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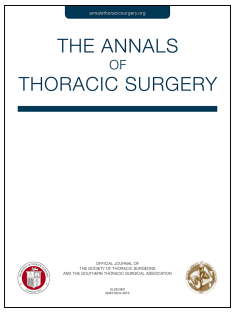

Beating vs Arrested Heart Isolated Tricuspid Valve Surgery: Long-term Outcomes

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Beating vs Arrested Heart Isolated Tricuspid Valve Surgery: Long-term Outcomes

Running head: beating heart isolated tricuspid surgery

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Abstract

Background: Isolated tricuspid valve (TV) surgery is a rare procedure generally considered at high risk of perioperative mortality and poor long-term outcomes. Surgical treatment can be performed with either an arrested heart (AH) or beating heart (BH) technique.

Aim of this study is to compare the outcomes of isolated tricuspid surgery with two different approaches.

Methods: The SUR-TRI study is a multicenter international retrospective study enrolling adult patients who underwent isolated tricuspid valve procedures (n=406, 56±16 years; 56% female) at 13 international sites. AH and BH strategies were performed in 253 and 153 cases, respectively. Propensity score-matched analysis was used to compare groups.

Results: After matching, 129 pairs were obtained and analyzed. The 30-day mortality rate was 6.2 vs 5.0% in the AH and BH groups, respectively (p=0.9). The rates of acute renal failure requiring replacement therapy (3 vs 10%, p=0.02) and stroke (0 vs 1.8%, p=0.08) were numerically higher in the AH group. The 6-year survival rate was 67±6 vs 78±5% in the AH and BH groups, respectively (p=0.18), while freedom from cardiac death was 75±5 vs 84±4% (p=0.21). The six-year composite cardiac endpoint of cardiac death and reoperation rate was 60±9 vs 86±5% (p=0.024) comparing AH-TV replacement and BH-TV repair groups.

Conclusions: Isolated tricuspid valve surgery performed with a beating heart strategy is a safe option and resulted in a trend of increased long-term survival and freedom from reoperation when compared with the standard arrested heart technique. Patients undergoing beating heart valve repair had the best long-term outcome.

Keywords

Tricuspid valve, Isolated tricuspid valve disease, surgery, beating heart, survival

Abbreviations

TV: Tricuspid valve

TR: Tricuspid regurgitation

EuroSCORE: European System for Cardiac Operative Risk Evaluation

CPB: Cardio-pulmonary bypass

NYHA: New York Heart Association

EF: Ejection fraction

COPD: Chronic Obstructive Pulmonary Disease

RV: Right ventricle

BH: Beating Heart

AH: Arrested Heart

TVR: Tricuspid Valve Replacement

TVr: Tricuspid Valve Repair

Interest in tricuspid valve disease has rapidly increased in recent years, with the recognition of a large number of symptomatic patients left untreated in the general population (1-3). Moreover, the introduction of new and minimally invasive treatment strategies such as transcatheter techniques has resulted in a large discussion regarding the clinical benefits, patient selection and outcomes (4,5).

Isolated tricuspid valve (TV) surgery represents the therapy of choice for "patients affected by severe regurgitation who are still symptomatic despite optimal medical therapy or showing progressive RV dilatation/dysfunction" (6). However, the procedure is rarely performed and is generally associated with a high incidence of postoperative adverse events and reduced survival. A recently published analysis of 1041 patients treated in the United States showed a progressive increase in the number of operations performed per year. The overall operative mortality rate was 8.8%, with a significant advantage of repair over replacement (p=0.009) (7).

Tricuspid valve surgery, both repair and replacement, can be performed either with an on-pump beating heart or an arrested cardioplegic heart (8,9). Several factors, including etiology of tricuspid disease, right ventricular function, preoperative pulmonary hypertension and liver or renal disease play a distinct role in patient outcomes and the surgical approach (10,11). The surgical technique may affect results, adverse event rates and late survival. No randomized clinical trial comparing beating heart and arrested heart strategies have been reported yet.

The aim of the current study is to compare the early and long-term outcomes of patients undergoing isolated tricuspid valve surgery with the standard cardioplegic arrested heart (AH) or a beating heart (BH) technique.

Material and Methods

Design and data collection

The International SUR-TRI study (Surgical-Tricuspid Study) is a multicenter retrospective study initiated by the Department of Cardiac Surgery at the Medical University of Vienna involving 13 international cardiac surgery units with experience in valve surgery and tricuspid disease treatment. The study has been approved by the Ethical Committee of the Medical University of Vienna (1289/2019) and is not funded. Each participating center underwent ethical approval according local criteria. Need for informed consent was waived for retrospective data collection.

All adult patients (age >18 years) operated on from 2008 to 2019 in the participating centers were enrolled (Supplemental Figure 1, Supplemental Table 1-2). The exclusion criteria were age <18 years, congenital etiology of tricuspid disease, previous heart transplantation or left ventricular assist device implantation and concomitant indications for other major cardiac procedures, such as coronary artery bypass grafting, repair/replacement of other heart valves, aortic aneurysm treatment, pericardiectomy, and atrial or ventricular septal defect closure.

Baseline presurgical clinical and echocardiographic features as intraoperative characteristics were retrospectively collected at each center by the international study consortium. Constant communication and periodical meetings between leading and secondary centers were carried out. Long-term follow-up was performed by institutional database analysis or direct assessment by local investigators. Clinical follow-up was complete regarding survival (dead or alive), cause of death (cardiac or not) and reoperation. The median follow-up duration was 21 months, with a range of 1-131 months.

End-points

The primary end-point was aimed to evaluate differences between the two surgical strategies regarding long-term outcomes in terms of:

- overall survival;
- freedom from death for cardiac causes (chronic heart failure, myocardial infarction,

major arrythmias, major cardiovascular events);

- cumulative endpoint of freedom from cardiac death and reoperation on the tricuspid valve (cardiac event-free survival).

The secondary end-point was to assess any difference in terms of thirty-day mortality and rate of perioperative adverse events.

Statistical analysis

Descriptive statistical methods were applied to depict the study population at baseline. Continuous, normally distributed variables are presented as the mean ± standard deviation; skewed data are presented as the median and interquartile range (25^{th} and 75^{th} percentiles). Categorical variables are presented as numbers (%). Differences between groups were compared with Student's t-test for normally distributed variables and the Mann-Whitney U test for nonnormally distributed variables. Categorical variables are summarized as the number and percentage of subjects in each category, and differences were compared with the Pearson chi-square test.

The propensity score was obtained using machine-learning-random forest and overlapping was tested with a common support plot (Supplemental Figure 2); 1:1 matching with different calipers from 0.5 to 0.65 was tested, choosing the best one (0.20) (12). The variables included in the propensity model were age, sex, diabetes, NYHA class, previous stroke, dialysis, EuroSCORE II, COPD, previous cardiac surgery, LVEF, TR severity, urgency/emergency, repair/replacement, and sternotomy/thoracotomy. The balance of the two matched groups was tested with the standardized mean difference (SMD), which was considered optimal below 0.20. Adverse events were analyzed as proportions of the number of patients. The observed mortalities are described as rates (%). Early and late mortality rates were described with the means of descriptive statistics. All deaths for unknown reasons were considered cardiac death. A Kaplan-Meier analysis was performed to assess overall survival, freedom from cardiac

death and freedom from a composite of cardiac death and reoperation on the tricuspid valve. Differences between curves were compared using the log-rank test. Cox regression was used to adjust curves for differences between the two groups. All reported p-values were considered statistically significant if below 0.05. R-Studio version 1.1.463 (2009-2018) was used for all statistical analyses.

Results

Patient demographics

A total of 406 consecutive patients (n=406, 56±16 years; 56% female) were enrolled in the international SUR-TRI study (Supplemental Figure 1). Surgery was indicated for endocarditis in 27% of patients, for functional regurgitation in 45%, for rheumatic disease in 10% and for other etiologies (degenerative, pacemaker-related, carcinoid syndrome, unknown) in the remaining 18%. A repair strategy was carried out in 188 patients (46%), and 21% of surgeries were executed in an urgency/emerging setting.

The beating heart strategy was applied in 153 patients (37%) (BH group), while the arrested heart technique was applied in the remaining cases (AH group, n=253). Annual trend of procedures is resumed in Supplemental Figure 3-4. Rate of BH approach remained almost stable during years with a peak in 2010 and 2011.

Patients in the BH group (n=153) underwent re-do procedures more frequently (53 vs 35%, p=0.0001), exhibited a higher preoperative risk profile with EuroSCORE II (p=0.02) and CRS score (13) (4.7 ± 2.8 vs 4.0 vs 2.0), and access was more frequently performed with a minimally invasive procedure (36 vs 22%, p<0.05). Patients treated with the AH technique (n=253) were more frequently endocarditis (36 vs 12%, p<0.001) and more frequently underwent repair (53 vs 38; p=0.003) with longer CPB times (102 ± 51 vs 90 ± 50 minutes, p=0.01).

From this cohort, a propensity matched cohort of 129 pairs representing 258 unique patients was generated. Table 1 shows the main characteristics of the AH and BH groups before and after matching.

Perioperative adverse events and mortality

Twenty-two patients (5.4%) in the entire SUR-TRI cohort (n=406) experienced death during the first 30 days. After propensity matching, no difference was found between the study groups (AH: n=8; 6.2% vs BH: n=7; 5%; p=0.9).

In the matched population, 13 patients in the AH group (10%) vs 4 (3%) in the BH group experienced acute renal failure requiring replacement therapy (p=0.02); 1.6% of AH patients (n=2) had a postoperative neurological deficit with a duration of more than 24 h vs no patients in the BH group (p=0.08). Rate of new-onset atrial fibrillation was two-fold increased in the BH group (20.2% vs 10.9 %, p= 0.04).

No differences were recorded in terms of postoperative permanent pacemaker implantation (9.3 vs 11.6%, p=0.68), blood transfusion (51 vs 58%, p=0.3), re-exploration for bleeding (10.9 vs 7.8%, p=0.4), or length of stay in the AH vs BH group respectively. Table 2 shows the main postoperative adverse events.

Long-term results

In the matched population (n=258), 44 late death occurred of whom 27 were cardiac related.

Freedom from death for any cause in the AH group was 83±4%, 75±5% and 67±6% vs 91±3%, 82±4% and 78±5% in the BH group at 1, 3 and 6 years (p= 0.18) (Fig.1).

Freedom from cardiac death at 1, 3 and 6 years was 84±4%, 80±4% and 75±5% vs 91±3%, 86±4% and 84±4% in the AH and BH group, respectively (p=0.21) (Fig. 2).

Eleven patients, 5 in the AH group and 6 in BH, underwent reoperation on the tricuspid valve during follow-up period. Reoperation occurred in 3 cases for recurrence of TR after isolated

repair and in 8 cases for late prothesis dysfunction. Freedom from reoperation at 1, 3, 6 years was 97±1%, 96±2% and 93±3% vs 98±2%, 98±2% and 95±9% in the AH and BH group, respectively (p=0.2).

However, 6-years composite cardiac event-free survival (cardiac death + reoperation) was 68±6% vs 81±4% in the AH and BH group respectively (p=0.12) (Fig. 3).

Stratifying the matched cohorts in four groups according to either AH or BH and to either repair or replacement (AH-TVReplacement vs AH-TVrepair vs BH-TVReplacement vs BH-TVrepair) and comparing long-term cardiac event-free survival between AH-TV replacement and BH-TV repair, statistical significance was reached (60±9 vs 86±5; p=0.024) (Table 3, Fig 4).

Adjusting curves for endocarditis and previous cardiac surgery, no differences were found between AH and BH, yet. Again, long-term cardiac event-free survival was significantly lower in AH-TV replacement subset compare to patients having BH-TV repair, even after the adjustment (p=0.043).

Comment

The tricuspid valve, which for a long time was referred to as the “forgotten valve”, has recently been intensively discussed in the cardiovascular community. Despite an increasing number of dedicated devices and treatment strategies, patient selection, surgical indication, correct timing and outcome prediction represent a matter of debate (14,15).

Isolated tricuspid operations are generally considered high-risk for perioperative adverse events with reduced long-term survival (16). Large follow-up data and multicenter experiences are scarce.

The role of surgery for isolated tricuspid disease was recently analyzed by Axtelli and coauthors (17) in a retrospective, propensity score-matched analysis of 3276 patients over 15

years: 62 comparable pairs (mean age 52 years) treated with surgery vs medical therapy (median follow-up of 2.6 years). The study did not show any benefit of surgery in terms of late survival, and surgery was not significantly associated with a better outcome in the multivariate analysis (HR 1.24, p=0.28). However, matched sample size was small and no data were reported regarding the surgical technique (AH or BH).

A recent paper on 95 patients from Hamandi and co-authors (18) reported an operative mortality of 3.2% with a rate of stroke occurred of 2.1% and acute renal failure of 5.3% (18). Comparing these data with our entire SUR-TRI population (n=406), mortality was slightly reduced in the Hamandi data (3.2% vs 5.4%) while rate of complications (Stroke: 2.1 vs 0.9% and kidney injury: 5.3% vs 4.6%) was in the same range. Main differences could be associated with the study design and volume of the patients enrolled.

The prognostic role of beating heart surgical treatment of the tricuspid pathology has been poorly investigated in the current literature.

Pfanmueller and coauthors reported a retrospective single-center analysis of 105 cases (mean age 61±15 years, 42% males, 63 with beating heart) (19). The authors reported an overall 30-day mortality rate of 8.6% (11.9% vs 6.3% in the AH and BH groups (p=0.1)) with a five-year survival rate of 66±9% vs 69±7% (p=0.9). The authors concluded that the two techniques showed no significant difference, and the BH approach was feasible with optimal echocardiographic results and low neurological complications. Importantly, the groups were not comparable in terms of age, previous cardiac surgery or etiology, and no matching was performed. Baraki et al reported the results of 92 consecutive patients (AH, n=44 vs BH, n=48), observing no difference in terms of the perioperative complication rate or 30-day mortality, with an increased reoperation rate in the BH group when compared with AH (p=0.039) and a trend of reduced late survival even not statistically significant (survival at 5 years AH:75% vs BH:54%, p=0.062) (20).

The present study reports the results of a 10-year retrospective dataset of 13 international

cardiac surgery units. Data from an entire cohort of 406 patients were propensity matched to obtain 129 pairs of comparable patients taking into account preoperative, intraoperative and echocardiographic features with the aim of comparing beating heart and cardioplegic arrest techniques. Our results showed a comparable 30-day mortality rate (6.2% vs 5.0 in the AH and BH groups, respectively (p=0.9)). However, a reduced rate of acute renal failure (3% vs 10%, p=0.02) and the complete absence of permanent neurological events (0 vs 1.6%, p=0.08) were recorded in the BH cohort. Rate of re-exploration for bleeding was high in the whole population with no differences between groups (BH:7.8% vs AH:10.8%, p=0.4) and related with right side heart disease and coagulopathy associated with chronic TR.

In accordance with previously published experience (19,20) we reported a similar 6-year rate of overall survival (BH: 78±5 vs AH: 67±6%, p = 0.18), cardiac death (BH: 84±4 vs AH: 75±5%, p = 0.21) and cardiac event-free survival rate (BH: 81±4 vs AH:68±6%; p=0.12) between AH and BH groups. Contrary to the not matched study from Baraki and colleagues (20), a trend of increased survival and freedom from reoperation in the beating heart patients was observed in our series (Figure 1-2-3-4).

Patients affected by tricuspid disease who undergo surgical correction frequently present with reduced RV function, and published data support the negative effect of CPB on RVF in arrested heart surgery (21,22). Rate of acute renal failure needing replacement therapy was higher in the AH population (10 vs 3%, p=0.02) and this data may negatively affect late survival.

We performed a subgroup analysis dividing the matched population in four sub-cohort (AH-TVReplacement vs AH-TVrepair vs BH-TVReplacement vs BH-TVrepair) and reported an increased survival and freedom from reoperation (p=0.024) going from a more physiologic approach with the combination of beating heart and tricuspid valve repair (BH-TVr) to a more “aggressive” technique of valve replacement and cardioplegic arrest (AH-TVR) (Table 3-figure 4). Survival benefit of valve tricuspid valve repair techniques is well known in

literature (16) and stated in the international guidelines. Anyhow, the combination of valve repair with a beating heart strategy resulted in this series in significantly improved long term results.

Results from the SUR-TRI study showed that beating heart strategies have promising late outcomes and should be considered when discussing the results of isolated tricuspid surgery. Surgical instruments that enable the delivery of annular sutures (23) or the performance of annular plication (24) are under investigation and may play a role in the future of surgical tricuspid therapy. Similarly, emerging of "off-pump and beating heart" transcatheter options for TR treatment are showing promising results in patients denied for surgery due to increased risk (4,25).

To the best of our knowledge, this was the largest published series involving isolated TV patients and analyzing results with a matched technique.

In conclusion, isolated tricuspid valve surgery performed with a beating heart strategy is a safe option, exhibited reduced perioperative adverse events, such as acute renal failure and stroke, and resulted in a trend of higher long-term event-free survival than the standard arrested heart technique. Combination of valve repair in a beating heart set-up exhibited better late results. Further analyses with larger cohort of patients are necessary.

Study limitations

Data collection was performed retrospectively with no on-site monitoring. Differences between participating centers in term of surgical technique, volume and timing for surgery were recorded and may alter results and conclusions. Indeed, surgical technique, surgical experience and approach to either repair/replacement or application of beating/arrested heart strategy was not controlled by a study protocol but completely associated to surgeon's decision as part of a retrospective analysis. Therefore, local attitudes may play a role in the observed results.

Propensity match technique was adopted to reduced differences. Anyhow, several parameters as quantification of right ventricular function and geometry or laboratory testing for liver and renal disease were not included in the model for elevated rate of missing data.

Although clinical follow-up data were complete, echocardiographic follow-up data were missing in 25% of patients. Therefore, we could not analyze recurrence of TR during follow-up. A prospective assessment of this rare cohort of patients is the main objective of the on-going SUR-TRI registry dataset. The number of patients enrolled is still limited, and a larger cohort would probably lead to statistically relevant differences in the observed outcomes.

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Table 1. *Baseline patient characteristics before and after matching*

	Entire Cohort (n=406)			***Propensity Matched Sample (n=258)***		
Variable	Arrested Heart (n=253)	Beating Heart (n=153)	*SMD*	Arrested Heart (n=129)	Beating Heart (n=129)	*SMD*
Age, year ± SD[a]	55 ± 16	57 ± 15	0.128	56 ± 15	58 ± 15	0.103
Male Sex, n (%)	113 (45)	68 (44)	-0.022	56 (43)	52 (40)	-0.026
Diabetes, n (%)	35 (14)	24 (16)	0.086	19 (15)	24 (19)	0.106
NYHA[b] III-IV, n (%)	123 (49)	76 (50)	0.021	64 (50)	66 (51)	0.031
Previous stroke, n (%)	14 (6)	8 (5)	0.017	10 (8)	8 (6)	-0.069
Dialysis, n (%)	5 (2)	8 (5)	-0.106	4 (3)	6 (5)	0.069
COPD, n (%)	39 (15)	15 (10)	-0.255	19 (15)	14 (11)	-0.196
Ejection fraction < 55, %	67 (27)	46 (30)	0.081	38 (30)	39 (30)	-0.016
Moderato/severe TR[c], n (%)	239 (95)	147 (96)	0.128	123 (95)	123 (95)	0.000
Previous cardiac surgery, n (%)	78 (31)	93 (61)	0.687	53 (41)	72 (56)	-0.301
Endocarditis, n (%)	88 (35)	19 (12)	-0.757	30 (23)	19 (15)	-0.258
EuroSCORE II, (%)	3 (1-5)	4 (2-7)	0.193	3 (2-6)*	4 (2-7)	0.075
Urgency/Emergency, n (%)	65 (23)	27 (17)	-0.208	(22)	26 (20)	-0.004
Median Sternotomy, n (%)	226 (89)	115 (75)	-0.547	108 (84)	102 (79)	-0.183
Repair (TVr), n (%)	135 (53)	59 (39)	-0.313	65 (50)	54 (42)	-0.175

**median value and quartiles*

Table 2. *Postoperative Features*

	Propensity Matched Sample		
Variables	Arrested Heart (n=129)	Beating Heart (n=129)	*P*
Length of stay, days	10 (7-19) **	13 (8-23)	0.07
PMK implantation, n (%)	12 (9.3)	15 (11.6)	0.68
Re-exploration for bleeding, n (%)	14 (10.9)	10 (7.8)	0.4
Acute Renal Failure*, n (%)	13 (10.1)	4 (3)	**0.02**
Blood Transfusion, n (%)	66 (51)	75 (58)	0.3
Stroke, n (%)	2 (1.6)	0 (0)	0.08
Atrial Fibrillation, n (%)	14 (10.9)	26 (20.2)	**0.04**
Pericardial Effusion, n (%)	6 (4.7)	8 (6.2)	0.8
Post Operative Ejection fraction, %	56 ± 9	57 ± 9	0.9
30-day mortality	8 (6.2)	7 (5)	1.0

*=needing dyalisis or hemofiltration ***median value and quartiles*

Table 3. *Six-Years outcomes according group stratification for repair and replacement technique in the arrested and beating heart technique*

	Arrested Heart (n=129)		***Beating Heart (n=129)***		
	TV repair (n=65)	TV replacement (n=64)	TV repair (n=54)	TV replacement (n=75)	*p-value (all)*
Survival	68 ± 8	66 ± 8	85 ± 6	72 ± 6	0.25*
Cardiac Survival	79 ± 6	70 ± 8	88 ± 5	82 ± 5	0.35*
Freedom form cardiac death and reoperation on TV	76 ± 7	60 ± 9	86 ± 5	78 ± 6	0.09§

**no statistical difference was found in pairwise comparison*

§ p-value BH-TV repair vs AH-Tv replacement was 0.024

Figure Legends

Figure 1. Survival of the propensity matched population (n=258). Overall survival of patients who received arrested heart (AH, blue line) surgery compared with the beating heart (BH, red line) technique. 95% CLs are plotted.

Figure 2. Freedom from cardiac death in the matched population comparing arrested heart (AH, blue line) surgery with the beating heart (BH, red line) technique. 95% CLs are plotted.

Figure 3. Freedom from composite end-points of late cardiac death and reintervention of the tricuspid valve, comparing arrested heart (AH, blue line) surgery with the beating heart (BH, red line) technique. 95% CLs are plotted.

Figure 4. Freedom from composite endpoints of late cardiac death and reintervention of the tricuspid valve, comparing AH+TV replacement (AH_TVR) vs AH+ TV repair (AH_TVr) vs BH + TV repair (BH_TVr) vs BH + TV replacement (AH_TVR).

Supplementary files

Supplemental Figure 1. Patients enrolled at each study site from 2008 up to 2019

Supplemental Figure 2. Common support shows good overlapping of the two strategies: beating heart (red) and arrested heart (green)

Supplemental Figure 3. Annual volume trend from 2008 up to 2019.

Supplemental Figure 4. Annual volume trend from 2008 up to 2019 comparing AH and BH strategy.

Supplemental Table 1. Amount of Procedures performed per center and technique used (Beating vs Arrested Heart)

Supplemental Table 2. Amount of Procedures performed per center and technique used (Repair vs Replacement)