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Steps Forward in Minimally Invasive Cardiac Surgery: 10-Year Experience**This is the author's manuscript**

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Steps forward in minimally invasive cardiac surgery: 10-year experience

Running Head. Minimally invasive cardiac surgery

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Abstract

Background: Minimally invasive cardiac surgery (MICS) has constantly evolved over the past years and new technologies have been introduced. Aims of this study are to analyze the evolution of our 10-year experience in MICS and to highlight outcomes in different spans of time.

Methods: Patients undergoing MICS for mitral valve and/or tricuspid valve and/or atrial septal defect or atrial masses from November 2005 to November 2015 were retrospectively analyzed. A comparative analysis was performed by identifying 2 groups: the control group (in the first time span of our experience) and the tailored group (patients that underwent surgery after a full preoperative anatomical evaluation with allocation to the proper setting).

Results: During the study period 971 patients underwent MICS. MICS procedures increase from 44% in 2006 to 96% in 2015. Subgroup analysis revealed a significant decrease in the rate of procedures performed with retrograde arterial perfusion (99.1% versus 91.7%, p<.0001), a significant increase in the rate of complex mitral valve procedures (22.4% versus 7.9%, p<.0001), and a significant decrease in the rate of stroke (from 5.2% to 1%, p<.001) in the tailored group. The logistic regression analysis showed that the tailored approach was a protective factor against neurological complications.

Conclusions: The present study shows the considerable and attractive results of our decision making process based on the tailored approach: the 10-year outcome analysis demonstrates a trend toward a progressive decrease in the overall rate of post-operative complications and a significant protective effect of the tailored approach on the occurrence of stroke.

Minimally invasive cardiac surgery (MICS) has constantly evolved over the past years; new technologies and surgical approaches have been introduced with the aim to create a patient-tailored approach [1-3]. Concomitantly, several centers all over the world have developed experience and confidence with the different settings available: retrograde arterial perfusion (RAP) through the femoral artery and trans-thoracic aortic clamp (TTC) (Scanlan International, Inc., Minneapolis, MN USA), RAP and endoaortic balloon (EAB) occlusion (Intralclude®, Edwards Lifesciences, Irvine, CA), RAP and fibrillating or beating heart, antegrade arterial perfusion (AAP) through the ascending aorta and EAB occlusion, and AAP through the axillary artery and TTC.

Remarkable early and long-term outcomes are, to date, reported in multicenter studies, metanalysis and reviews of the literature [4-7]; however, there is still debate regarding the role of arterial perfusion and aortic clamping on the occurrence of major neurological and vascular complications [3,4]. Moreover, it is well-known that one of the drawbacks of the minimal invasive approach is the demanding learning curve for the surgeon and for the whole team [8].

The MICS program started at the University of Turin—Cardiothoracic Department—in 2005. Since 2009, the *tailoring* decision-making process has been introduced with the mean to reduce the rate of peri-operative complications and to reach the best possible clinical outcome [3]: a preoperative vascular screening for all the patients eligible for MICS has been introduced, and all the MICS arterial perfusion and aortic clamping settings available have been taken into consideration in the pre-operative surgical planning.

Aims of this study are to analyze the evolution of our institutional 10-year experience in MICS and to highlight outcomes in different spans of time.

MATERIAL and METHODS

From November 2005 to November 2015, 988 consecutive patients with diagnosis of severe mitral valve (MV) disease, and/or severe tricuspid valve disease, and/or atrial septal defect, or atrial masses were enrolled for MICS at our Department. Immediate intraoperative conversion to median sternotomy was required in 17 out of 988 patients (1.7%) (Figure 1). Causes of conversion were related to extensive lung adhesions in 14 cases, and to peripheral vascular complications

before cardiopulmonary bypass onset in 3 cases. These patients were not considered in the main statistical analysis.

Right mini-thoracotomy approach for MICS used in our Department has been previously described [2,3,9,10]. Since April 2009, MICS patients started to be screened preoperatively for adequate vascular access either by aorto-iliac-femoral angiography at the time of cardiac catheterization or by computed tomography angiogram (the tailored group). In the same period we gained all the MICS arterial perfusion and aortic clamping settings available. Therefore, after a full preoperative work-up based upon clinical history and anatomy, each patient started to be allocated to the most appropriate approach: in the case of previous cardiac surgery procedures the RAP with EAB setting was used mostly; in the case of dilated ascending aorta (diameter>40mm), RAP with TTC was predominantly used; in the case of tortuous and atheromatous aorto-iliac-femoral vessels, AAP through the ascending aorta and EAB or AAP through the axillary artery and TTC were preferred [2,3]. The selection of one setting in respect to the others was patient orientated and independent from the surgeon's learning curve.

During the first part of the study period, all the procedures were performed by one surgeon, during the second part 2 young surgeons started to performed MICS at our Department.

Patient population during the study period is shown in Figure 1. Simple MV repair was defined as MV anuloplasty and posterior leaflet resection; complex MV repair was defined as MV anuloplasty and anterior/bileaflets repair or posterior leaflet repair with chords.

Statistical Analysis

Analysis was performed retrospectively for the 10-year period. For continuous variables data were represented with mean and standard deviation or with median and interquartile range; for categorical variables data were represented with frequency and percentage. Sequential probability cumulative sum (CUSUM) failure analysis, was used as figure of the overall 30-day mortality rate.

Further comparative analysis was performed by identifying 2 consecutive study periods: from November 2005 to March 2009 and from April 2009 to November 2015. Comparison for outcomes between the 2 groups was assessed by Chi-square or Fisher test for categorical variables and by

Mann-Whitney or t test for continuous variables. Results of the logistic regression model were expressed with odds ratio (OR) and with a 95% confidence interval (CI). All tests were two-tailed, and $p < .05$ was considered statistically significant. Statistical analyses were conducted using SAS software package (version 9.3, SAS Institute, Cary, NC).

RESULTS

During the study period, 971 patients underwent MICS at our Department; in the same period 384 patients with comparable diagnosis underwent surgery through standard median sternotomy (Figure 1).

Figure 2 shows the trend of the procedures performed through the minimally invasive approach and through the standard sternotomy approach over the 10-year study period: respectively from 44% (68 out of 153) in 2006 to 95% in 2015 (128 out of 135) for the MICS group and from 56% in 2006 (85 out of 153) to 5% in 2015 (7 out of 135) for the sternotomy group.

Overall MICS preoperative patients characteristics and comorbidities are listed in Table 1; operative data and post-operative outcomes are reported in Table 2. Figure 3 shows the arterial cannulation strategies and aortic clamping techniques over the study period; overall, RAP with EAB collected 567 patients (58.4%), RAP with TTC collected 294 patients (30.3%), AAP with EAB collected 65 patients (6.7%), and 45 patients underwent beating/fibrillating heart surgery (4.6%). MV surgery was performed in 847 cases (87.2%); of these, 474 cases were MV repairs (56%) and 373 cases were MV or mitral prosthesis replacements (44%). Figure 4 shows the evolution of the degenerative MV surgery over the study period. Associated MV procedures were tricuspid valve surgeries in 104 out of 847 cases (12.3%), and atrial septal defect or patent foramen ovale closures in 70 out of 847 cases (8.3%). Isolated tricuspid valve surgery was performed in 52 cases (5.4%), isolated atrial septal defect closure was performed in 45 cases (4.6%), and atrial masses exeresis in 25 cases (2.6%). Main MICS-related complications during the study period are reported in Table 2. The risk-adjusted CUSUM failure curve for the entire cohort of patients is shown in Figure 5.

Apart from age (patients in the control group were younger) and previous cardiac surgery procedures (higher rate of redo in the control group), there were no significant differences in patients characteristics between the control and tailored groups at baseline (Table 1). Analysis of

the consecutive study periods revealed a significant increase in the rate of complex MV procedures performed in the tailored group (22.4% versus 7.9% in the control group, $p<.0001$), and a significant decrease in the rate of procedures performed with RAP in the same group (91.7% versus 99.1% in the control group, $p<.0001$). Particularly, the rate of RAP and EAB significantly decreased in the tailored group, while the rate of procedures performed with RAP and TTC, and with AAP and EAB in the same group significantly increased ($p<.001$). Cardiopulmonary bypass and aortic clamping times were longer in the tailored group. A significant decrease in the rate of stroke (from 5.2% to 1%, $p<.001$) and a significant increase in the rate of re-exploration for bleeding (from 1.9% to 4.9%, $p=.051$) were recorded in the tailored group (Table 2). Twenty-two out of 38 patients re-explorated for bleeding in the tailored group underwent surgery through RAP and TTC (57.9%); of these, 1 patient required reoperation for bleeding at the cardioplegia cannula insertion site; 11 patients required reoperation for bleeding from the chest wall ports; in the other cases no active bleeding was reported.

Logistic regression analysis showed that the tailored approach is a protective factor for stroke (adjusted OR: .240; 95% CI .094 to .619). No influence of the tailored approach on 30-day mortality was highlighted (Table 3).

COMMENT

Over the last 20 years, MICS has rapidly evolved due to the development of strategies involving arterial and venous cannulation, aortic clamping and myocardial preservation [1,2]. Several settings have been described and have become routine in the surgical practice of centers all over the world; however, there is still debate in the literature regarding their role on the occurrence of major neurological and vascular complications [3,4,11].

This study analyzes the evolution of our 10-year institutional experience in MICS, and highlights clinical and surgical practice changes adopted with the mean to reduce the rate of MICS-related complications. Comparison between 2 consecutive study periods shows improved post-operative outcomes in the tailored group; logistic regression analysis proved that the tailored approach is able to reduce post-operative rate of major neurological complications.

The consecutive study periods analysis shows a stable increase in the adoption of the minimal invasive approach and a slowly decrease in the rate of procedures performed through standard sternotomy at our Department (Figure 2). The twist point (deepest increase in MICS practice and deepest decrease in standard sternotomy approach) is located in 2009, when the new settings available allowed us to extend the MICS program also to patients before not eligible, such as patients with severe peripheral vascular disease. Particularly valuable for this subgroup of high risk patients was the introduction of the AAP through the ascending aorta with EAB because it allowed us to avoid RAP and retrograde balloon manipulation in atherosomatous arteries; despite the fact that the production of this cannula has been suspended for regulatory reasons in 2014, our experience underlines that it is definitely a useful and safe tool to adopt in order to extend MICS also in patients with peripheral vasculopathy [2]. After the cannula withdrawal, patients with severe peripheral disease in the present study, underwent MICS with AAP through the axillary artery and TTC. Another reason for the increased MICS practice since 2009, was that, after a first phase of learning curve, also patients requiring more demanding surgical procedures (i.e. in the case of MV infective endocarditis) started to be taken into consideration for the minimal invasive approach [12].

The main step forward during the study period is definitely related to the MICS techniques for arterial perfusion and aortic clamping (Figure 3). During the first time span of our experience the setting of choice was the EAB with RAP (91% of cases in the first 3-year period). Subsequently, with the growing skill of the team and the evidences in the literature, our practice was critically reevaluated and shifted from a standard setting toward an approach tailored to the specific patient [3,4]. From 2009, all the modes of arterial perfusion and aortic clamping available were taken into consideration and adapted to the patient; Figure 3 shows a comparable distribution of the different types of setting since 2009. Our choice was not to replace the peripheral arterial cannulation by a central approach, as previously reported by other authors [1,13], but to determine the finest setting for the patient. This decision making process has been supported by an algorithm that, taking into consideration patient anatomical and clinical details (previous cardiac surgery, aorto-iliac-femoral vessels disease or high tortuosity, ascending aorta dilation), helps the surgeon to address the

patient toward a specific setting (RAP with EAB, RAP with TTC, direct ascending aorta cannulation with EAB, or axillary artery cannulation with TTC) [2].

When looking at the subgroup of patients without peripheral vascular disease, the setting of choice in the present cohort of patients was the RAP with EAB. This can be explained bearing in mind that this setting doesn't require to open the pericardium extensively to get a full exposure of all the ascending aorta, it doesn't require to perform a purse-string and to place a cardioplegia/vent needle into the ascending aorta, and it doesn't require to get a further port in the first intercostals space to set the aortic cannula or the aortic clamp, consequently it requires less surgical dissection with a lower risk of bleeding. The higher adoption of the TTC setting, according to the tailoring strategy in the second time span of the study period, can explain the higher rate of re-exploration for bleeding in this subgroup of patients [14]. Moreover in this period two young surgeons started to join the MICS program at our Department; therefore we have to consider also an higher rate of complications related to the beginning of the learning curve.

Cardiopulmonary bypass and clamping times were longer in the tailored era. Longer clamping times in the tailored group can be first of all explained with the higher rate of complex MV procedures performed; longer surgical times can also depend on the learning curve of the new surgeons joining the MICS program in this period.

It is well known that one of the drawbacks of MICS is the challenging learning curve that is potentially capable to prevent the patient from the benefits of a minimal access approach [8]. Therefore the MICS adoption demands a close outcome analysis, especially during the initial phase of the application. CUSUM curve represents one of the best risk adjustment model of mortality for this purpose. Indeed, it has the advantage of taking into account time and predicted risk of failure (in this case logistic EuroSCORE) [15]; the resulting chart runs parallel to the x axis when the complication rate is as expected, turns upward when more complications than expected occur, and turns downward when a favorably low complication rate is observed [8]. CUSUM analysis of our 10-year experience shows that, after a slight accumulation of failures in the early years (from 2006 to 2010), outcome became consistently downward (ie, fewer deaths than expected). From 2012 to 2013, however, the complication rate started to rise again, and this

cluster of failure prompted a review: this time point is congruent with a number of new surgeons joining the MICS program at our Department.

To assess the evolution of the learning curve over the study period, a subgroup of patients with diagnosis of degenerative MV disease was taken into consideration. Figure 4 shows a progressive increase in the rate of complex MV repair over the 10-year period. Moreover, when looking at the simple MV repair line, we can see a dramatic decrease in the rate of procedures performed since 2012. This is expression of another of the main changes in philosophy and techniques of our Department during the study period: over the years, surgery on the MV has switched toward a “respect rather than resect” approach [16].

The present study clearly demonstrates the considerable and attractive results of our decision making process based on the tailored approach: despite a comparative rate of comorbidities and surgical risk factors over the 10-year period, the outcome analysis shows a trend toward a progressive decrease in the overall rate of MICS-related complications and a significant protective effect of the tailored approach on the occurrence of major neurological complications. It is known in the literature that longer CPB and clamping times are well-defined risk factors for neurological complications during cardiac surgery; this is not consistent with the results of the present study and this can be explained considering that, even with longer surgical times for more complex surgical procedures, the experience gained through the study period has allowed our team to reduce the overall rate of complications, including the rate of stroke.

Limitations

This study has several limitations that are important to consider when interpreting the main findings. First, it is based on a retrospective analysis. Secondly, the time span of data collection is long and can cause some bias (new technology, new surgeons joining the MICS program). In addition, it figures only a single-center experience, which may limit its generalizability to other centers.

Conclusions

The awareness of the surgeon should be addressed toward a proper selection of the patient and allocation to the safest approach, more than toward the identification of the ideal setting to apply for all the patients.

To improve safety and predictability of the operation, patients undergoing minimal invasive surgery have to be screened for vascular disease. Moreover, to our knowledge, the vast majority of centers in the world are confident with only one of the minimal access approaches that have been proposed for cardiac surgery, and there are very few centers that tailor the strategy on the patient's characteristics. Actually, we believe that the latter is the best policy for a program of MICS: all the setting available must be part of a safe minimal invasive program and surgeons dedicated to it must be confident with all of them in order to tailor different perfusion and aortic clamping techniques to the patient.

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TABLE 1. Overall and subgroups patients characteristics and comorbidities.

	Overall (n=971)	Control group (n=210)	Tailored group (n=761)	p-value
Age, mean (SD)	62.5 (4.1)	58.8 (14.9)	63.6 (13.7)	<.0001
Male gender, n (%)	503 (51.8)	107 (51.0)	396 (52.0)	.781
BMI, mean (SD)	24.5 (4.4)	24.3 (3.8)	24.6 (4.5)	.866
Hypertension, n (%)	552 (56.9)	124 (41.0)	428 (56.3)	.479
Renal failure, n (%)	84 (8.7)	15 (7.1)	69 (9.1)	.377
Pre-op creatinine, mean (SD)	1.1 (0.7)	1.1 (0.6)	1.1 (0.7)	.323
COPD, n (%)	71 (7.3)	17 (8.1)	54 (7.1)	.622
Diabetes, n (%)	94 (9.7)	14 (6.7)	80 (10.5)	.095
Peripheral vasculopathy, n (%)	25 (2.6)	5 (2.4)	20 (2.6)	.841
Atrial fibrillation, n (%)	361 (37.2)	72 (34.3)	289 (38.0)	.327
Pre-op neurological deficit, n (%)	80 (8.3)	22 (10.5)	58 (7.7)	.188
Logistic EuroSCORE I, mean (SD)	7.6 (9.7)	4.0 (2.1)	7.7 (9.9)	.210
Previous cardiac surgery, n (%)	251 (25.9)	75 (35.7)	176 (23.1)	<.001
Ejection fraction, mean (SD)	59.5 (10.8)	58.3 (12)	59.7 (10.4)	.370

SD: standard deviation; BMI: body mass index; pre-op: pre-operative; COPD: chronic obstructive pulmonary disease; EuroSCORE: European system for cardiac operative risk evaluation.

TABLE 2. Overall and subgroups patients operative data and postoperative outcomes.

	Overall (n=971)	Control group (n=210)	Tailored group (n=761)	p-value
MV surgery, n (%)	847 (87.2)	178 (84.8)	669 (87.9)	<.0001
Simple MV repair, n (%)	310 (36.6)	73 (41.0)	237 (35.4)	
Complex MV repair, n (%)	164 (19.4)	14 (7.9)	150 (22.4)	
MV/MP replacement, n (%)	373 (44.0)	91 (51.1)	282 (42.2)	
TV surgery, n (%)	156 (16.1)	35 (16.7)	121 (15.9)	.789
ASD surgery, n (%)	115 (11.8)	33 (15.7)	82 (10.8)	.049
Atrial masses exeresis, n (%)	25 (2.6)	3 (1.4)	22 (2.9)	.236
AF crio-ablation, n (%)	110 (11.3)	17 (8.1)	93 (12.2)	.094
RAP, n (%)	906 (93.3)	208 (99.1)	698 (91.7)	<.0001
RAP+EAB, n (%)	567 (58.4)	191 (90.9)	376 (49.4)	
RAP+TTC, n (%)	294 (30.3)	6 (2.9)	288 (37.8)	<.0001
AAP+EAB, n (%)	65 (6.7)	2 (0.9)	63 (8.3)	
CPB, min, median (Q1-Q3)	120 (100.5-146)	104.5 (86.5-127)	125 (105-150.5)	<.0001
Ao clamp, min, median (Q1-Q3)	87 (70-105)	75 (58-87)	91 (74-108)	<.0001
Techniques switch, n (%)	16 (1.6)	5 (2.4)	11 (1.4)	.341
Ao dissection, n (%)	5 (0.5)	3 (1.4)	2 (0.3)	.071
Conversion to sternotomy, n %)	8 (0.8)	4 (1.9)	4 (0.5)	.072
ICU stay, days, median (Q1-Q3)	1 (1-2)	1 (1.2)	1 (1-2)	.212
Re-exploration, n (%)	42 (4.3)	4 (1.9)	38 (4.9)	.051
Stroke, n (%)	19 (2)	11 (5.2)	8 (1)	<0.001
Hemodialysis, n (%)	28 (2.9)	8 (3.8)	20 (2.6)	.359
Hospital stay, median (Q1-Q3)	7 (6-10)	7 (6-10)	7 (6-10)	.809
30-day mortality, n (%)	25 (2.6)	8 (3.8)	17 (2.2)	.202

MV: mitral valve; MP: mitral prosthesis; TV: tricuspid valve; ASD: atrial septal defect; AF: atrial fibrillation; RAP: retrograde arterial perfusion; EAB: endoaortic balloon; TTC: trans-thoracic aortic clamping; AAP: antegrade arterial perfusion; CPB: cardio-pulmonary by-pass; Ao: aortic; ICU: Intensive care unit.

TABLE 3. OR estimate for outcomes of the tailored approach.

	OR (CI)	Adjusted OR (CI)
Stroke*	.192 (.076; .484)	.240 (.094; .619)
30-day mortality**	.577 (.245; 1.356)	.528 (.182; 1.535)

OR: odd ratio; IC: confidence interval.

* Adjusted for EuroSCORE I, ejection fraction, preoperative neurological events, and previous cardiac surgery procedures.

** Adjusted for age, EuroSCORE I, ejection fraction, diabetes, preoperative kidney dysfunction, preoperative neurological events, chronic obstructive pulmonary disease, peripheral vasculopathy, and previous cardiac surgery procedures.

FIGURES

Figure 1: Patient population during the study period.

Figure legend: CPB: cardiopulmonary bypass; MICS: minimal invasive cardiac surgery.

Figure 2: Overall cardiac surgery procedures over the study period.

Figure legend: MICS: minimal invasive cardiac surgery.

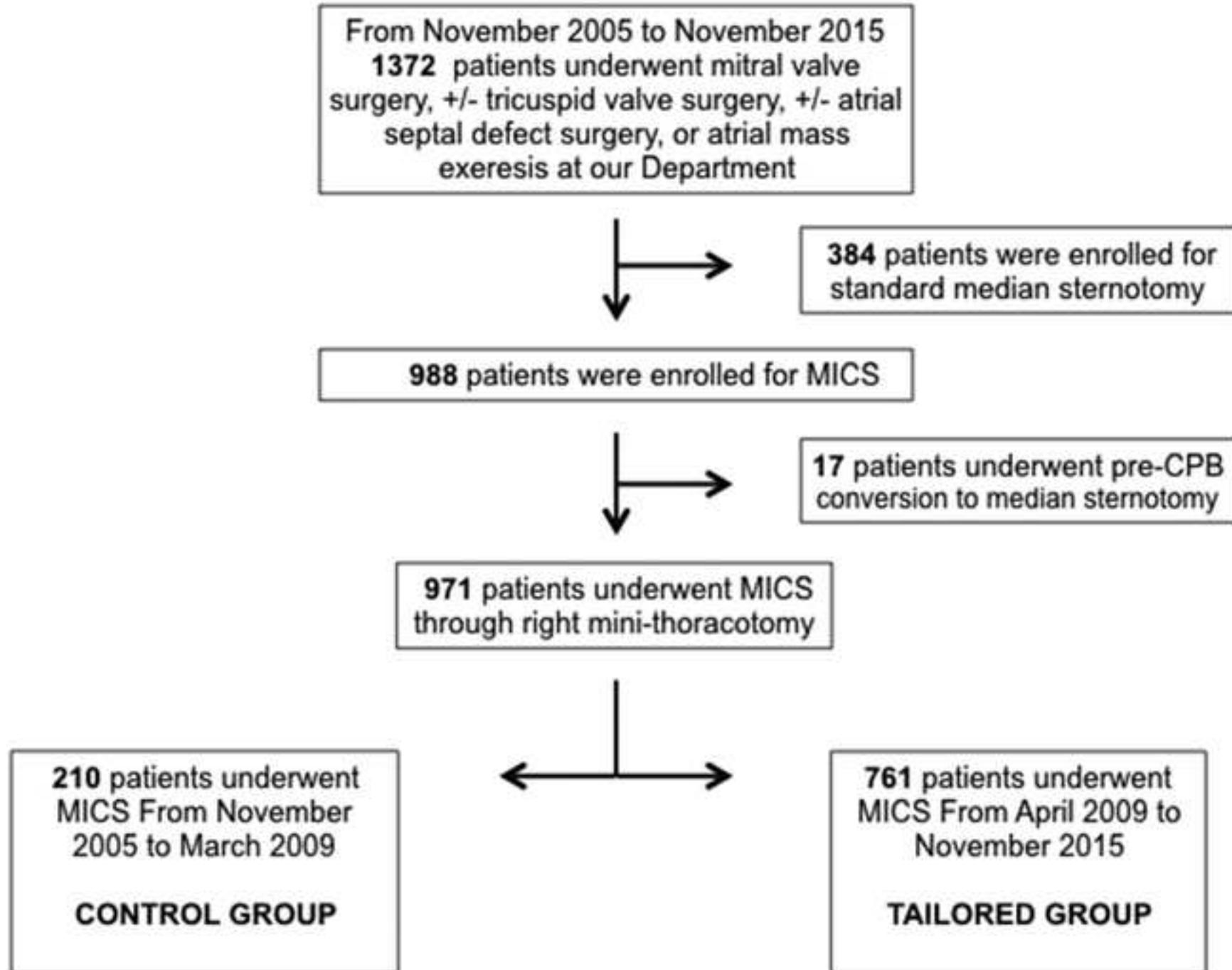
Figure 3: Evolution of arterial perfusion and aortic clamping techniques.

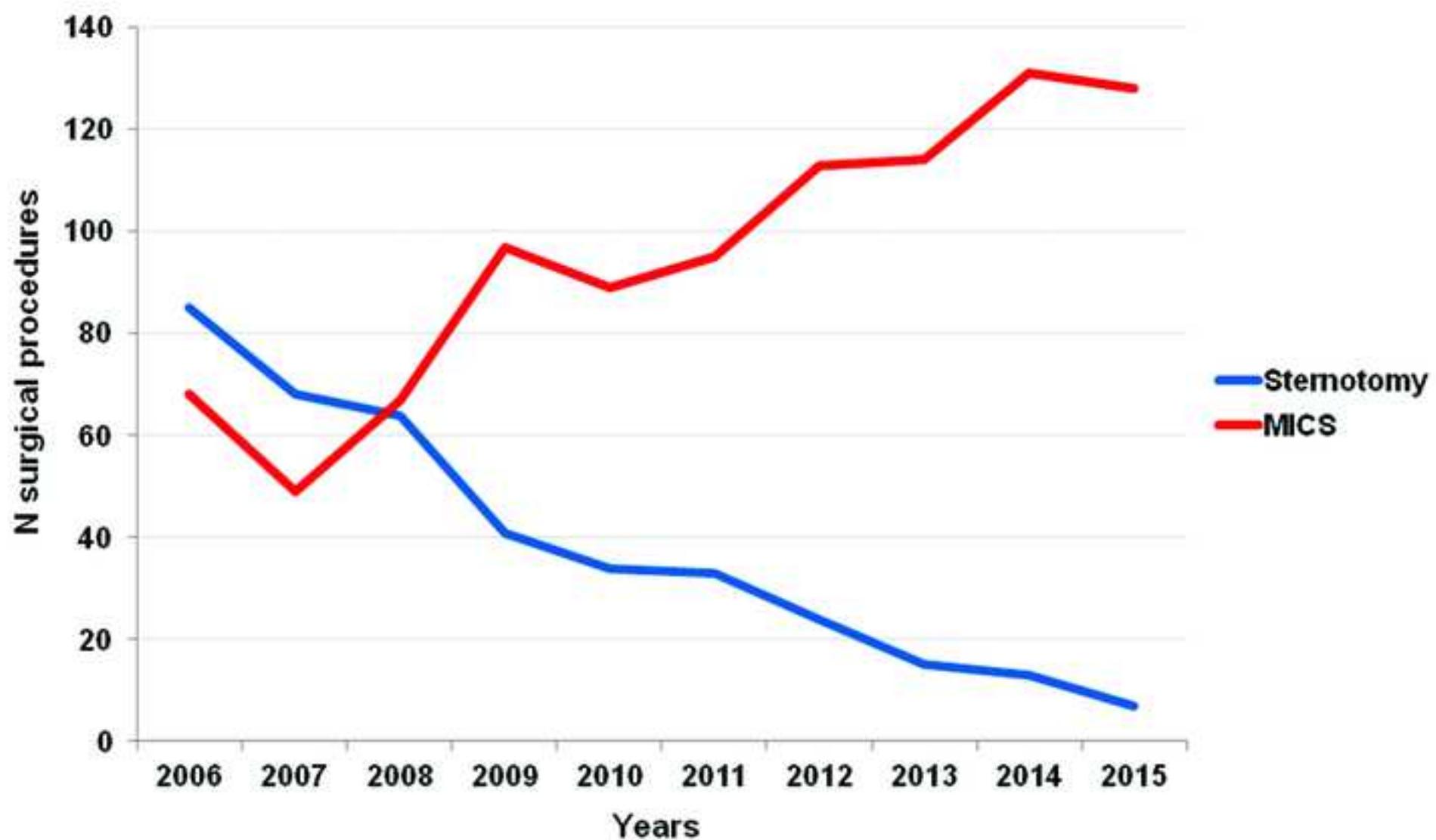
Figure legend: RAP: retrograde arterial perfusion; TTC: trans-thoracic aortic clamp; EAB: endoaortic balloon; AAP: antegrade arterial perfusion.

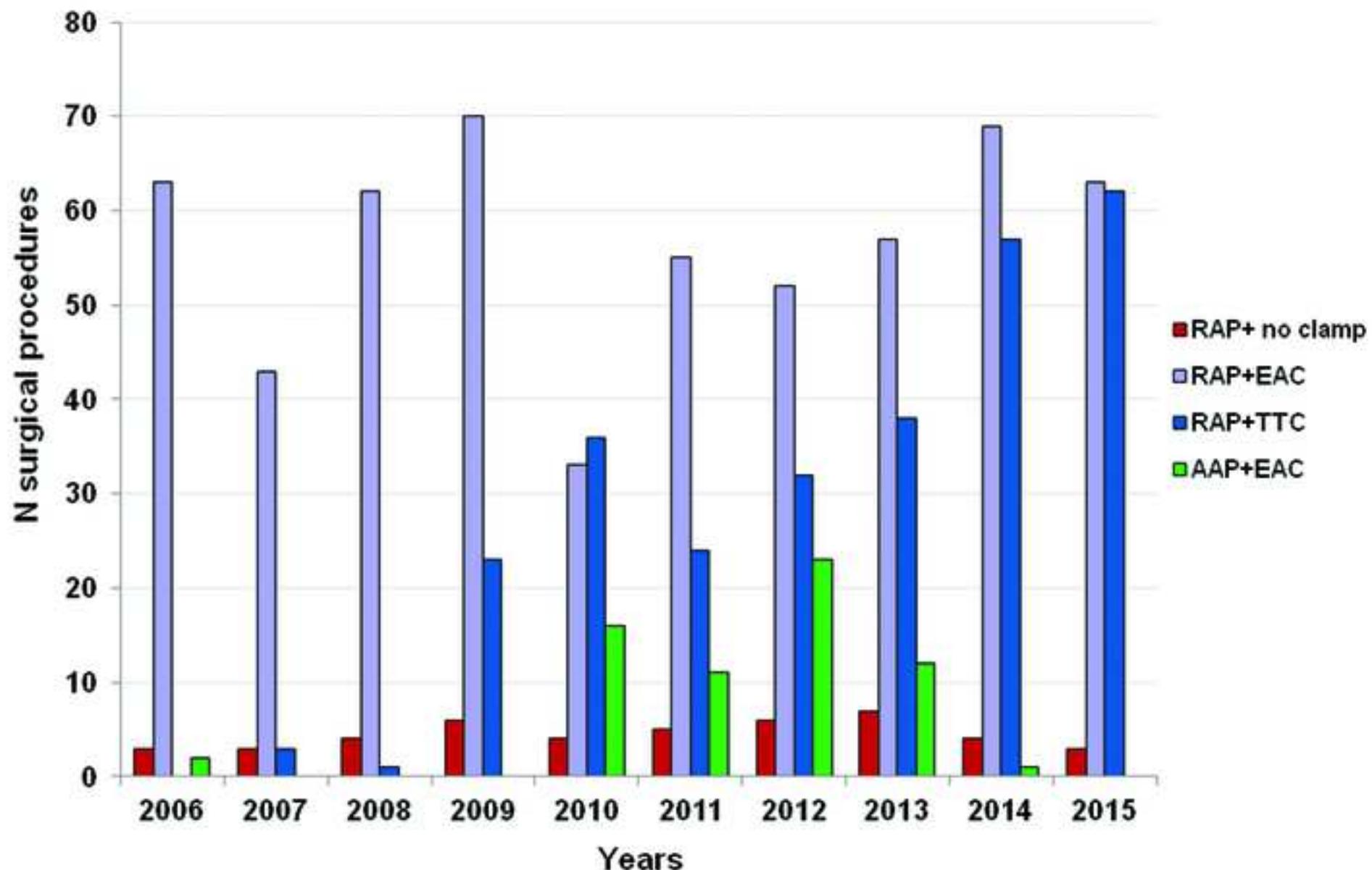
Figure 4: Overall mitral valve surgery procedures.

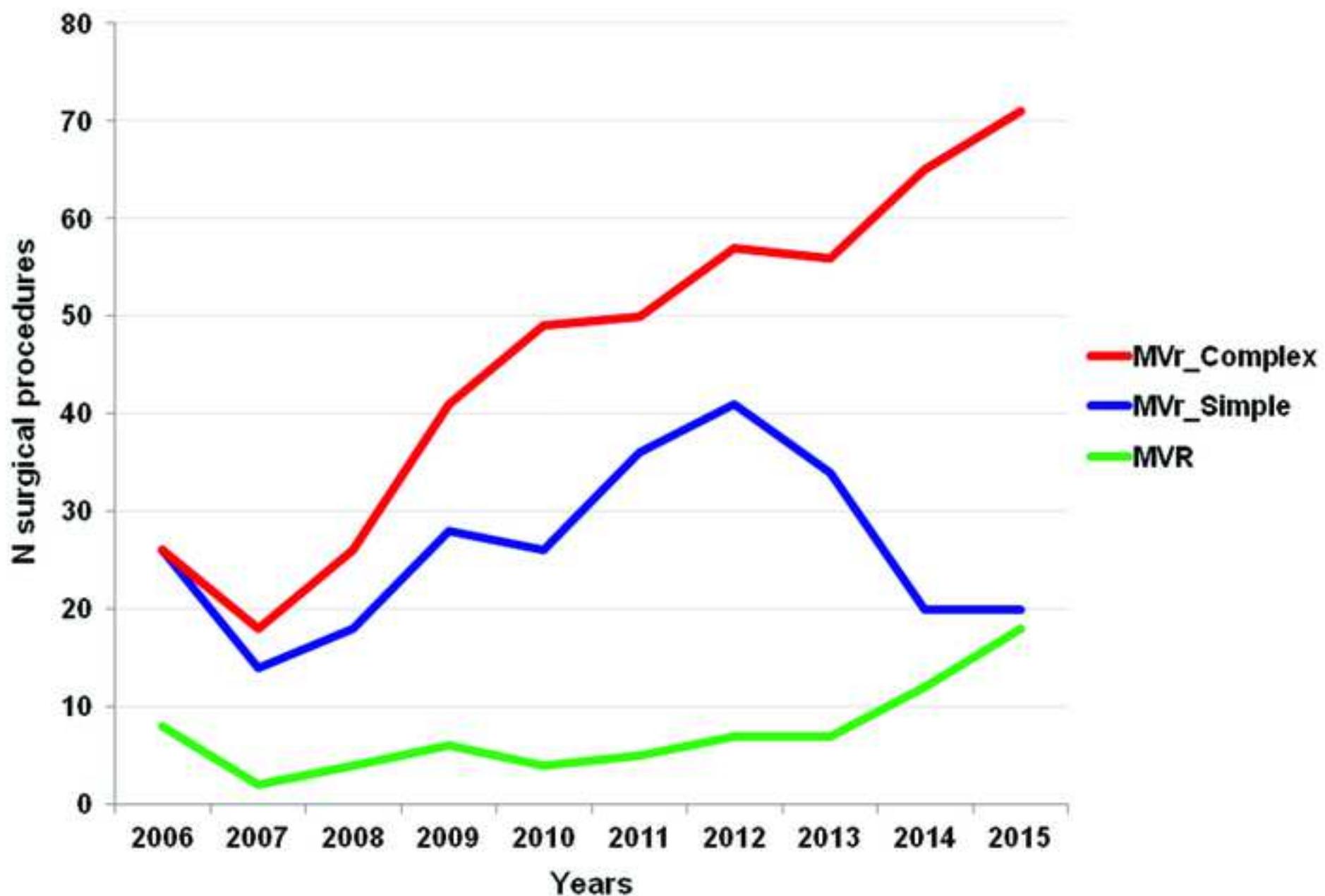
Figure legend: MVR: mitral valve repair; MVR: mitral valve replacement.

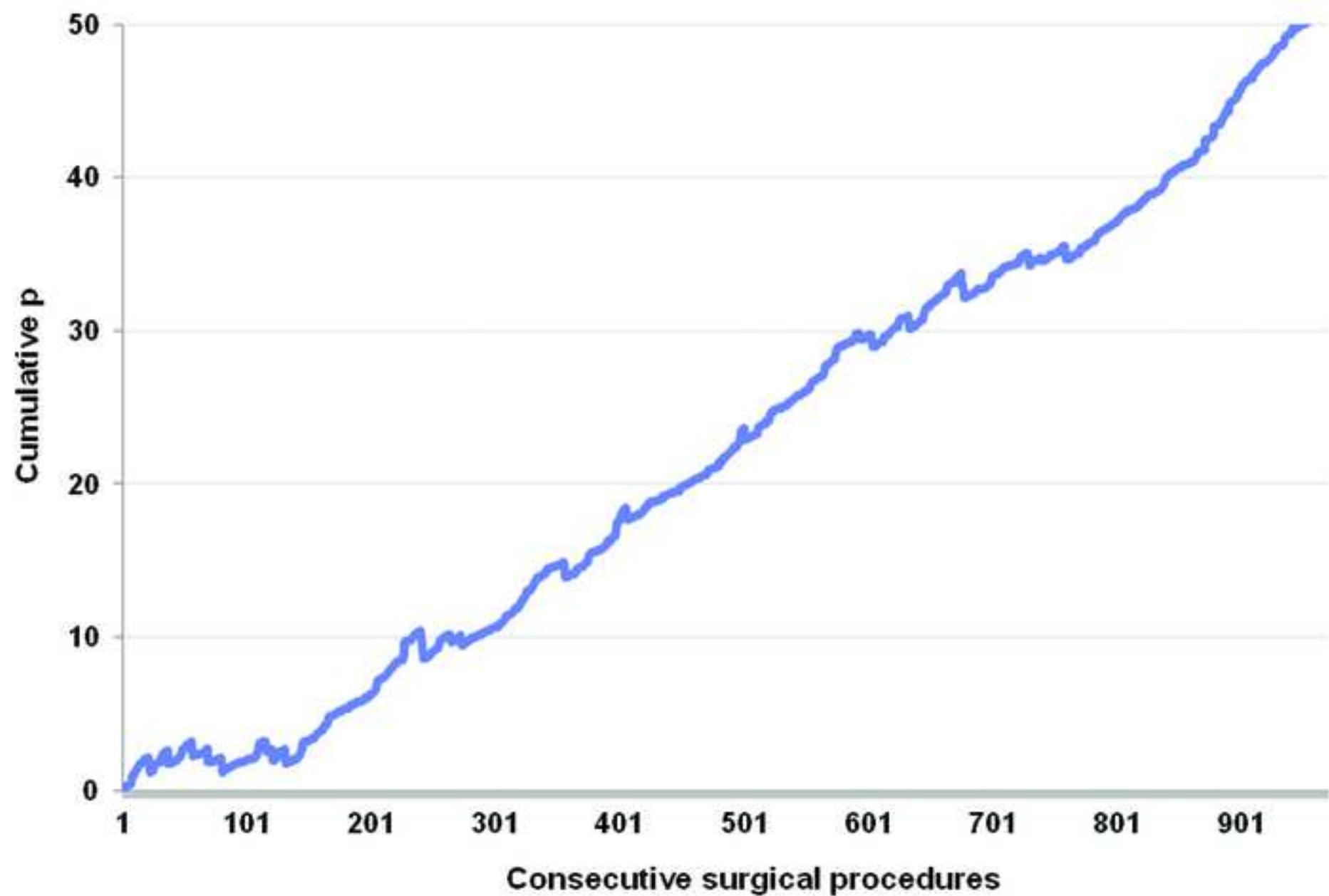
Figure 5: 30-day mortality sequential probability cumulative sum failure analysis.











The Annals of Thoracic Surgery - Original Manuscript

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Running Head. Minimally invasive cardiac surgery

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Abstract

Background: Minimally invasive cardiac surgery (MICS) has constantly evolved over the past years and new technologies have been introduced. Aims of this study are to analyze the evolution of our 10-year experience in MICS and to highlight outcomes in different spans of time.

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Methods: Patients undergoing MICS for mitral valve and/or tricuspid valve and/or atrial septal defect or atrial masses from November 2005 to November 2015 were retrospectively analyzed. A comparative analysis was performed by identifying 2 groups: the control group (in the first time span of our experience) and the tailored group (patients that underwent surgery after a full preoperative anatomical evaluation with allocation to the proper setting).

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Results: During the study period 971 patients underwent MICS. MICS procedures increase from 44% in 2006 to 96% in 2015. Subgroup analysis revealed a significant decrease in the rate of procedures performed with retrograde arterial perfusion (99.1% versus 91.7%, p<.0001), a significant increase in the rate of complex mitral valve procedures (22.4% versus 7.9%, p<.0001), and a significant decrease in the rate of stroke (from 5.2% to 1%, p<.001) in the tailored group. The logistic regression analysis showed that the tailored approach was a protective factor against neurological complications.

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Conclusions: The present study shows the considerable and attractive results of our decision making process based on the tailored approach: the 10-year outcome analysis demonstrates a trend toward a progressive decrease in the overall rate of post-operative complications and a significant protective effect of the tailored approach on the occurrence of stroke.

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INTRODUCTION

Minimally invasive cardiac surgery (MICS) has constantly evolved over the past years; new technologies and surgical approaches have been introduced with the aim to create a patient-tailored approach [1-3]. Concomitantly, several centers all over the world have developed

experience and confidence with the different settings available: retrograde arterial perfusion (RAP) through the femoral artery and trans-thoracic aortic clamp (TTC) (Scanlan International, Inc., Minneapolis, MN USA), RAP and endoaortic balloon (EAB) occlusion (Intralude®, Edwards Lifesciences, Irvine, CA), RAP and fibrillating or beating heart, antegrade arterial perfusion (AAP) through the ascending aorta and EAB occlusion, and AAP through the axillary artery and TTC.

Remarkable early and long-term outcomes are, to date, reported in multicenter studies, metanalysis and reviews of the literature [4-7]; however, there is still debate regarding the role of arterial perfusion and aortic clamping on the occurrence of major neurological and vascular complications [3,4]. Moreover, it is well-known that one of the drawbacks of the minimal invasive approach is the demanding learning curve for the surgeon and for the whole team [8].

The MICS program started at the University of Turin—Cardiothoracic Department—in 2005. Since 2009, the *tailoring* decision-making process has been introduced with the mean to reduce the rate of peri-operative complications and to reach the best possible clinical outcome [3]: a preoperative vascular screening for all the patients eligible for MICS has been introduced, and all the MICS arterial perfusion and aortic clamping settings available have been taken into consideration in the pre-operative surgical planning.

Aims of this study are to analyze the evolution of our institutional 10-year experience in MICS and to highlight outcomes in different spans of time.

MATERIAL and METHODS

From November 2005 to November 2015, 988 consecutive patients with diagnosis of severe mitral valve (MV) disease, and/or severe tricuspid valve disease, and/or atrial septal defect, or atrial masses were enrolled for MICS at our Department. Immediate intraoperative conversion to median sternotomy was required in 17 out of 988 patients (1.7%) (Figure 1). Causes of conversion were related to extensive lung adhesions in 14 cases, and to peripheral vascular complications before cardiopulmonary bypass onset in 3 cases. These patients were not considered in the main statistical analysis.

Right mini-thoracotomy approach for MICS used in our Department has been previously described [2,3,9,10]. Since April 2009, MICS patients started to be screened preoperatively for adequate vascular access either by aorto-iliac-femoral angiography at the time of cardiac catheterization or by computed tomography angiogram (the tailored group). In the same period we gained all the MICS arterial perfusion and aortic clamping settings available. Therefore, after a full preoperative work-up based upon clinical history and anatomy, each patient started to be allocated to the most appropriate approach: in the case of previous cardiac surgery procedures the RAP with EAB setting was used mostly; in the case of dilated ascending aorta (diameter>40mm), RAP with TTC was predominantly used; in the case of tortuous and atheromatous aorto-iliac-femoral vessels, AAP through the ascending aorta and EAB or AAP through the axillary artery and TTC were preferred [2,3]. The selection of one setting in respect to the others was patient orientated and independent from the surgeon's learning curve.

During the first part of the study period, all the procedures were performed by one surgeon, during the second part 2 young surgeons started to performed MICS at our Department.

Patient population during the study period is shown in Figure 1. Simple MV repair was defined as MV anuloplasty and posterior leaflet resection; complex MV repair was defined as MV anuloplasty and anterior/bileaflets repair or posterior leaflet repair with chords.

Statistical Analysis

Analysis was performed retrospectively for the 10-year period. For continuous variables data were represented with mean and standard deviation or with median and interquartile range; for categorical variables data were represented with frequency and percentage. Sequential probability cumulative sum (CUSUM) failure analysis, was used as figure of the overall 30-day mortality rate.

Further comparative analysis was performed by identifying 2 consecutive study periods: from November 2005 to March 2009 and from April 2009 to November 2015. Comparison for outcomes between the 2 groups was assessed by Chi-square or Fisher test for categorical variables and by Mann-Whitney or t test for continuous variables. Results of the logistic regression model were expressed with odds ratio (OR) and with a 95% confidence interval (CI). All tests were two-tailed,

and $p < .05$ was considered statistically significant. Statistical analyses were conducted using SAS software package (version 9.3, SAS Institute, Cary, NC).

RESULTS

During the study period, 971 patients underwent MICS at our Department; in the same period 384 patients with comparable diagnosis underwent surgery through standard median sternotomy (Figure 1).

Figure 2 shows the trend of the procedures performed through the minimally invasive approach and through the standard sternotomy approach over the 10-year study period: respectively from 44% (68 out of 153) in 2006 to 95% in 2015 (128 out of 135) for the MICS group and from 56% in 2006 (85 out of 153) to 5% in 2015 (7 out of 135) for the sternotomy group.

Overall MICS preoperative patients characteristics and comorbidities are listed in Table 1; operative data and post-operative outcomes are reported in Table 2. Figure 3 shows the arterial cannulation strategies and aortic clamping techniques over the study period; overall, RAP with EAB collected 567 patients (58.4%), RAP with TTC collected 294 patients (30.3%), AAP with EAB collected 65 patients (6.7%), and 45 patients underwent beating/fibrillating heart surgery (4.6%). MV surgery was performed in 847 cases (87.2%); of these, 474 cases were MV repairs (56%) and 373 cases were MV or mitral prosthesis replacements (44%). Figure 4 shows the evolution of the degenerative MV surgery over the study period. Associated MV procedures were tricuspid valve surgeries in 104 out of 847 cases (12.3%), and atrial septal defect or patent foramen ovale closures in 70 out of 847 cases (8.3%). Isolated tricuspid valve surgery was performed in 52 cases (5.4%), isolated atrial septal defect closure was performed in 45 cases (4.6%), and atrial masses excision in 25 cases (2.6%). Main MICS-related complications during the study period are reported in Table 2. The risk-adjusted CUSUM failure curve for the entire cohort of patients is shown in Figure 5.

Apart from age (patients in the control group were younger) and previous cardiac surgery procedures (higher rate of redo in the control group), there were no significant differences in patients characteristics between the control and tailored groups at baseline (Table 1). Analysis of the consecutive study periods revealed a significant increase in the rate of complex MV procedures performed in the tailored group (22.4% versus 7.9% in the control group, $p < .0001$), and

a significant decrease in the rate of procedures performed with RAP in the same group (91.7% versus 99.1% in the control group, $p<.0001$). Particularly, the rate of RAP and EAB significantly decreased in the tailored group, while the rate of procedures performed with RAP and TTC, and with AAP and EAB in the same group significantly increased ($p<.001$). Cardiopulmonary bypass and aortic clamping times were longer in the tailored group. A significant decrease in the rate of stroke (from 5.2% to 1%, $p<.001$) and a significant increase in the rate of re-exploration for bleeding (from 1.9% to 4.9%, $p=.051$) were recorded in the tailored group (Table 2). Twenty-two out of 38 patients re-explorated for bleeding in the tailored group underwent surgery through RAP and TTC (57.9%); of these, 1 patient required reoperation for bleeding at the cardioplegia cannula insertion site; 11 patients required reoperation for bleeding from the chest wall ports; in the other cases, no active bleeding was reported.

Logistic regression analysis showed that the tailored approach is a protective factor for stroke (adjusted OR: .240; 95% CI .094 to .619). No influence of the tailored approach on 30-day mortality was highlighted (Table 3).

COMMENT

Over the last 20 years, MICS has rapidly evolved due to the development of strategies involving arterial and venous cannulation, aortic clamping and myocardial preservation [1,2]. Several settings have been described and have become routine in the surgical practice of centers all over the world; however, there is still debate in the literature regarding their role on the occurrence of major neurological and vascular complications [3,4,11].

This study analyzes the evolution of our 10-year institutional experience in MICS, and highlights clinical and surgical practice changes adopted with the mean to reduce the rate of MICS-related complications. Comparison between 2 consecutive study periods shows improved post-operative outcomes in the tailored group; logistic regression analysis proved that the tailored approach is able to reduce post-operative rate of major neurological complications.

The consecutive study periods analysis shows a stable increase in the adoption of the minimal invasive approach and a slowly decrease in the rate of procedures performed through standard sternotomy at our Department (Figure 2). The twist point (deepest increase in MICS

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practice and deepest decrease in standard sternotomy approach) is located in 2009, when the new settings available allowed us to extend the MICS program also to patients before not eligible, such as patients with severe peripheral vascular disease. Particularly valuable for this subgroup of high risk patients was the introduction of the AAP through the ascending aorta with EAB because it allowed us to avoid RAP and retrograde balloon manipulation in atherosomatous arteries; despite the fact that the production of this cannula has been suspended for regulatory reasons in 2014, our experience underlines that it is definitely a useful and safe tool to adopt in order to extend MICS also in patients with peripheral vasculopathy [2]. After the cannula withdrawal, patients with severe peripheral disease in the present study, underwent MICS with AAP through the axillary artery and TTC. Another reason for the increased MICS practice since 2009, was that, after a first phase of learning curve, also patients requiring more demanding surgical procedures (i.e. in the case of MV infective endocarditis) started to be taken into consideration for the minimal invasive approach [12].

The main step forward during the study period is definitely related to the MICS techniques for arterial perfusion and aortic clamping (Figure 3). During the first time span of our experience the setting of choice was the EAB with RAP (91% of cases in the first 3-year period). Subsequently, with the growing skill of the team and the evidences in the literature, our practice was critically reevaluated and shifted from a standard setting toward an approach tailored to the specific patient [3,4]. From 2009, all the modes of arterial perfusion and aortic clamping available were taken into consideration and adapted to the patient; Figure 3 shows a comparable distribution of the different types of setting since 2009. Our choice was not to replace the peripheral arterial cannulation by a central approach, as previously reported by other authors [1,13], but to determine the finest setting for the patient. This decision making process has been supported by an algorithm that, taking into consideration patient anatomical and clinical details (previous cardiac surgery, aorto-iliac-femoral vessels disease or high tortuosity, ascending aorta dilation), helps the surgeon to address the patient toward a specific setting (RAP with EAB, RAP with TTC, direct ascending aorta cannulation with EAB, or axillary artery cannulation with TTC) [2].

When looking at the subgroup of patients without peripheral vascular disease, the setting of choice in the present cohort of patients was the RAP with EAB. This can be explained bearing in

mind that this setting doesn't require to open the pericardium extensively to get a full exposure of all the ascending aorta, it doesn't require to perform a purse-string and to place a cardioplegia/vent needle into the ascending aorta, and it doesn't require to get a further port in the first intercostals space to set the aortic cannula or the aortic clamp, consequently it requires less surgical dissection with a lower risk of bleeding. The higher adoption of the TTC setting, according to the tailoring strategy in the second time span of the study period, can explain the higher rate of re-exploration for bleeding in this subgroup of patients [14]. Moreover in this period two young surgeons started to join the MICS program at our Department; therefore we have to consider also an higher rate of complications related to the beginning of the learning curve.

Cardiopulmonary bypass and clamping times were longer in the tailored era. Longer CPB times can be explained bearing in mind that an higher number of patients in the second time span underwent surgery through the TTC setting or through the direct ascending aorta cannulation and these settings take longer than the EAB setting (more extensive surgical dissections and an additional port are required to get the ascending aorta for the cannula insertion, rather than the vent insertion, rather than the TTC placement). Longer clamping times can be explained taking into consideration the higher rate of complex MV procedures performed in the tailored group. Then, again, we have to consider the beginning of the learning curve of the new surgeons joining the MICS program with consequently longer surgical times. Longer clamping times in the tailored group can be first of all explained with the higher rate of complex MV procedures performed; longer surgical times can also depend on the learning curve of the new surgeons joining the MICS program in this period.

It is well known that one of the drawbacks of MICS is the challenging learning curve that is potentially capable to prevent the patient from the benefits of a minimal access approach [8]. Therefore the MICS adoption demands a close outcome analysis, especially during the initial phase of the application. CUSUM curve represents one of the best risk adjustment model of mortality for this purpose. Indeed, it has the advantage of taking into account time and predicted risk of failure (in this case logistic EuroSCORE) [15]; the resulting chart runs parallel to the x axis when the complication rate is as expected, turns upward when more complications than expected

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occur, and turns downward when a favorably low complication rate is observed [8]. CUSUM analysis of our 10-year experience shows that, after a slight accumulation of failures in the early years (from 2006 to 2010), outcome became consistently downward (ie, fewer death than expected). From 2012 to 2013, however, the complication rate started to rise again, and this cluster of failure prompted a review: this time point is congruent with a number of new surgeons joining the MICS program at our Department.

To assess the evolution of the learning curve over the study period, a subgroup of patients with diagnosis of degenerative MV disease was taken into consideration. Figure 4 shows a progressive increase in the rate of complex MV repair over the 10-year period. Moreover, when looking at the simple MV repair line, we can see a dramatic decrease in the rate of procedures performed since 2012. This is expression of another of the main changes in philosophy and techniques of our Department during the study period: over the years, surgery on the MV has switched toward a “respect rather than resect” approach [16].

The present study clearly demonstrates the considerable and attractive results of our decision making process based on the tailored approach: despite a comparative rate of comorbidities and surgical risk factors over the 10-year period, the outcome analysis shows a trend toward a progressive decrease in the overall rate of MICS-related complications and a significant protective effect of the tailored approach on the occurrence of major neurological complications. It is known in the literature that longer CPB and clamping times are well-defined risk factors for neurological complications during cardiac surgery; this is not consistent with the results of the present study and this can be explained considering that, even with longer surgical times for more complex surgical procedures, the experience gained through the study period has allowed our team to reduce the overall rate of complications, including the rate of stroke.

Limitations

This study has several limitations that are important to consider when interpreting the main findings. First, it is based on a retrospective analysis. Secondly, the time span of data collection is long and can cause some bias (new technology, new surgeons joining the MICS program). In

addition, it figures only a single-center experience, which may limit its generalizability to other centers.

Conclusions

The awareness of the surgeon should be addressed toward a proper selection of the patient and allocation to the safest approach, more than toward the identification of the ideal setting to apply for all the patients.

To improve safety and predictability of the operation, patients undergoing minimal invasive surgery have to be screened for vascular disease. Moreover, to our knowledge, the vast majority of centers in the world are confident with only one of the minimal access approaches that have been proposed for cardiac surgery, and there are very few centers that tailor the strategy on the patient's characteristics. Actually, we believe that the latter is the best policy for a program of MICS: all the setting available must be part of a safe minimal invasive program and surgeons dedicated to it must be confident with all of them in order to tailor different perfusion and aortic clamping techniques to the patient.

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TABLE 1. Overall and subgroups patients characteristics and comorbidities.

	Overall (n=971)	Control group (n=210)	Tailored group (n=761)	p-value
Age, mean (SD)	62.5 (4.1)	58.8 (14.9)	63.6 (13.7)	<.0001
Male gender, n (%)	503 (51.8)	107 (51.0)	396 (52.0)	.781
BMI, mean (SD)	24.5 (4.4)	24.3 (3.8)	24.6 (4.5)	.866
Hypertension, n (%)	552 (56.9)	124 (41.0)	428 (56.3)	.479
Renal failure, n (%)	84 (8.7)	15 (7.1)	69 (9.1)	.377
Pre-op creatinine, mean (SD)	1.1 (0.7)	1.1 (0.6)	1.1 (0.7)	.323
COPD, n (%)	71 (7.3)	17 (8.1)	54 (7.1)	.622
Diabetes, n (%)	94 (9.7)	14 (6.7)	80 (10.5)	.095
Peripheral vasculopathy, n (%)	25 (2.6)	5 (2.4)	20 (2.6)	.841
Atrial fibrillation, n (%)	361 (37.2)	72 (34.3)	289 (38.0)	.327
Pre-op neurological deficit, n (%)	80 (8.3)	22 (10.5)	58 (7.7)	.188
Logistic EuroSCORE I, mean (SD)	7.6 (9.7)	4.0 (2.1)	7.7 (9.9)	.210
Previous cardiac surgery, n (%)	251 (25.9)	75 (35.7)	176 (23.1)	<.001
Ejection fraction, mean (SD)	59.5 (10.8)	58.3 (12)	59.7 (10.4)	.370

SD: standard deviation; BMI: body mass index; pre-op: pre-operative; COPD: chronic obstructive pulmonary disease; EuroSCORE: European system for cardiac operative risk evaluation.

TABLE 2. Overall and subgroups patients operative data and postoperative outcomes.

	Overall (n=971)	Control group (n=210)	Tailored group (n=761)	p-value
MV surgery, n (%)	847 (87.2)	178 (84.8)	669 (87.9)	<.0001
Simple MV repair, n (%)	310 (36.6)	73 (41.0)	237 (35.4)	
Complex MV repair, n (%)	164 (19.4)	14 (7.9)	150 (22.4)	
MV/MP replacement, n (%)	373 (44.0)	91 (51.1)	282 (42.2)	
TV surgery, n (%)	156 (16.1)	35 (16.7)	121 (15.9)	.789
ASD surgery, n (%)	115 (11.8)	33 (15.7)	82 (10.8)	.049
Atrial masses exeresis, n (%)	25 (2.6)	3 (1.4)	22 (2.9)	.236
AF crio-ablation, n (%)	110 (11.3)	17 (8.1)	93 (12.2)	.094
RAP, n (%)	906 (93.3)	208 (99.1)	698 (91.7)	<.0001
RAP+EAB, n (%)	567 (58.4)	191 (90.9)	376 (49.4)	
RAP+TTC, n (%)	294 (30.3)	6 (2.9)	288 (37.8)	<.0001
AAP+EAB, n (%)	65 (6.7)	2 (0.9)	63 (8.3)	
CPB, min, median (Q1-Q3)	120 (100.5-146)	104.5 (86.5-127)	125 (105-150.5)	<.0001
Ao clamp, min, median (Q1-Q3)	87 (70-105)	75 (58-87)	91 (74-108)	<.0001
Techniques switch, n (%)	16 (1.6)	5 (2.4)	11 (1.4)	.341
Ao dissection, n (%)	5 (0.5)	3 (1.4)	2 (0.3)	.071
Conversion to sternotomy, n %	8 (0.8)	4 (1.9)	4 (0.5)	.072
ICU stay, days, median (Q1-Q3)	1 (1-2)	1 (1.2)	1 (1-2)	.212
Re-exploration, n (%)	42 (4.3)	4 (1.9)	38 (4.9)	.051
Stroke, n (%)	19 (2)	11 (5.2)	8 (1)	<0.001
Hemodialysis, n (%)	28 (2.9)	8 (3.8)	20 (2.6)	.359
Hospital stay, median (Q1-Q3)	7 (6-10)	7 (6-10)	7 (6-10)	.809
30-day mortality, n (%)	25 (2.6)	8 (3.8)	17 (2.2)	.202

MV: mitral valve; MP: mitral prosthesis; TV: tricuspid valve; ASD: atrial septal defect; AF: atrial fibrillation; RAP: retrograde arterial perfusion; EAB: endoaortic balloon; TTC: trans-thoracic aortic clamping; AAP: antegrade arterial perfusion; CPB: cardio-pulmonary by-pass; Ao: aortic; ICU: Intensive care unit.

TABLE 3. OR estimate for outcomes of the tailored approach.

	OR (CI)	Adjusted OR (CI)
Stroke*	.192 (.076; .484)	.240 (.094; .619)
30-day mortality**	.577 (.245; 1.356)	.528 (.182; 1.535)

OR: odd ratio; IC: confidence interval.

* Adjusted for EuroSCORE I, ejection fraction, preoperative neurological events, and previous cardiac surgery procedures.

** Adjusted for age, EuroSCORE I, ejection fraction, diabetes, preoperative kidney dysfunction, preoperative neurological events, chronic obstructive pulmonary disease, peripheral vasculopathy, and previous cardiac surgery procedures.

FIGURES

Figure 1: Patient population during the study period.

Figure legend: CPB: cardiopulmonary bypass; MICS: minimal invasive cardiac surgery.

Figure 2: Overall cardiac surgery procedures over the study period.

Figure legend: MICS: minimal invasive cardiac surgery.

Figure 3: Evolution of arterial perfusion and aortic clamping techniques.

Figure legend: RAP: retrograde arterial perfusion; TTC: trans-thoracic aortic clamp; EAB: endoaortic balloon; AAP: antegrade arterial perfusion.

Figure 4: Overall mitral valve surgery procedures.

Figure legend: MVr: mitral valve repair; MVR: mitral valve replacement.

Figure 5: 30-day mortality sequential probability cumulative sum failure analysis.