the sino-atrial node. The atrial anastomoses can be performed easily, reducing from 8 possible single-vessel anastomoses for complete transplantation to 4 (**Figure 1**).

However, several studies have demonstrated that the drawback of this technique consists in enlarged, figure-of-eight configured right and left atria without a physiological geometry between the donor and the recipient's atria [14]. This non physiological geometry can lead to (i) higher incidence of mitral and tricuspid valve incompetence, (ii) rhythm disturbances [14] and (iii) tendency of thrombus formation and septal aneurysm [15]. Because of these problems, some authors, as Sir Magdi Yacoub, Banner and Dreyfus some time later [16–18] proposed a more anatomical surgical technique with complete excision of the recipient's atria and direct anastomoses to the left pulmonary veins, right pulmonary veins, inferior venae cavae (IVC), and superior venae cavae (SVC). No technical complications occurred, but the benefit of this procedure on clinical outcome had to be demonstrated, at least in the 1990s.

Sievers and co-workers [19] in 1991, and the Wythenshawe group [20] in 1993, introduced into clinical practice the bicaval transplantation technique (BC), characterized by two arterial, one left atrial, and two caval anastomoses, leaving the right atrium intact and leaving only a small posterior part of recipient's left atrial tissue between the pulmonary veins (**Figure 2**). Potential

Biatrial Technique



Biatrial Technique

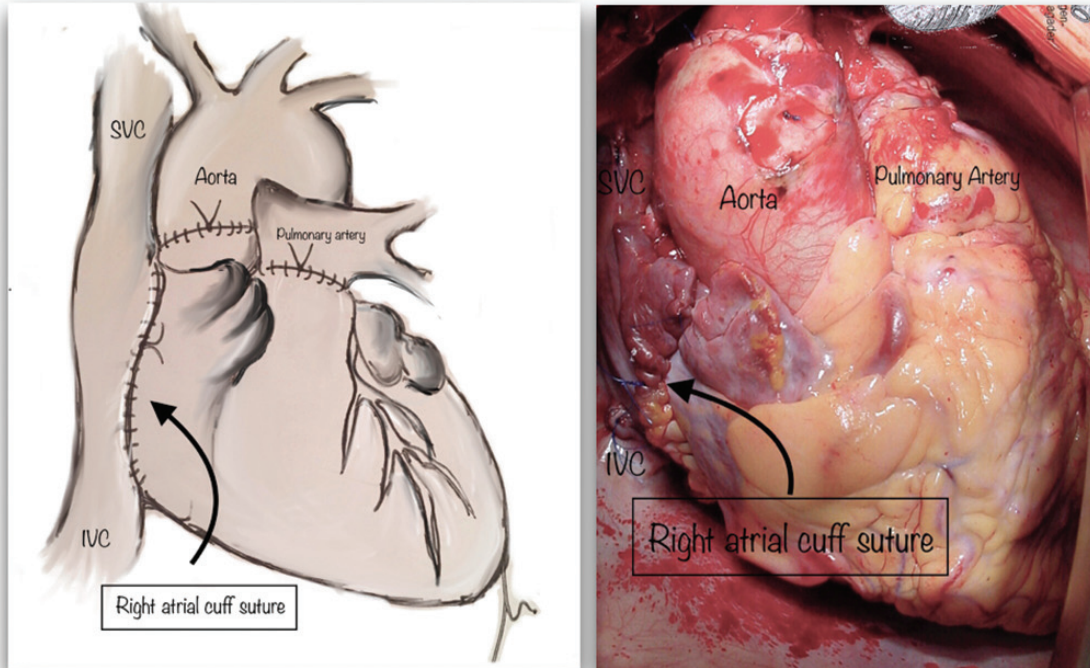
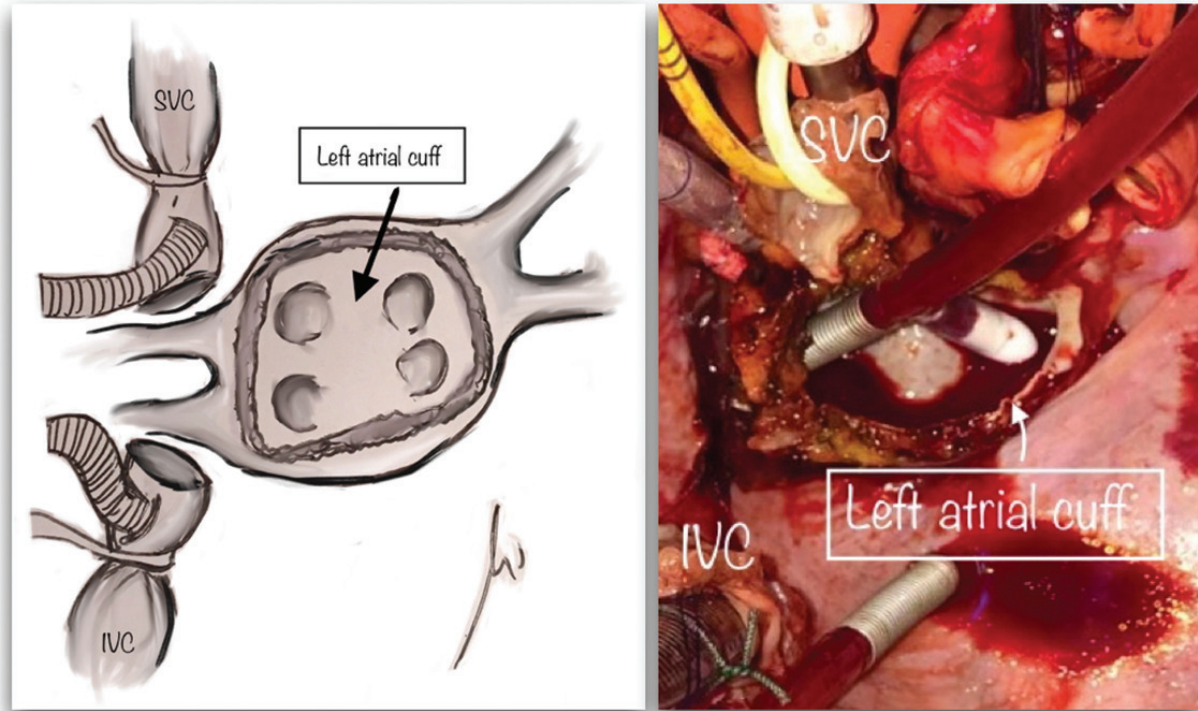


Figure 1. A schema of the Biatrial technique for orthotopic cardiac transplantation is shown. In the left (A), after cardiectomy, the double atrial cuff is distinguishable, with the interatrial septum with the foramen. In the right, (B) the right atrial cuff suture is represented.

Bicaval Technique



Bicaval Technique

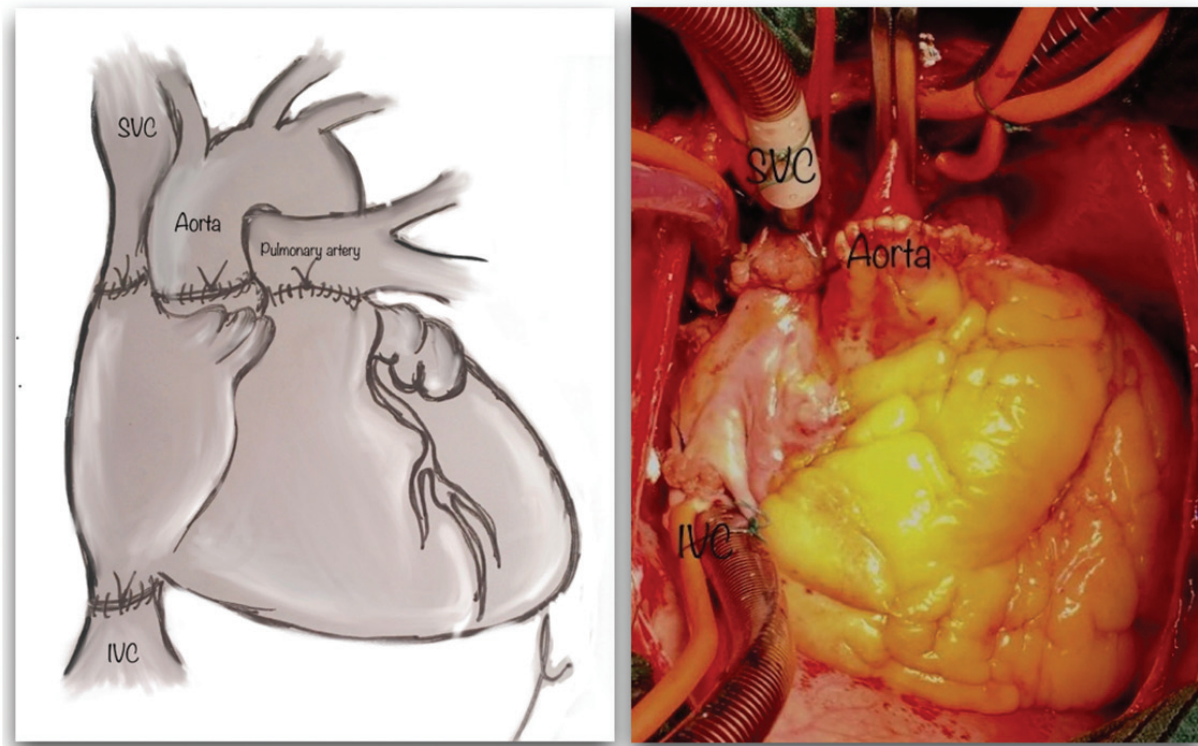


Figure 2. The schema of the Bicaval technique has been designed. In the left side (A), both cavas and the left atrial cuff are prepared after cardiectomy, while in the right side (B) the final result with both superior and inferior vena cava sutures.

shortcomings of the BC technique include the marginally prolonged ischemic transplantation time, which is likely of no clinical relevance, as well as some sort of stenosis at the level of the venous anastomoses. Both problems, however, can be neutralized by refined surgical techniques.

2. Biatrial vs. bicaval technique: Best evidences

During the 1990s, many single center reports, with variable potency and sample size have been published, comparing both techniques from different points of view and outcomes, like post-operative mortality, length of operation in terms of ischemic organ time, length of hospital stay, need for permanent pace maker, echocardiographic findings, exercise capacity and long-term survival.

Remarkable is the paper of Sun et al. [21] with a total of 615 enrolled patients. Among them, 322 were transplanted using the BC technique and 293 using the BA technique. There was no statistically significant difference in terms of early mortality (within 30 post-operative days) between the two groups (3.4% in the BC group vs. 4.8% in the BA group, p 0.5). The average follow-up period was 4.0 ± 3.0 years (ranging from 1 to 11 years). There was no significant difference between groups (3.8 ± 3.5 years in Group 1, 3.8 ± 3.8 years in Group 2). Survival rates at 1, 5 and 10 years were 93, 89 and 87% in the BC group and 89, 82 and 80% in the BA group, respectively. Long-term survival differed significantly between the two groups and the cumulative proportion of survival was significantly higher in the BC group than in the BA group (p 0.05). In the univariate regression analysis, several echocardiographic parameters, such as left atrial diameter, mitral regurgitation, tricuspid regurgitation, left ventricular ejection fraction, right ventricular ejection fraction and surgical techniques, were predictors of long-term survival. Both mitral and tricuspid regurgitation were weakly associated with mortality. There were significant correlations between left and right ventricular ejection fraction and surgical techniques with mortality outcome. Using a multivariate model of analysis, left and right ventricular ejection fraction remained significant risk factors for mortality. When adjusted for left and right ventricular ejection fraction, the surgical techniques (BC vs. BA) significantly influenced mortality outcome in the multivariate analysis. Any significant difference in the incidence of mitral regurgitation between BC and BA transplant patients was demonstrated. However, tricuspid valve regurgitation was much more common in the BA group than in the BC group. They concluded that the BC technique helps to decrease atrial size and tricuspid regurgitation, and better preserves right and left heart function, resulting in improved long-term survival after heart transplantation compared with the BA technique.

Other authors have demonstrated that the BC technique leads to an increased parasympathetic reinnervation compared with the standard technique, which might be of clinical relevance because an increase in blood pressure control, by larger reflex changes in heart rate, might improve adaptation to various stimuli and to physical exercise [22].

However the best way to reach some conclusion is by analyzing papers with the strongest evidences. Relevant among these, two multicenter studies from the UNOS database and other two meta-analysis (see **Table 1**).

Author/ year	Institution	Study Type	Patients	TVR	PM Insertion	Mortality	Survival
Wartig et al. 2014 [30]	Sahlgrenska University Hospital, Gothenburg, Sweden	Retrospective Cohort Study	BA: 221 BC: 226	BA: Mild: 103 (37%) Moderate/ Severe: 63 (61%)* BC: Mild: 169 (61%) Moderate/ Severe: 39 (38%)	NA	48 (9.9%)	1 year: 84%* 5 years: 73% 10 years: 58% 15 years: 43% 20 years: 27%
Davies et al. 2010 [23]	Columbia University, New York, USA	Retrospective Review UNOS database	BA: 11.919 (59.3%) BC: 7.661 (38.1%) Total: 519 (2.6%)	NA	BA: 576 (5.1%) BC: 146 (2.0%) Total: 11 (1.9%)	BA: 8.9% BC: 7.6% Total: 9.5%	BA: 1 year: 85.6%* 5 years: 72.2%* 10 years: 51.1%* BC: 1 year: 87.1% 5 years: 73.5% 10 years: 57.4%
Weiss et al. 2008 [24]	Johns Hopkins Medical Institution, Baltimore, USA	Retrospective Review UNOS database	BA: 6.724 BC: 5.207	NA	BA: 343 (5.3%) BC: 103 (2.0%)	BA: 30-days: 6.6% 1 year: 13.4% BC: 30-days: 5.4% 1 year: 11.5%	BA: 30-days: 93% 1 year: 86% 3 years: 79% 5 years: 72% BC: 30-days: 94% 1 year: 87% 3 years: 81% 5 years: 75%
Locali et al. 2008 [28]	Universidade Federal São Paulo, Brazil	Meta-analysis	BA: 914 BC: 872	BA: 310/685 (45.2%) BC: 184/593 (31%)	NA	BA: 102/547 (18.6%) BC: 64/585 (10.9%)	NA
Schnoor et al. 2007 [10]	Medical University Schleswig- Holstein, Luebeck, Germany	Meta-analysis	BA: 1.803 BC: 1.968	BA: 153/261 (58.6%) BC: 61/211 (28.9%)	NA	BA: 18/110 (16.4%) BC: 9/118 (7.6%)	NA

BA: biatrial; BC: bicaval; NA: not analyzed; PM: pace-maker; TVR: tricuspid valve repair; *= p< .01.

Table 1. Overview and outcomes of Biatrial vs. Bicaval for orthotopic heart transplantation.

Davies et al. [23] recently reported from the UNOS data base an analysis of 20,999 transplantsations performed on adult patients with no congenital heart disease between 1997 and 2007, including the type of anastomosis performed. Patients were stratified accordingly to the atrial anastomosis technique: standard BA (atrial group, n. 11,919 [59.3%]), BC (caval group, n. 7661 [38.1%]), or total orthotopic (total group, n. 519 [2.6%]). First of all, until 2003, the BA technique

was used more frequently than the BC one, while the number of total transplantation decreased. In 2006, more than 34% of the cases of cardiac transplantation were performed with the “standard” or BA technique. The percentage of transplantations performed with the BC technique was higher at higher-volume transplant centers.

Regarding the outcomes, the need for permanent pacemaker was increased in patients in the atrial group (n. 576, 5.1%) requiring a PPM before discharge more often (odds ratio [vs. the caval group], 2.6; 95% CI, 2.2–3.1) than the caval group (n. 146, 2.0%) or the total group (n. 11, 1.9%; odds ratio [vs. the caval group], 1.0, 95% CI, 0.6–1.7). Multivariate predictors of the need for PPM implantation included BA anastomosis (odds ratio, 3.1; 95% CI, 2.5–3.9), donor age of 60–69 years (odds ratio, 2.9; 95% CI, 1.5–5.3), donor age of 50–59 years (odds ratio, 2.0; 95% CI, 1.6–2.5), donor age of 40–49 years (odds ratio, 1.3; 95% CI, 1.0–1.6), recipient inotropic support at transplantation (odds ratio, 1.5; 95% CI, 1.2–1.7), donor history of hypertension (odds ratio, 1.2; 95% CI, 1.0–1.4), and transplantation year (odds ratio, 1.04; 95% CI 1.01–1.07 [per year]); use of T4 before organ retrieval (odds ratio, 0.8; 95% CI, 0.6–0.9) was protective.

In terms of hospital length of stay, patients in the atrial group had longer posttransplantation stay (21.1 days) than those in the caval group (19.3 days, $P < 0.0001$).

In univariate analysis atrial group patients had a higher incidence of postoperative death (8.9%; odds ratio, 1.17; 95% CI, 1.05–1.30) than those in the caval group (7.6%; odds ratio, 0.83; 95% CI, 0.75–0.93); postoperative mortality in the total group (9.5%; odds ratio, 1.14; 95% CI, 0.86–1.53) was not significantly different from the one seen in either of the other groups. However, the logistic regression model predicting postoperative death did not include the type of anastomosis.

Also in the long-term outcomes, the need for PPM implantation was significantly higher among patients in the atrial group, ($P < 0.0001$): at 2 years, 8.6% required a pacemaker versus only 5.4% in the BC group and 4.0% in the total group. Multivariate predictors of the interval time between transplantation and PPM insertion included other factors, like recipient age (odds ratio, 1.006; 95% CI, 1.001–1.012 [per year]), transfusions between listing and transplantation (odds ratio, 1.2; 95% CI, 1.0–1.4), donor age of 50 to 59 years (odds ratio, 1.6; 95% CI, 1.3–2.0), donor’s age of 60 to 69 years (odds ratio, 2.2; 95% CI, 1.3–3.7), transplantation year (odds ratio, 1.25; 95% CI, 1.21–1.28 [per year]), and BA anastomosis (odds ratio, 2.5; 95% CI, 2.2–2.9); ventricular assistance device at transplantation was protective in this model (odds ratio, 0.7; 95% CI, 0.6–0.9). There was a small but significant difference in long-term survival between the atrial and caval groups in univariate analysis (survival at 1 year, 85.6 vs. 87.1%; at 5 years, 72.2 vs. 73.5%; at 10 years, 51.1 vs. 57.4%; $P < 0.0168$). Multivariate Cox proportional hazards regression analysis confirmed the decreased survival among patients in the atrial group (hazard ratio, 1.11; 95% CI, 1.04–1.19). There was no difference in graft survival, renal failure-free survival, and transplant coronary atherosclerosis-free survival, based on anastomotic technique.

Three years before the UNOS analysis from Davies et al. [23], Weiss et al. [24] conducted a retrospective review of the UNOS database from January 1999 to December 2005. A total of 14,418 patients underwent first-time OHT during this period. After exclusion of patients aged

less than 18 years (n. 1831) and more than 80 years (n. 2), orthotopic total transplants (n. 482), heterotopic transplants (n. 4) and those without data on transplant technique (n. 139), the final study population was 11,931. Of these, 5207 (43%) received the BC anastomotic technique, with follow-up through September 2006. Almost 10,000 patient less than the population analyzed by Davies et al. [23]. Weiss et al. concluded that there was no difference in survival between BC and BA techniques when modeled with long-term follow-up and adjusted for confounding variables. Although the mortality rates were higher for the BA group at 30 days and 1, 3 and 5 years, this represents unadjusted mortality, which disappears in both the logistic regression and proportional hazards model for all time-points. Comparing both studies, we can conclude that probably the results obtained by Davies et al., due to the sample size and the interval period, are complementary to those obtained in the previous Weiss' UNOS analysis, giving more conclusive information. Also the BC technique gives the advantage of decreasing both the need of PPM and the post-operative mortality, but also influences positively the long term survival.

Regarding two relevant meta-analysis, the first one, published by Schnoor et al. [10] in 2007, provides evidences that the expected theoretic advantages of BC transplantation, in comparison with the standard technique, have come true in clinical practice. The meta-analysis included 23 retrospective and 16 prospective studies. In prospective trials, a reduction in right atrial pressure was found. The absolute difference in right atrial pressure is probably of no clinical relevance at rest but it probably could be on exertion. It has been suggested that the patients with BC heart transplant may have superior exercise performance in comparison with BA heart transplant. An attempt to solve this dilemma has been done in 2011 by Czer et al. [25]: he did not found any significant difference in the exercise capacity between patients with BA versus BC techniques for orthotopic heart transplantation. Other factors such as cardiac denervation and immunosuppressive drug effect, or physical deconditioning, may be more important determinants of subnormal exercise capacity after heart transplantation. Nevertheless, the reduction in morbidity and postoperative complications and the simplicity in the BC technique suggest that the BC heart transplantation offers advantages when compared to the standard BA technique.

Another study by Aleksic et al. demonstrated that the BC technique improves resting hemodynamics in patients with high preoperative pulmonary vascular resistance as highlighted by higher cardiac output and index with lower right atrial pressures. Further studies by Aleksic et al. showed that the BC technique improved hemodynamics during episodes of cellular rejection (grade 1B-1R or greater) and during antibody-mediated rejection [26, 27].

Other conclusions from the Schnoor meta-analysis confirmed the outcomes of other single center results, like a higher rate of sinus rhythm after transplantation in the BC group, as well as the significantly reduced rate of tricuspid valve regurgitation, the prevention of contraction abnormalities by the acute atrial enlargement with the standard technique, and the asynchrony of recipient and donor atrial innervation, improving hemodynamic effects after BC transplantation. The enlargement and distension of the atria typical of the standard technique might not only induce an impairment of the electrical impulse initiation and conduction, triggering arrhythmias, but also promote atrial thrombus formation, most likely avoided using the BC technique.

Another relevant meta-analysis is the one conducted by the Brazilian group from San Paolo. Fagionato et al. [28] aimed at increasing the statistical power of the evidences supporting the new techniques against the BA transplantation, thus adding significance to the results of Schnoor et al. They demonstrated many advantages of the BC technique on the BA one: first of all, the ischemia time in the BC group, even when longer, as found in some studies, is compensated by a better cardiac performance with the new techniques, since adequate ventricular filling is dependent on a satisfactory atrial function. Furthermore, the incidence of atrial arrhythmias was lower in the group undergoing BC transplantation, like in Schnoor's study. This can be explained by the preservation of the sino-atrial node integrity. Modifications in the atrial geometry predispose to atrial arrhythmias, as well as increased internal pressure, since these events prolong the electrical conduction time. The severity of the newly developed arrhythmias is known to be also related and proportional to the severity of the rejection. Fagionato's results show no differences between the transplantation techniques in terms of rejection, concluding that the episodes of atrial arrhythmias are mainly due to greater deformity and atrial pressure. In this context, the rejection episodes can also be related to the degree of tricuspid valve regurgitation. In 2002, Aziz et al. [29] showed that individuals with moderate or severe tricuspid regurgitation have a higher number and intensity of rejection events. On the other hand, the progression of cardiac cellular rejection may be accompanied by oedema and papillary muscle dysfunction, or trigger asymmetrical right ventricular contractility, thus leading to tricuspid valve regurgitation. Additionally, the high hydrophilic property of the valve leaflets glycosaminoglycans leads to increased oncotic pressure in the extracellular matrix during cellular rejection, thus causing oedema and precluding adequate function. In this regard, there is another outstanding study conducted from the Swedish group of Wartig et al. [30] that demonstrated in a pretty huge population the impact of the transplantation techniques on the tricuspid function, as well as its impact on survival. Tricuspid valve regurgitation after cardiac transplantation has been argued to be related to the number of biopsies (although this has been found to be contradictory), to the altered geometry of the right atrial anastomosis in the BA technique, to the preoperative recipient's pulmonary vascular resistance, to the ischemic time of the donor's heart, to the donor-recipient size mismatch, to the mismatch between the donor's heart and a large pericardial cavity of the recipient, or to the presence of TR already in the donor. Wartig et al. revised retrospectively their population of transplanted patient since 1984, comparing both cohorts of 221 patients receiving BA technique and 226 receiving BC technique. They observed first that the incidence of early significant TR after HTx was more common after the BA technique than after the BC technique. Furthermore, they demonstrated with a multivariate logistic regression analysis that the BA technique was the only significant predictor of early moderate to severe TR (odds ratio [OR], 2.70; 95% confidence interval [CI], 1.68–4.32; p 0.001). More interestingly, they found that moderate and severe TR at discharge was associated with impaired long-term survival. Moreover, it has been previously shown that the degree of TR is related not only to degree of symptoms and right-sided heart pressures but also to progressive renal dysfunction. When stratifying for technique, we found more patients with significant TR in the BA group at early and also 5-year follow-up, compared to the BC group; however, there was no difference at 10 year of follow-up between groups. The explanation might be that patients in the BA group with significant TR died before 10-year follow-up.

A good option to palliate the high incidence of tricuspid regurgitation is that patients undergoing HTx should have a prophylactic tricuspid valve annuloplasty [31, 32]. This may be a good option using the BA technique is used, but when the BC technique is used, prophylactic tricuspid annuloplasty not only becomes cumbersome intraoperatively, but also unnecessary because none or mild TR appears to be the case in approximately 80% of patients.

In light of these facts, the superiority of the BC technique demonstrated in many scientific relevant papers is undebatable. For this reason, some Authors postulated that the BA transplantation technique should no longer be considered the gold standard for transplantation, and should only be used in selected cases. Thus, today there is no more room for questioning whether there are advantages of the BC or total techniques over the BA technique, but it is legitimate to research possible advantages of one technique over the other, providing the patients with the best treatment.

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