Long-term Outcome of complete TGA: What to look for?

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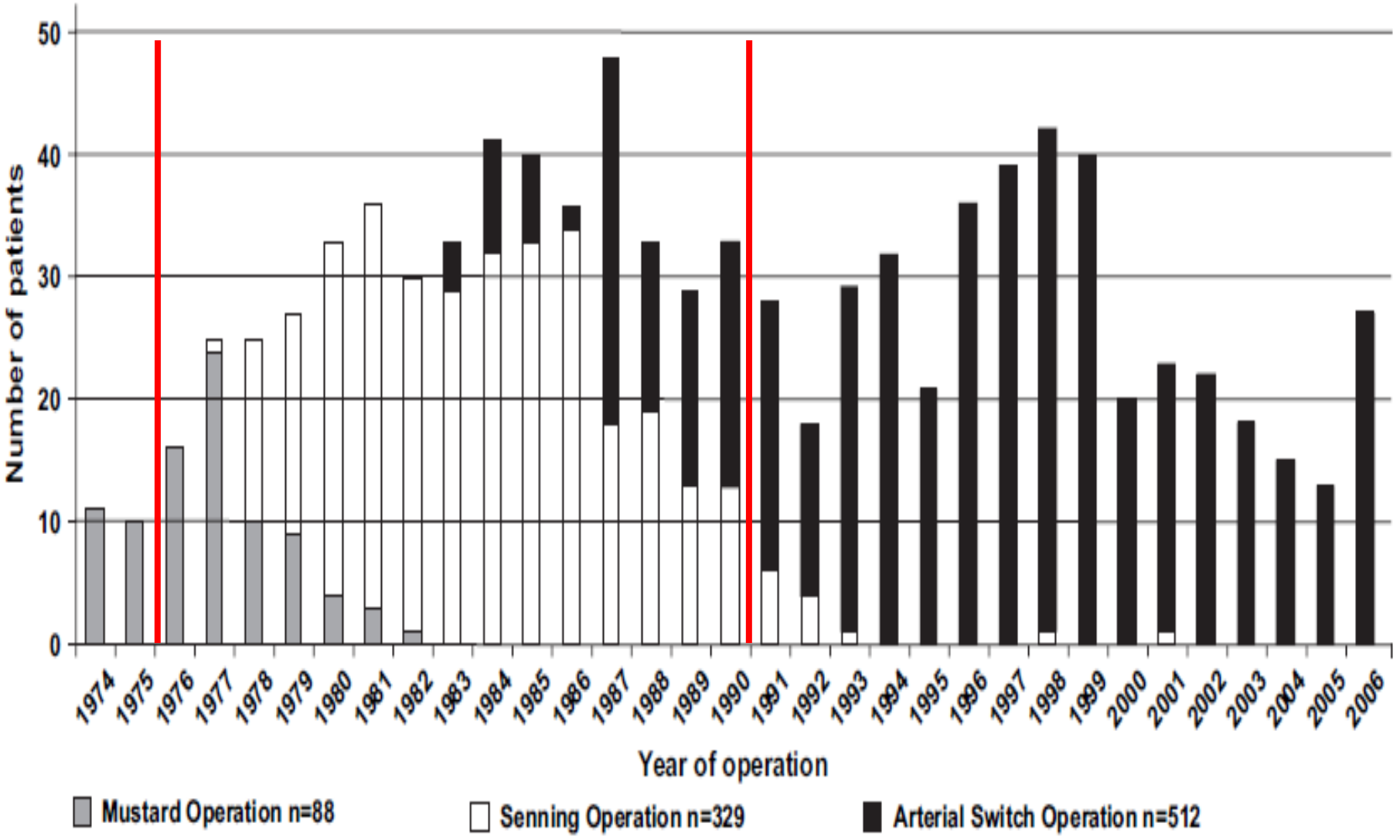

FIGURE 1. Number of operations stratified by type of operation and year between 1974 and 2006.

Contents

- Atrial vs. Arterial Switch Operation
- ASO Era
  - Cardiovascular outcomes
  - Exercise performance
  - NeoAortic problem
  - Vasomotor function of CA

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Improvement in long-term survival after hospital discharge but not in freedom from reoperation after the change from atrial to arterial switch for transposition of the great arteries

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Objective: To compare survival, freedom from reoperation, and functional status between atrial switch and arterial switch operations for transposition of the great arteries.

Methods: Data from 88, 329, and 512 patients who underwent Mustard, Senning, and arterial switch operations between 1974 and 2006 were analyzed.

Results: In-hospital mortalities were 8.0% for Mustard, 4.6% for Senning, and 6.4% for arterial switch. Presence of ventricular septal defect (hazard ratio 3.3, $P < .001$) was the only risk factor for in-hospital mortality in multivariate analysis. Follow-up for Mustard was 22.6 ± 8.1 years, for Senning was 18.2 ± 5.7 years, and for arterial switch was 9.5 ± 5.7 years. Highest survival at 20 years was after arterial switch (96.6% ± 1.3%), followed by Senning (92.6% ± 1.5%) and Mustard (82.4% ± 4.3%). Transposition with ventricular septal defect (hazard ratio 3.1, $P < .001$), transposition with ventricular septal defect and left ventricular outflow tract obstruction (hazard ratio 3.0, $P = .029$), and Mustard operation (hazard ratio 2.1, $P = .011$) emerged as risk factors for late death, with arterial switch a protective factor (hazard ratio 0.3, $P = .010$). Highest freedom from reoperation at 20 years was after Senning (88.7% ± 1.9%), followed by arterial switch (75.0% ± 6.4%) and Mustard (70.6% ± 5.4%). Presence of complex transposition (hazard ratio 2.1, $P < .001$), previous palliative operation (hazard ratio 1.8, $P = .016$), surgery between 1985 and 1995 (hazard ratio 2.6, $P = .002$), surgery after 1995 (hazard ratio 3.5, $P < .001$), and Mustard operation (hazard ratio 3.3, $P < .001$) emerged as risk factors for reoperation.

Conclusion: Change from atrial to arterial switch led to improved long-term survival after hospital discharge but not to lower incidence of reoperation. Survival and freedom from reoperation are determined by morphology.

TABLE I. Perioperative variables of 929 patients with transposition of the great arteries who underwent the Mustard, Senning, or arterial switch operation

Characteristic	Atrial switch		Arterial switch (n = 512)	*P* value*
	Mustard (n = 88)	Senning (n = 329)		
TGA with IVS (No.)	44 (50%)	221 (64.1%)	317 (61.9%)	.633
TGA with VSD (No.)	31 (35.2%)	71 (21.6%)	186 (36.3%)	<.001
TGA with LVOTO (No.)	7 (8.0%)	15 (4.6%)	1 (0.2%)	<.001
TGA with VSD and LVOTO (No.)	6 (6.8%)	22 (6.7%)	8 (1.6%)	<.001
VSD (No.)	37 (42.4%)	93 (28.3%)	194 (37.9%)	.038
LVOTO (No.)	13 (14.8%)	37 (11.2%)	9 (1.8%)	<.001
Palliative operation (No.)	32 (36.4%)	25 (7.6%)	67 (31.6%)	.846
Balloon atrial septostomy (No.)	75 (85.2%)	307 (93.3%)	354 (69.1%)	<.001
Age at correction (y, mean ± SD)	2.7 ± 2.4	0.8 ± 1.3	0.2 ± 0.9	<.001
Weight at correction (kg, mean ± SD)	11.3 ± 5.3	6.5 ± 3.1	4.0 ± 3.1	<.001
In-hospital mortality (No.)	7 (8.0%)	15 (4.6%)	33 (6.4%)	.487

TGA, Transposition of the great arteries; *IVS*, intact ventricular septum; *VSD*, ventricular septal defect; *LVOTO*, left ventricular outflow tract obstruction. *Atrial switch (both Mustard and Senning operations) versus arterial switch.

TABLE 3. Significant risk factors for late death among 874 survivors through hospitalization after the Mustard, Senning, or arterial switch operation

	Univariate analysis			Multivariate analysis		
Risk factor	Hazard ratio	95% CI	*P* value*	Hazard ratio	95% CI	*P* value*
Complex TGA	2.9	1.7–5.2	<.001			
TGA with VSD	2.5	1.4–4.3	.001	3.1	1.7–5.5	<.001
TGA with VSD and LVOTO	2.6	1.0–6.6	.042	3.0	1.1–7.9	.029
VSD	3.0	1.7–5.2	<.001			
Palliative operation	3.2	1.8–5.7	<.001			
Surgical period						
1985–1995	0.6	0.3–1.0	.066			
>1995	0.1	0.0–0.6	.014			
TGA with VSD						
Mustard operation	4.2	2.0–9.0	<.001			
Senning operation	2.3	1.1–4.8	.021			
Mustard operation	3.6	2.0–6.5	<.001	2.3	1.2–4.2	.011
Arterial switch operation	0.3	0.1–0.6	.002	0.3	0.1–0.8	.010
Age at operation >30 d	3.1	1.4–6.7	.005			

CI, Confidence interval; *TGA*, transposition of the great arteries; *VSD*, ventricular septal defect; *LVOTO*, left ventricular outflow tract obstruction. *Level of significance between the groups of dichotomous variables listed in the first column, except for the variables of surgical period 1985–1995 and surgical period >1995, for which reference is surgical period <1985.

TABLE 4. Reoperations among 874 survivors through hospitalization after the Mustard, Senning, or arterial switch operation

Procedure			Arterial
All reoperations			
No. of reoperations			
No. of patients			
Closure of baffle leak			
Enlargement of systemic venous tunnel			
Enlargement of pulmonary venous tunnel			
Enlargement of subvalvular pulmonary stenosis			
Enlargement of valvular pulmonary stenosis			
Enlargement of supravalvul pulmonary stenosis			
Enlargement of pulmonary arterial stenosis			
Enlargement of left ventricular outflow tract and aortic arch			
Aortic valve replacement			
Banding or debanding of pulmonary artery			
Arterial switch and atrial redirection			
Procedure of tricuspid valv			
Closure of residual ventricular septal defect			
Other	2 (5.4%)	2 (5.3%)	5 (7.2%)

Percentages refer to percentage of total number of operations in group.

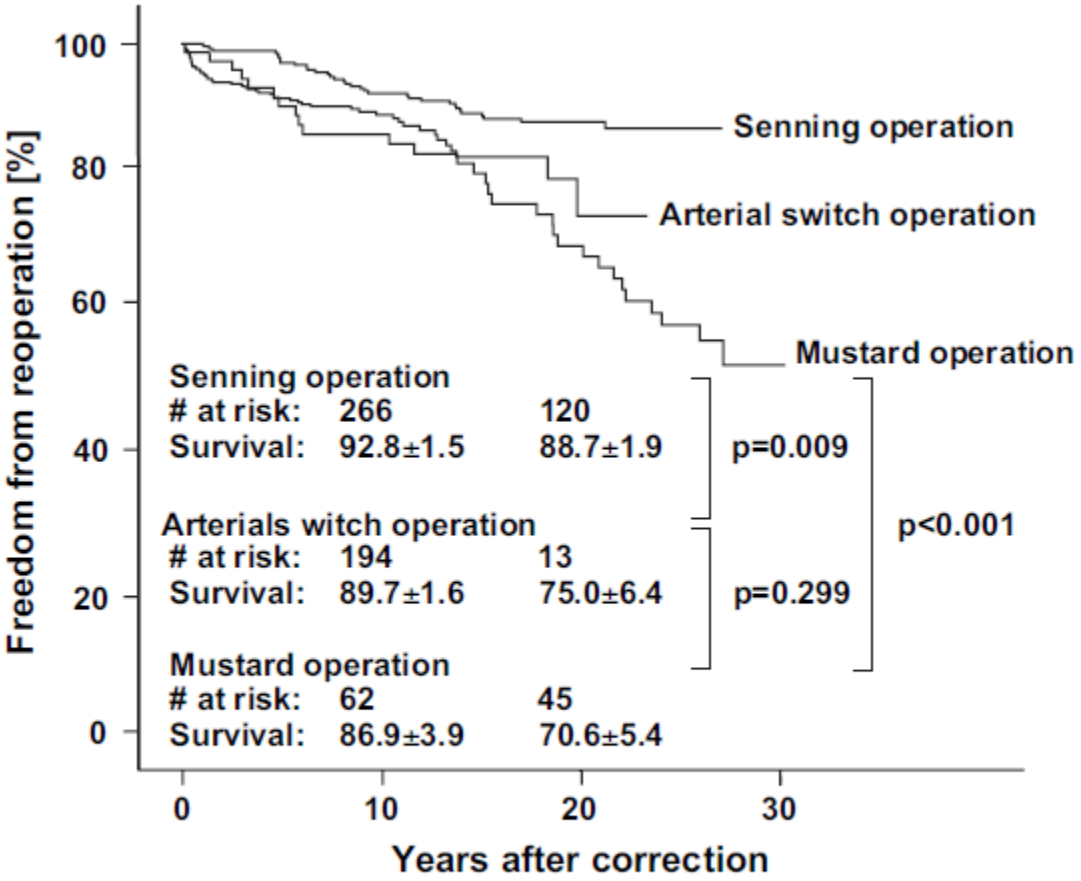

FIGURE 3. Estimated freedom from reoperation among survivors of initial hospitalization after correction stratified by type of operation.

Table 1
Group characteristics according to the technique used to repair transposition of the great arteries

Variable	ASO (n = 28)	Mustard (n = 34)	p Value
Body mass index (kg/m^2)	23.5 ± 4.2	23.3 ± 3	0.82
Age (yrs)	20.6 ± 2.1	20.6 ± 3.4	0.56
Age at operation (mos)	0.13 (0.03—12.1)	10.7 (1.7—76.2)	<0.0001*
Follow-up after operation (yrs)	20.5 ± 2.1	19.3 ± 3.7	0.14
New York Heart Association class			<0.0001*
I	28	14	
II	0	16	
III	0	4	
Pacemaker	0	12 (43%)	<0.0001*
Heart rate at rest (beats/min)	77 ± 12	74 ± 14	0.42
Maximal heart rate (beats/min)	174 ± 15	158 ± 27	0.006*
Systolic blood pressure at rest (mm Hg)	113 ± 17	118 ± 11	0.20
Maximal systolic blood pressure during exercise (mm Hg)	180 ± 26	178 ± 24	0.83
Vo_{2max} (ml/kg/min)	29.5 ± 5.9	26.5 ± 5.4	0.05*
Vo_{2max} (% of predicted)	80 ± 16	69 ± 16	0.007*
Respiratory exchange ratio	1.14 ± 0.11	1.09 ± 29	0.02*
Forced expiratory volume in 1 second (% of predicted)	84 ± 18	95 ± 20	0.026*
N-terminal pro—brain natriuretic peptide (ng/ml)	42 (18—323)	172 (26—1,018)	<0.0001*

Claudia Junge, Am J Cardiol 2013

The change from the atrial to the arterial switch

- Improved long-term survival
- Improved functional status

  NYHA Fc I atrial 66-93% vs ASO all most all
- Not to lower incidence of reoperation.
- Both survival and freedom from reoperation are determined by the morphology.

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Cardiovascular Outcomes After the Arterial Switch Operation for D-Transposition of the Great Arteries

- 400 ASO patients
  1983-1999, Boston Children Hospital
- F-U post ASO, years
  18.7years
- IVS 59.5%, VSD 38.3%
  TB anomaly 2.3%

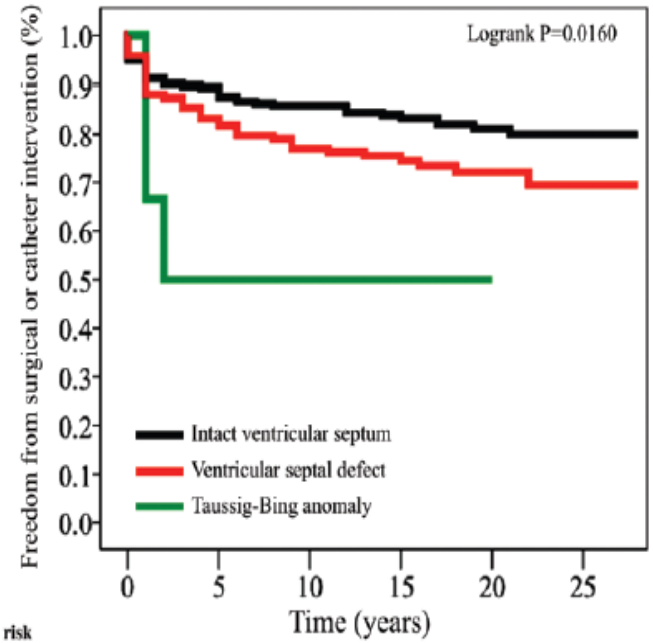
Characteristic	All Patients n=400
Age,* days	5 (3, 10)
Weight, kg	3.5±0.8
Height, cm	51.3±4.5
Associated malformations, n (%)	
Aortic arch anomaly†	26 (6.5)
Multiple VSDs	29 (7.2)
LVOT gradient ≥50 mm Hg	6 (1.5)
Abnormal AVV attachment‡	6 (1.5)
Coronary anatomy, n (%)	
Normal	264 (66.0)
Circumflex from RCA	72 (18.0)
Single RCA	17 (4.3)
Single LCA	7 (1.8)
Inverted	10 (2.5)

Paul Khairy, Circulation 2013

Table 2. Surgical and Catheter-Based Interventions in Perioperative Survivors After the Arterial Switch Operation (n=374)

	n (%)
Surgical Reintervention	
Coronary intervention	2 (0.5)
Aortic reconstruction at anastomosis	2 (0.5)
Pulmonary artery reconstruction/plasty at anastomosis	25 (6.7)
Aortic valve plasty	4 (1.1)
Aortic valve replacement	2 (0.5)
Subaortic stenosis resection	5 (1.3)
Aortic arch/coarctation surgery	5 (1.3)
Pulmonary valve plasty	4 (1.1)
Subpulmonary stenosis/right ventricular outflow tract resection	1 (0.3)
Left pulmonary artery plasty	6 (1.6)
Right pulmonary artery plasty	6 (1.6)
Ventricular septal defect closure	1 (0.3)
Atrial septal defect closure	3 (0.8)
Mitral valvuloplasty	3 (0.8)
Permanent pacemaker	3 (0.8)
Implantable cardioverter-defibrillator	3 (0.8)
Total	48 (12.8)
Catheter-based intervention	
Aortic plasty/stenting at anastomosis	5 (1.3)
Pulmonary artery plasty/stenting at anastomosis	33 (8.8)
Aortic valve plasty	1 (0.3)
Aortic coarctation dilation/stenting	4 (1.1)
Pulmonary valve plasty	13 (3.5)
Right pulmonary artery dilation/stenting	20 (5.3)
Left pulmonary artery dilation/stenting	28 (7.5)
Superior vena cava dilation/stenting	2 (0.5)
Closure of aortopulmonary collaterals	6 (1.6)
Right ventricle to pulmonary artery homograft dilation	3 (0.8)
Intracoronary thrombolysis	1 (0.3)
Cavotricuspid isthmus ablation for typical atrial flutter	2 (0.5)
Total	60 (16.0)

Cardiovascular surgical or catheter-based intervention



Number at risk

Intact ventricular septum	225	201	193	150	82	20
Ventricular septal defect	143	119	110	78	43	4
Taussig-Bing anomaly	6	3	3	1	1	0

Figure 2. Freedom from cardiovascular surgical or catheter-based interventions. The Kaplan–Meier curves depict freedom from cardiovascular surgical or catheter-based interventions after the arterial switch operation, according to whether patients had an intact ventricular septum, ≥1 ventricular septal defect, or a Taussig-Bing anomaly.

Table 3. Factors Associated With Cardiovascular Surgical or Catheter-Based Intervention

Characteristic	Hazard Ratio	95% CI	*P*
Univariable			
Ventricular septal defect	1.59	1.03, 2.47	0.0376
Taussig-Bing variant	2.80	0.88, 9.18	0.0819
Aortic arch anomaly	3.73	2.02, 6.88	<0.0001
Coronary anomaly	1.37	0.88, 2.12	0.1636
Weight at time of arterial switch (per 1 kg reduction)	0.48	0.33, 0.70	0.0001
Height at time of arterial switch (per 1 cm reduction)	0.96	0.90, 1.02	0.1383
Multivariable			
Aortic arch anomaly	3.25	1.69, 6.27	0.0004
Weight at time of arterial switch (per 1 kg reduction)	0.61	0.41, 0.91	0.0144

Combined CV outcome in early survivor

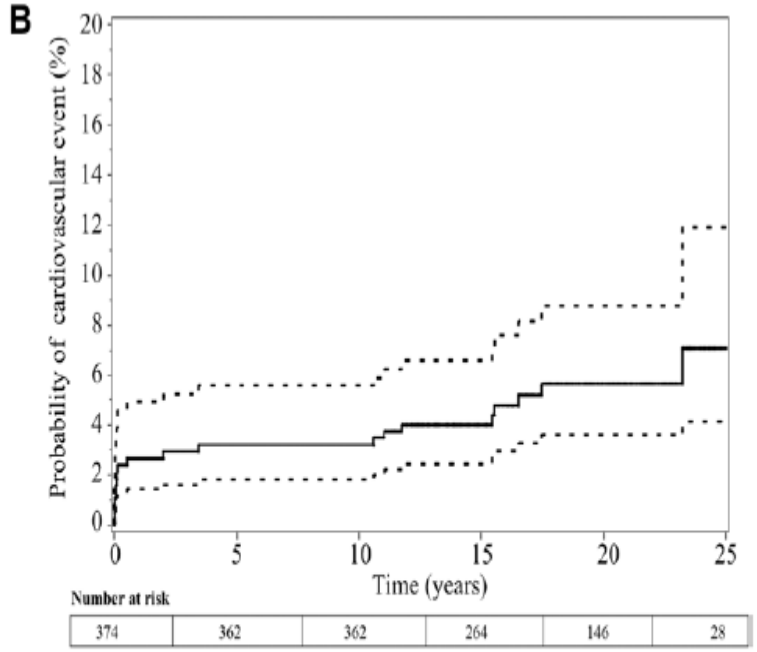


Figure 3. Cumulative probability of arrhythmia or sudden death (**A**) and of the combined cardiovascular outcome (**B**). Cumulative probability of arrhythmia or sudden death (**A**) and of the combined cardiovascular outcome (**B**) is plotted using the product-limit method. The dotted curves represent upper and lower 95% confidence limits.

Table 4. Factors Associated With the Combined Cardiovascular Outcome in Early Survivors

Characteristic	Hazard Ratio	95% CI	*P*
Univariable			
Single right coronary artery	5.12	1.50, 17.50	0.0092
Post-operative course in intensive care unit ≥7 days	2.79	0.94, 8.30	0.0651
Post-operative low cardiac output syndrome	8.08	1.86, 35.06	0.0052
Post-operative ventricular tachycardia	4.12	0.55, 30.86	0.1687
Chest open postoperatively	2.51	0.90, 6.95	0.0777
Multivariable			
Single right coronary artery	4.58	1.32, 15.90	0.0166
Post-operative low cardiac output syndrome	6.93	1.57, 30.62	0.0107

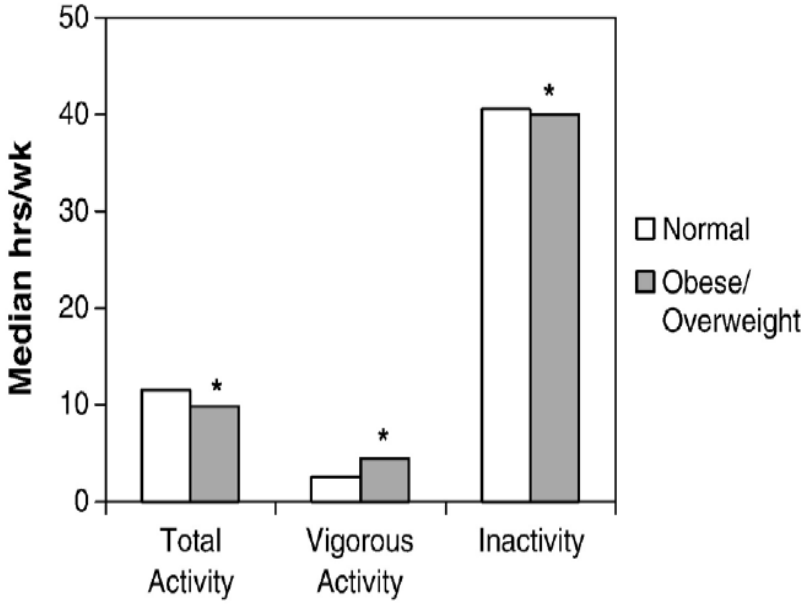
CI indicates confidence interval.

Functional capacity on latest F-U

New York Heart Association functional class, n (%)	
Class I	290 (97.3)
Class II	8 (2.7)
Class III or IV	0 (0)
Peak heart rate, bpm	180±18
Peak percent heart rate predicted, %	90.7±7.0
Heart rate reserve, bpm	101±21
Chronotropic index, %	83.9±10.9
Respiratory exchange ratio (RER)	1.16±0.09
Peak oxygen uptake, mL/kg/min	35.1±7.6
Percent maximum predicted peak oxygen uptake, %	86.1±15.1
Recognized comorbidities	
Coronary artery disease, n (%)	19 (5.2)
Hypertension, n (%)	12 (3.3)
Dyslipidemia, n (%)	2 (0.5)

Physical activity and restriction

106 ASO
Median age 14.2 yr



Activity level. *P = NS comparing OB/OW patients to normal-weight patients for total activity, vigorous activity, and inactivity. Hours per week of inactivity was significantly greater compared to hours per week of total activity in both normal-weight patients and OB/OW patients ($P < .001$, see text).

Table II. Activity restriction

	Normal-weight	OB/OW	P
Any activity			
Cardiologist	27%	27%	NS
Parent	42%*	38%*	NS
Aerobic activity			
Cardiologist	8%	6%	NS
Parent	26%†	33%‡	NS

- Obesity was not found to be related to activity restriction or early feeding practices
- Obesity and associated comorbidities may pose additional cardiovascular risk in ASO

Pasquali SP, Am Heart J 2009 CHOP USA

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Coronary artery pattern and age impact exercise performance late after the arterial switch operation

53ASO CHOP, US
FU 14.1 (7.7–20.6)year

TABLE 3. Predictors of exercise performance

	P value	
	Univariate	Multivariate
Lower maximum heart rate		
VSD	.009	.004
Variant coronary pattern	.04	.03
Lower raw VO_2	.001	
Lower percent predicted VO_2	.004	
Concurrent procedure w/ASO	.02	
Lower percent predicted VO_2		
Longer follow-up time	.001	<.001
VSD	.03	.05
Variant coronary pattern	.1	.09
Lower maximum heart rate	.004	
Concurrent procedure w/ASO	.007	

VSD, Ventricular septal defect; *ASO*, arterial switch operation; *VO_2*, peak oxygen consumption.

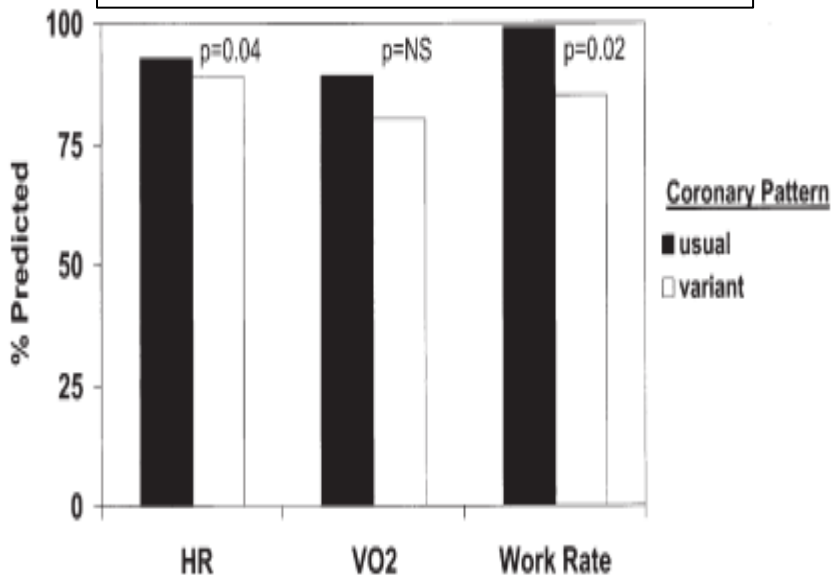


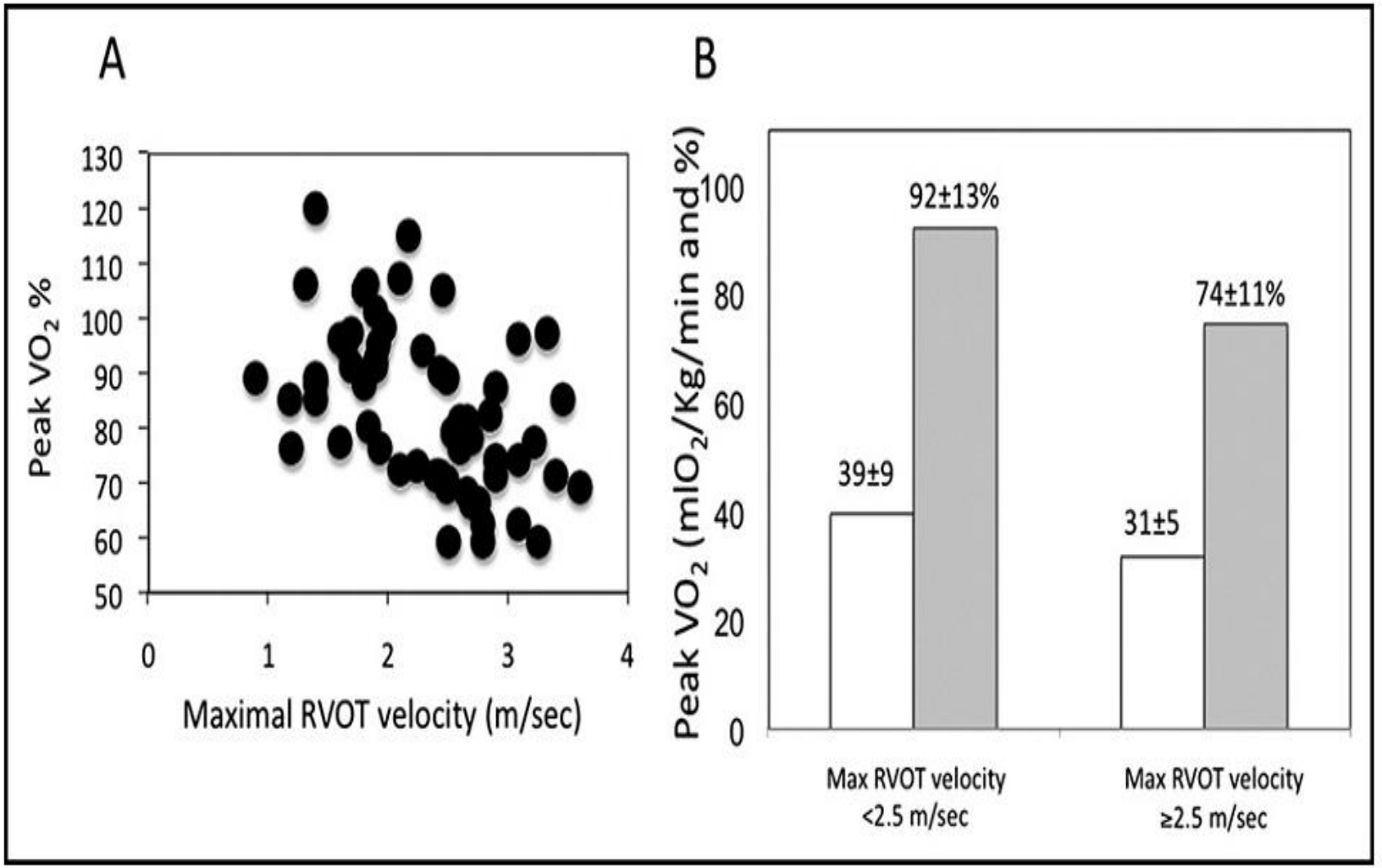
Figure 1. Peak exercise data. *HR*, Heart rate; *VO_2*, oxygen consumption; *NS*, not significant.

Pasquali SK, JTCS 2007

Exercise performance, ASO

- Potential for sympathetic denervation asso. with chronotrophic incompetence
- Length of follow up after ASO
- Abnormal CA reserve after ASO
  - alter balance between myocardial oxygen supply and demand.
- Physical deconditioning

Correlation VO2% and RVOTO



Exercise performance in TGA vs healthy control

Variable	Control Group (n = 15)	TGA Group (n = 15)	p Value
VO_{2peak} (ml/kg/min)	47.4 ± 6.4 (39.3–58.4)	41.1 ± 6.6* (32.1–55.5)	0.013
VO_{2peak} lean body mass (ml/kg/min)	58.2 ± 10.0 (46.1–85.4)	50.5 ± 7.1* (32.1–55.5)	0.021
VO_{2peak} (% of predicted)	94.6 ± 12.1 (75.6–111.5)	81.4 ± 10.9* (63.0–103.8)	0.004
Respiratory quotient	1.04 ± 0.03 (0.98–1.09)	1.03 ± 0.04 (0.98–1.12)	0.46
Peak workload (W)	179.3 ± 60.5 (96–320)	154.1 ± 61.6 (80–312)	0.27
Peak workload (W/kg)	3.7 ± 0.5 (2.7–4.7)	3.1 ± 0.6* (2.5–4.2)	0.005
Peak heart rate (beats/minute)	189 ± 9 (168–200)	180 ± 14 (155–202)	0.045
Heart rate after 1 min (beats/minute)	153 ± 17 (113–178)	149 ± 16 (126–179)	0.40
Heart rate after 3 min (beats/minute)	120 ± 16 (83–146)	118 ± 14 (89–146)	0.80

Data are presented as mean ± SD (minimum to maximum range).

* $p < 0.05$.

Elsje van Beek, Am J Cardiol 2010

- Reduced exercise capacity is relatively common in children and young adult, ASO
- Presence of RVOT obstruction seems to have on exercise capacity
- associated with large increase of Qp
  distention of blood vessel.
- **Anatomic obstruction might become more relevant during exercise**
- Complete cardiac reinnervation could take >5-10yr

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Long-Term Outcomes of the Neoaorta After Arterial Switch Operation for Transposition of the Great Arteries

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- 124 TGA, ASO

  FU median 7.2yr(1-23yr)
- NeoAo root dilation

  Z >2.5 66%
- NeoAV regurgitation 14%

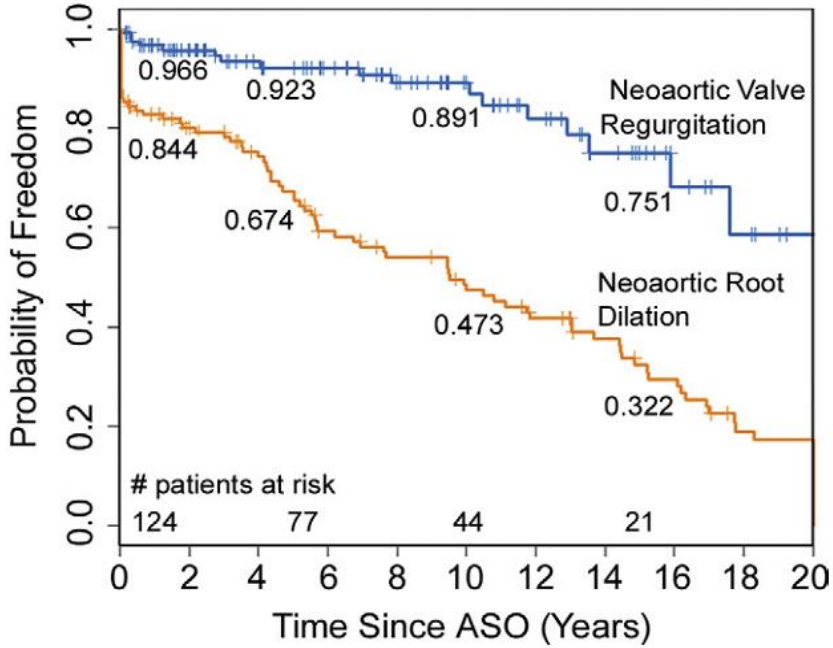


Fig 1. Kaplan-Meier analysis shows probability of freedom from neoaortic root dilation (z score > 2.5) and neoaortic regurgitation (at least moderate regurgitation) after arterial switch operation (ASO).

NeoAo Root and annulus Z score

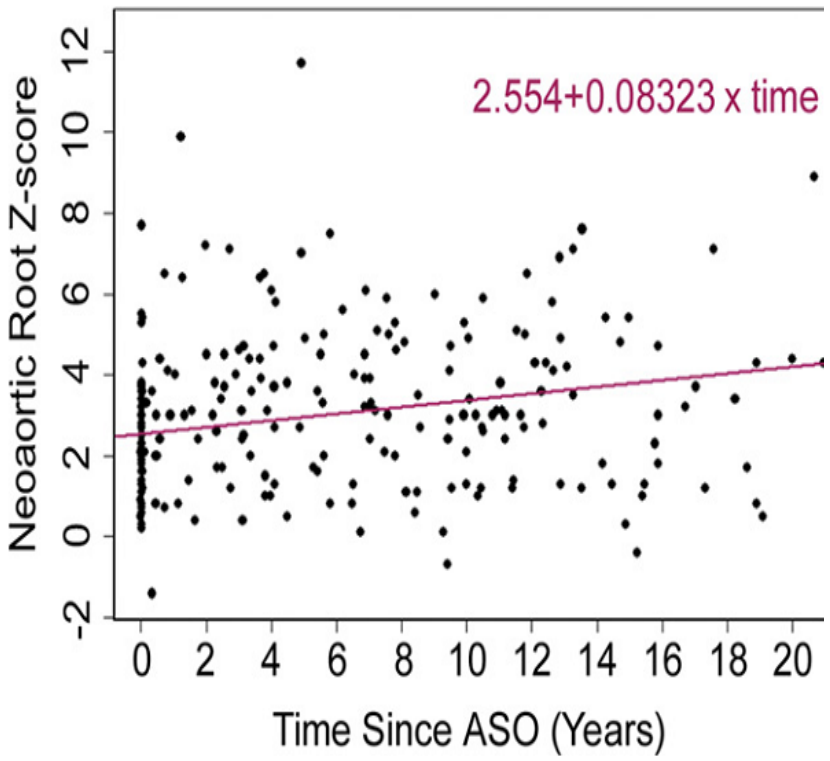


Fig 3. The neoaortic root z score increased over time after the arterial switch operation (ASO) at a rate of 0.08 per year.

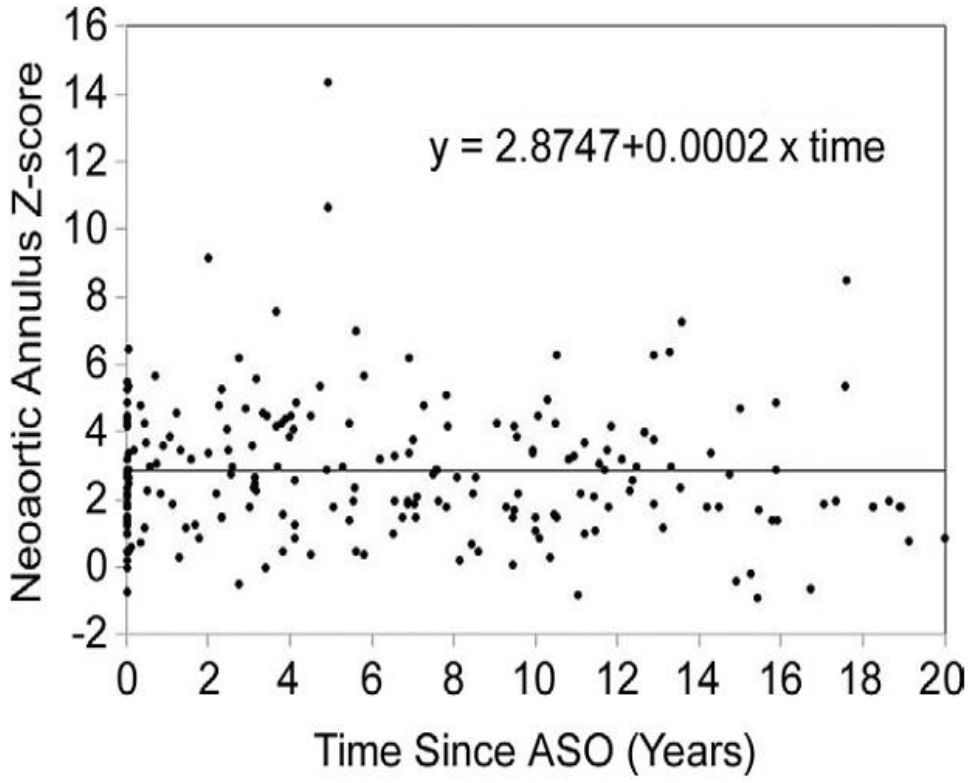


Fig 5. The neoaortic annulus z score increased over time after arterial switch operation (ASO) at a rate of 0.0002 per year.

Aortic Valve Regurgitation After Arterial Switch Operation for Transposition of the Great Arteries

Incidence, Risk Factors, and Outcome

Jean Losay, MD, Anita Touchot, MD, Andre Capderou, MD, PHD, Jean-Dominique Piot, MD, Emre Belli, MD, Claude Planché, MD, PHD, Alain Serraf, MD, PHD

Le Plessis-Robinson, France

- 1,156 TGA, ASO survivor, 1982-2000
- FU median 76.2months

presence of a ventricular septal defect (VSD) or AR at discharge multiplied the risk by 2 and 4, respectively. Freedom from AR was 77.9% and 69.5% at 10 and 15 years, respectively; hazard function for AR declined rapidly and slowly increased thereafter. Reoperation from AR was done in 16 patients with one death, valvuloplasty being unsuccessful. Freedom from reoperation for AR was 97.7% and 96.8% at 10 and 15 years, respectively; hazard function slowly increased from 2 to 16 years. Higher late mortality was not associated with AR.

CONCLUSIONS After ASO, AR was observed and was related to VSD with attending high pressure and flow and AR at discharge. Progression of AR was slow, but incidence increased with follow-up. Reoperation for AR was rare. Late aortic valve function warrants long-term monitoring. (J Am Coll Cardiol 2006;47:2057–62) © 2006 by the American College of Cardiology Foundation

Table 2. Risk Factors for AR

	With AR	Without AR	p
Univariate analysis: whole population			
Complex TGA (%) (TGA with VSD and TB)	25.8	74.2	<0.0001
TGA with VSD	22.3	77.7	<0.0001
Associated arch anomaly (%): IIA or CoA	29.2	70.8	<0.0001
Ao/PA size ≥1.5 (%)	23.6	76.4	<0.0152
Prior PAB (%)	29.3	70.7	<0.0003
Age at ASO (day)	66.3 ± 320.6	25.9 ± 68.8	<0.0005
AR at discharge (%): any grade	34.9	65.1	<0.0001
Univariate analysis: TGA and IVS			
Prior PAB (%)	28.0	9.8	0.0053
AR at discharge (%): any grade	23.2	8.3	<0.0001
Univariate analysis: TGA with VSD			
Taussig-Bing anomaly	38.9	22.3	0.0043
AR at discharge (%): any grade	45.0	14.2	<0.0001
Multivariate analysis			
Complex TGA	1.9		<0.0014
AR at discharge	4.1		<0.0001

AR = aortic regurgitation; CoA = coarctation, IIA = interrupted aortic arch; PA = pulmonary artery; other abbreviations as in Table 1.

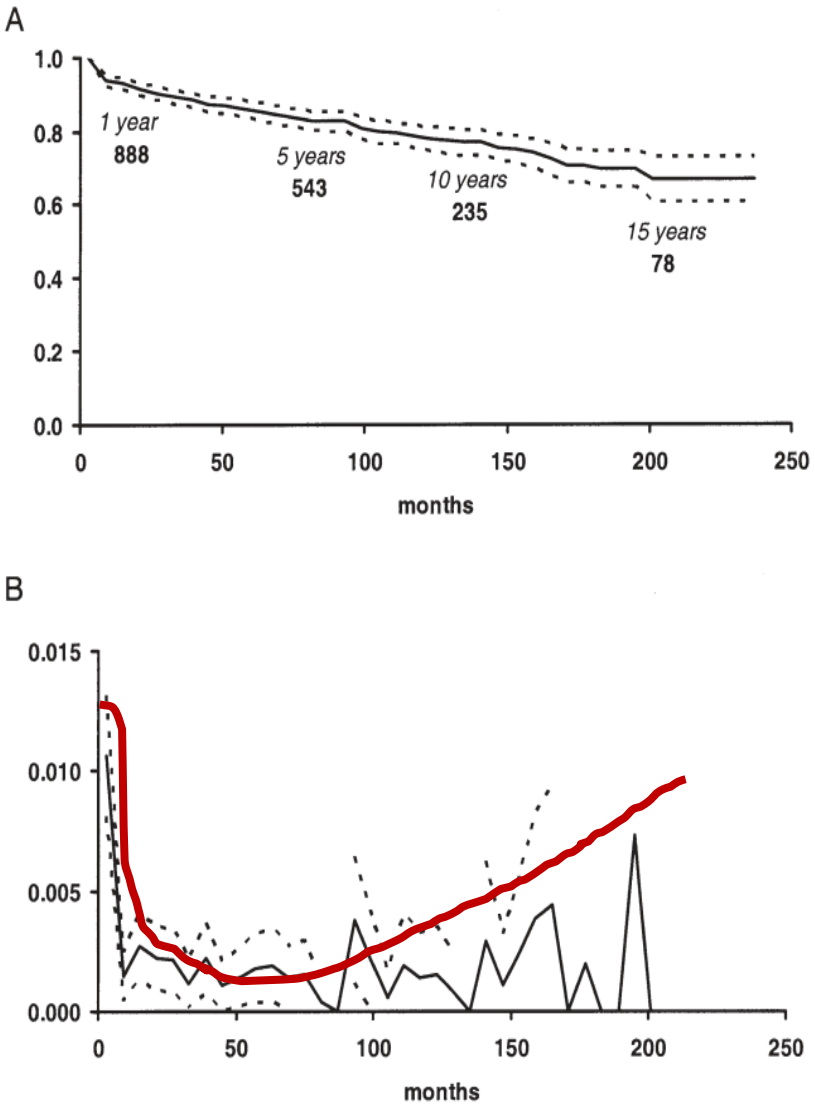


Figure 2. **(A)** Actuarial estimate of freedom from aortic regurgitation (AR) (grade ≥I) in the 1,156 hospital survivors after the arterial switch operation. Numbers indicate number of patients observed at the beginning of an interval. **(B)** Hazard function for AR in 1,156 survivors after the arterial switch operation. **Dotted lines** = 95% confidence interval.

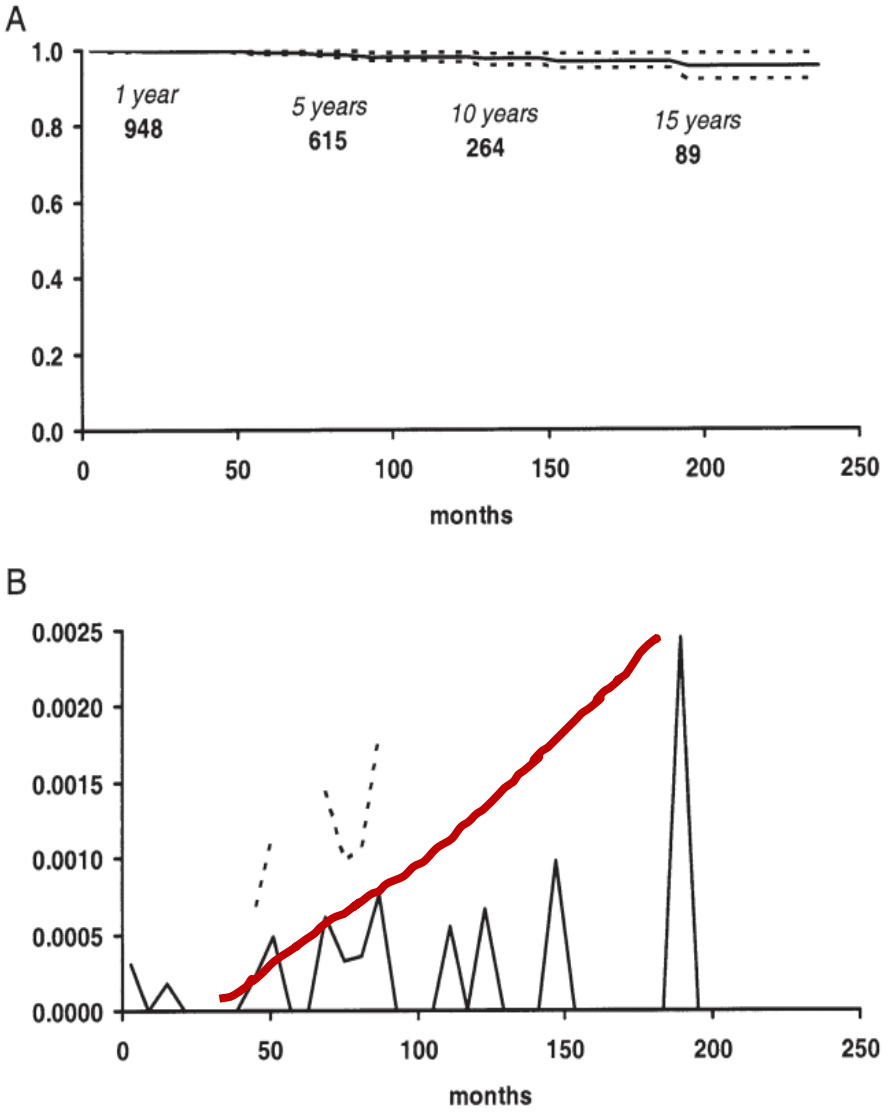


Figure 4. **(A)** Actuarial survival free of reoperation for aortic regurgitation for the 1,156 survivors. Numbers indicate number of patients observed at the beginning of interval. **(B)** Hazard function for reoperation for aortic regurgitation in the 1,156 survivors. **Dotted lines** = 95% confidence interval. Abbreviations as in Figure 2.

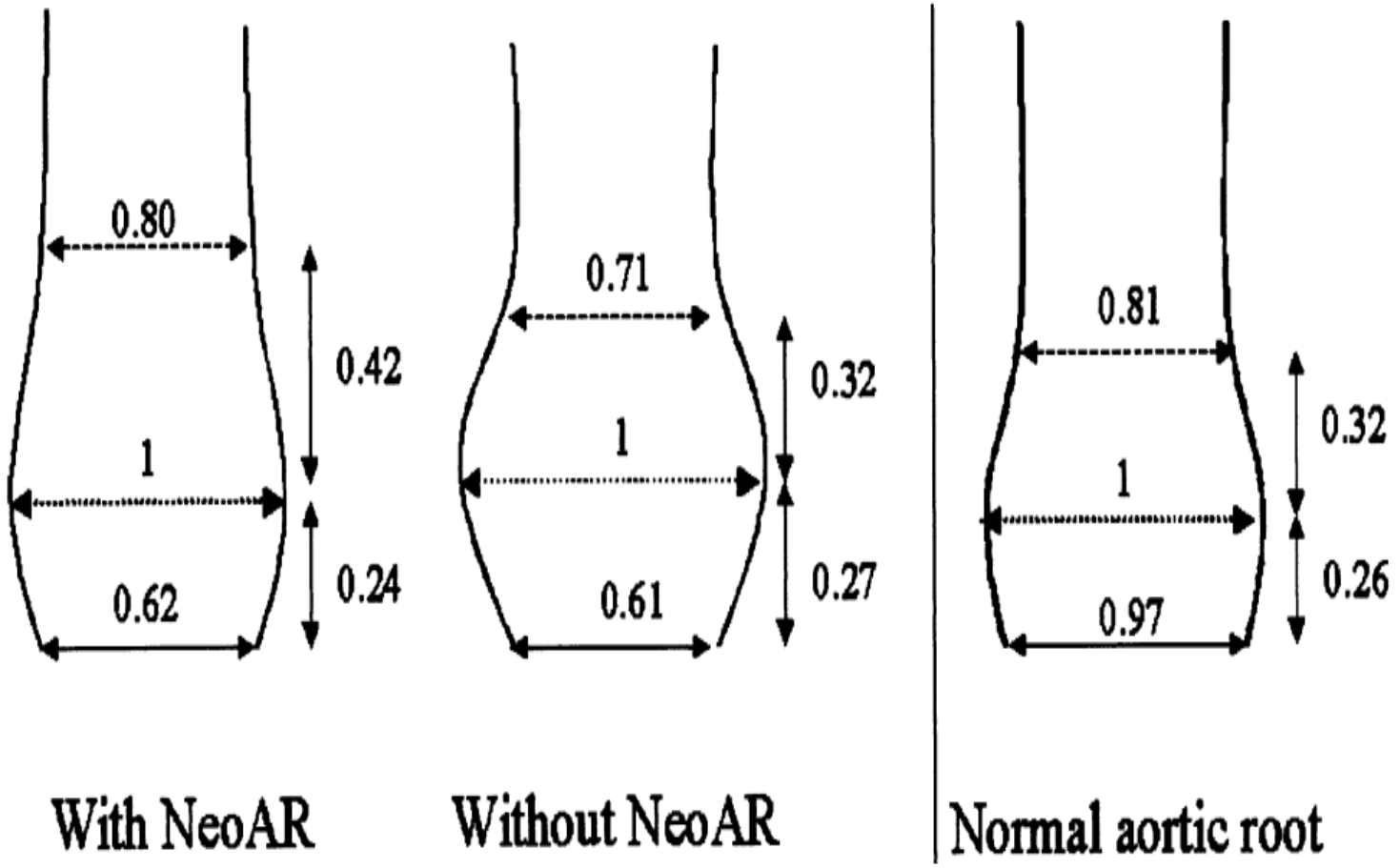
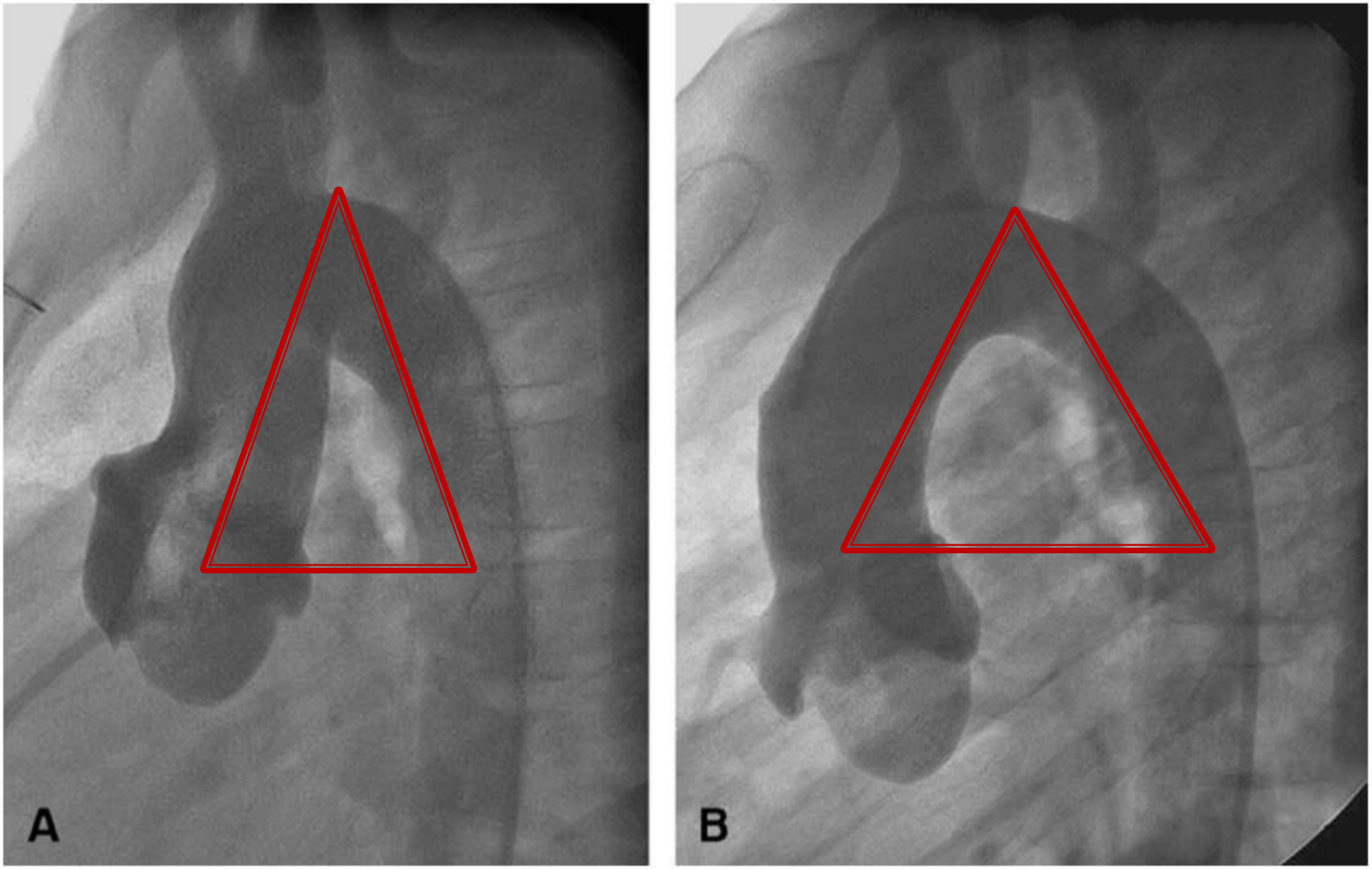


Figure 5. Shape of the neoaortic root of the patients with and without NeoAR. The normal human aortic root (modified from Kunzelman and colleagues[11]) is shown for comparison. The sinus diameter is represented by a value of 1, and all other values are represented by a fraction of this number. The figures are not in scale and are meant only to give information about the shape of the root.


A
B

Abnormal Vasomotor Function of the Epicardial Coronary Arteries in Children Five to Eight Years After Arterial Switch Operation

An Angiographic and Intracoronary Doppler Flow Wire Study

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Rome, Italy

- 19 TGA, ASO vs. 6 control
  Age 5.4yr
- Quantitative assessment of epicardial CA
  NG, adenosine, acethylcholine

Epicardial coronary arteries fail to dilate normally in children after ASO, and the calculated coronary flow volume reserve is consequently reduced. (J Am Coll Cardiol 2005;46:

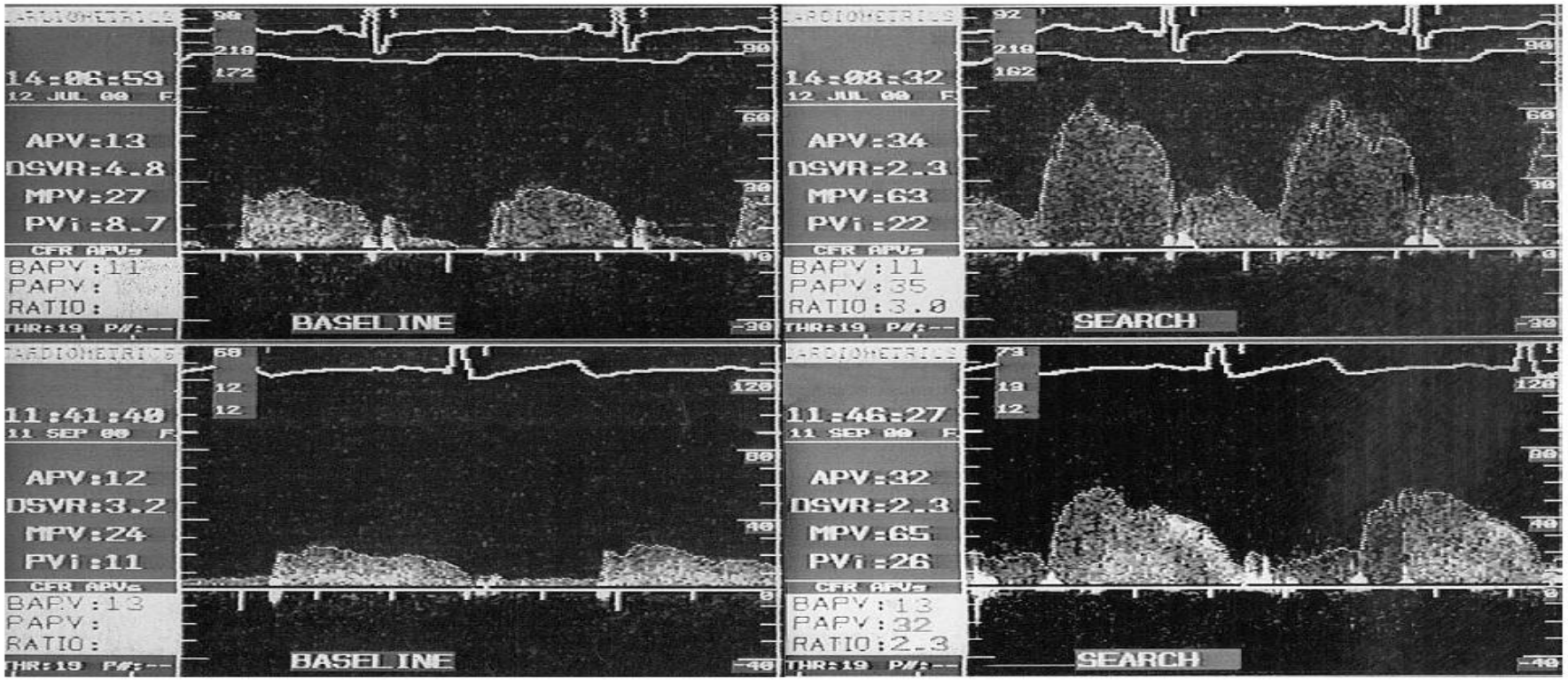
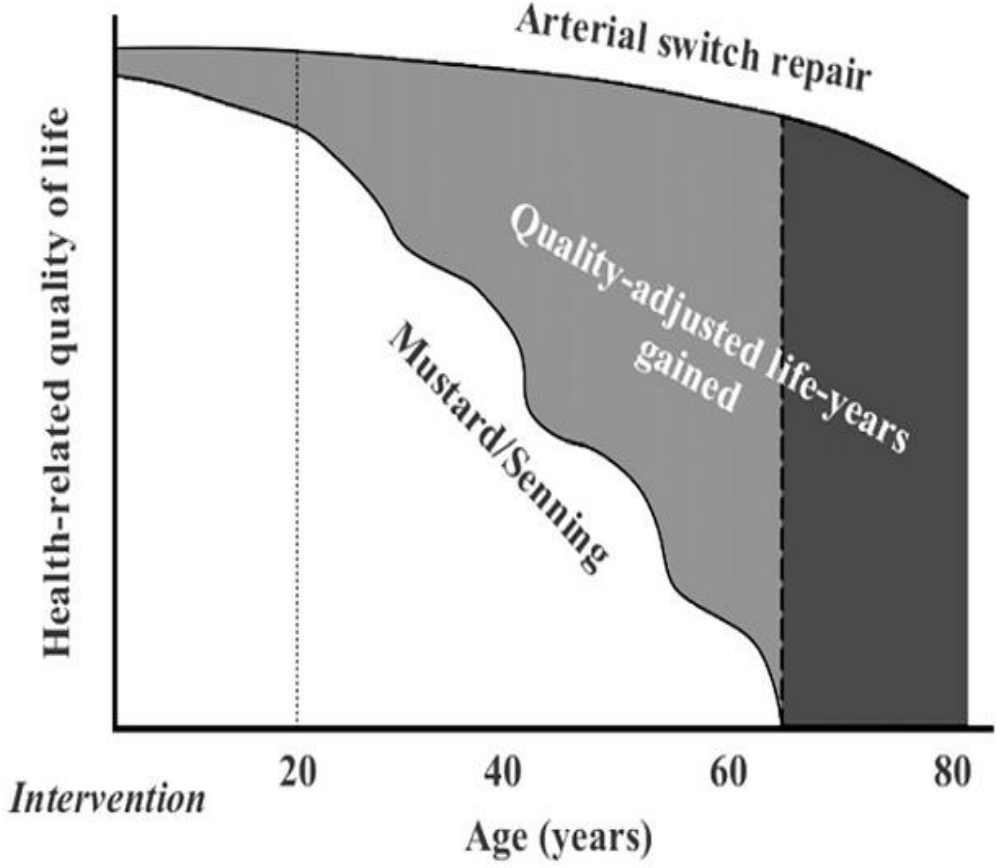


Table 6. Extrapolated Data for CFR Calculated With Administration of Adenosine

	CSA (mm^2)		Flow Volumes (ml/min)			
	Before NTG	After NTG	Before Adn	After Adn	CFR	
ASO group	6.4 ± 3.9	6.9 ± 5.2	57.3 ± 36.3	181.5 ± 198.1	2.7 ± 1.5	p = 0.0003
Control group	3.8 ± 1.4	6.1 ± 1.4	26.7 ± 9.9	133.6 ± 46.5	5 ± 0.5	

Adn = adenosine; other abbreviations as in Table 5.

Theoretical gain in Quality-adjusted life years(QALY) from ASO as compared atrial switch operation



- Low long-term Cx rate for ASO and near normal life expectancy.
- Gain is likely to become larger after 3rd-5th decade.
- QALY gain due to the extension of life expect to become apparent in later life

Summary

- The prevalence of long-term sequelae after ASO has remained relatively low compared to atrial switch repair
- A great number of patients require cardiac intervention or present with significant residual hemodynamic lesions, commonly affecting the right ventricular outflow tract and pulmonary arteries.

Summary

- Clinically relevant coronary complications are infrequent and still, not support the need for routine invasive coronary assessment in young population.
- It would seem premature to decree on the long-term outcome of ASO.
- Close surveillance of these patients in specialized centers is, however, strongly advisable


Thank You!