Long-Term Outcome of Mustard/Senning Correction for Transposition of the Great Arteries (TGA) in Sweden and Denmark

Running title: Vejlstrup et al.; Mustard & Senning in Sweden and Denmark

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Abstract

Background—The atrial switch operation Mustard- or Senning operation for transposition of the great arteries (TGA) was introduced in the late 1950s and was the preferred surgery for TGA until the early 1990s. The Mustard- and Senning operation involves extensive surgery in the atria and leaves the right ventricle as the systemic ventricle. The Mustard and Senning cohort is now well into adulthood and we begin to see the long-term outcome.

Methods and Results—All the six surgical centers that performed Mustard- and Senning operations in Sweden and Denmark, identified all operated TGA patients. Information about death was obtained in late 2007 and early 2008 from the Danish and Swedish Centralised Civil Register using the patients’ unique national Civil Registration Numbers. 468 atrial switch patients were identified. Perioperative 30 days mortality was 20% and 60% were alive after 30 years of follow-up. Perioperative mortality was significantly increased by the presence of a ventricular septal defect (VSD), left ventricular outflow obstruction (LVOTO), surgery early in the Mustard- and Senning era. However, only pacemaker implantation is predictive of long-term outcome (HR 1.90, 95% CI 1.05-3.46, p=0.04), once the TGA patient has survived the perioperative period. The risk of reoperation was correlated to the presence of associated defects and where the first Mustard/Senning operation was performed.

Conclusions—The long-term survival of patients with Mustard- and Senning correction for TGA appears to be primarily determined by factors in the right ventricle and tricuspid valve and not the timing of or the type of surgery in childhood. Cardiac function necessitating implantation of a pacemaker is associated with an increase in mortality.

Key words: heart defects, congenital, transposition of great vessels, prognosis, survival, pacemaker
Introduction

Transposition of the great arteries (TGA) is a congenital heart defect where the arterial trunks are connected to the morphologically inappropriate ventricles. Unpalliated TGA has a 90% mortality within the first year of life. Radical surgery in the form of the atrial switch operations was introduced by Åke Senning and William Mustard, and in the 1970s these procedures were routinely performed. In the 1980s the arterial switch operation (ASO) replaced the Mustard- and Senning operation. The initial short follow-up showed satisfactory results of ASO compared to Mustard- and Senning correction but long-term results have only recently been reported. The patient population with Mustard- and Senning correction is now well into adulthood making long-term follow-up possible. The population of patients with Mustard- and Senning correction represents a clinical challenge and can provide us with important insight into the consequences of having a morphological right ventricle as a systemic ventricle. Sweden and Denmark have a population of 14.5 millions. The Scandinavian social structure with general access to qualified healthcare and population based validated registries creates a unique opportunity for long-term follow-up of large numbers of patients. The centralized structure of tertiary cardiology centers and congenital surgery allowed us to study the whole population of Sweden and Denmark over a long period of time. The present study provides outcome data from a large, contemporary cohort of unselected, consecutive patients with TGA who underwent Mustard- and Senning procedures in Sweden and Denmark from 1967 to 2003.

Methods

We carried out a retrospective analysis of the medical records of patients who had either simple or complex TGA and who had undergone either Mustard or Senning operations. Historically
Sweden and Denmark had 6 centers performing congenital heart surgery. (The congenital heart centers were located in Copenhagen and Skejby in Denmark, and in Sweden in Stockholm, Uppsala, Lund and Gothenburg). All operation logbooks were reviewed and when a Mustard- and Senning operation was recorded the patient was included in the study for further review of medical records according to a pre-specified protocol. Patients with TGA who had a Rastelli correction or had more complex anatomy such as double outlet or single ventricle physiology, were excluded. Operation logbooks were examined by experienced cardiologists subspecialized in congenital heart disease at the respective units, who also performed the data extraction from hospital records in accordance with a pre-specified data collection form. In this cohort the first patient was operated in 1967 and the last Mustard operation was performed in 2003. (The first atrial switch operation, performed by Åke Senning in 1958 3 was not included since the patient was not living in Denmark or Sweden. After Senning’s initial landmark operation, no Mustard- and Senning procedures could be found in the logbooks until 1967, i.e., 9 years later.) In all 468 patients with TGA were identified and included in the study. In late 2007 and early 2008 all patients were cross-checked against the national death registries in order to verify mortality data and to define the date of death. The data was anonymized. Twenty-three patients from the operation diaries could not be identified and were not found in the death registry, they were presumed to have died during or after the operation. The substudy in Sweden was approved by the ethics committee in Gothenburg (Dnr.: 174-08. URL: www.epn.se). Ethics approval for anonymized retrospective studies of registries was not required in Denmark, but the study was approved by the Danish Datatilsynet (J.nr. 2009-41-3319, www.datatilsynet.dk).

**Statistical analysis**

The TGA patients were divided into two groups according to the time of surgery. The early era
was defined as surgery performed before or on the median date (4. November 1980), late era was defined as surgery performed after this date. Associations between categories of variables were measured by the $\chi^2$-test or trend test, and Student’s t-test was used for continuous variables. Binary logistic regression with backward elimination was performed to identify predictors of perioperative mortality (death within 30 days following surgery). Kaplan-Meier plots were used to illustrate survival curves and Cox proportional hazard model was used for initial univariate comparisons. Multivariable comparisons were performed using a Cox proportional hazard model (fitted by backward elimination using a threshold of $p < 0.1$ for elimination) after checking assumptions of proportionality. Additional Cox analyses of events (pacemaker implantation or reoperation) during the follow-up period were performed with these variables included as time dependent covariates. Continuous variables are summarized as means and 95% confidence intervals (CI), while categorical data are summarized as frequencies and percentages. Statistical calculations were done with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

**Results**

This analysis included all (n=468) patients operated for TGA in Denmark and Sweden with either the Mustard- or Senning operation between 1967 and 2003. Mean age at the time of surgery was 1.9 years (95% CI 1.7 years – 2.2 years) and 319 (68.2%) were males. Baseline characteristics of the included patients divided by country appear from table1. Patients in Denmark were operated significantly earlier than patients in Sweden and the Mustard operation was significantly more frequent in Denmark than in Sweden. There were no statistically significant differences in gender or frequency of associated heart defects between the two countries. The majority of children (385 (82%)) with TGA were operated before the age of three
and very few were operated after the age of six (25 (5%). Patients operated in the early era were significantly older (2.6 years, 95% CI 2.2 years -3.0 years) than those operated in the late era (1.3 years, 95% CI 1.2 years-1.4 years), p<0.01. Perioperative mortality (death within 30 days following surgery) was high (93 (20%)). In multivariable logistic regression only the era in which the patients were operated and the presence of an associated heart defects were associated with perioperative death (see table 2).

Median follow-up was 26.1 years (range 0.4 years – 60 years), 4 (<1%) patients emigrated and were lost for follow-up. During the observation period pacemaker implantation was performed in 63 patients (15%), reoperation was performed in 27 patients (7%) and 184 (39%) of the patients died or had a heart transplant (176 (38%) died and 8 (2%) had a heart transplant).

Implantation of a pacemaker was not associated with age at operation, gender, country, era of surgery, Mustard vs. Senning, or the presence of LVOT and/or VSD neither in uni- nor multivariable analyses (data not shown).

Kaplan Meier curve of survival for all patients in the study show a high perioperative mortality followed by a long period of low mortality (Figure 1).

Kaplan Meier curves of time to reoperation divided in early vs late surgery, Mustard vs. Senning, and associated heart defects are presented in figure 2 panel a-c. Even though it seems that the Mustard operation was strongly associated with reoperation after performing a multivariable cox regression analysis only surgery performed in Denmark was independently associated with reoperation see table 3. Only 5 (19%) of the 27 reoperations were performed in Sweden. Having LVOTO and/or VSD did not increase the risk of redo of the atrial switch.

Kaplan Meier curves of time to death or heart transplantation after primary surgery
divided in early vs late era, type of surgery, and associated heart defects are presented in figure 3 panel a-c. As presented in table 2, only surgery in the early era (i.e. surgery performed after 4 November 1980) and LVOT and/or VSD was associated with increased mortality. This was true both in a univariable analyses and in a multivariable analysis including all variables see table 4. However, if all patients that died within 30 days of surgery (perioperative death) were excluded from the analyses then none of the variables were associated with mortality, neither in uni- or multivariable analyses (data not shown).

If pacemaker implantation was included as a time dependent variable in a cox regression analysis of time to death or heart transplant the results were unaltered, however if patient who died perioperatively were excluded then pacemaker implantation is the only variable that was associated with increased mortality, HR 1.90, 95% CI 1.05-3.46, p=0.04. In a similar analysis where reoperation was included as a time dependent variable the Cox regression analysis showed that reoperation was not associated with increased risk of mortality and heart transplantation.

There were 6.2 million live births in Denmark and Sweden between 1967 and 2003 (Statistic Sweden (SBC) and Dansk Statistik). The incidence of TGA is 312 pr million 9, so approximately 1900 children with TGA were born in the study period. Only 468 had a Mustard/Senning operation, and a very small number of the TGA patients had an arterial switch operation in the surgical transition period in the late1990s.

Discussion

To the authors knowledge this is the largest study of survival after the atrial switch operation for transposition of the great arteries. The study includes all patients operated with the Mustard or Senning operation in Denmark and Sweden from 1967 through 2003 (n=468). From the
incidence of TGA in Scandinavia one can calculate that the majority of children born with TGA must have died before a Mustard- or Senning operation was even attempted. In a previous report from western-Sweden early in the era, all patients born with TGA were investigated. This study found that 40% children born and diagnosed with TGA died before surgery, most likely due to hypoxia or heart failure. Even after atrial septostomy patients with TGA have a high mortality, and this is rarely discussed when comparing Mustard/Senning operation with ASO, an operation most often performed before the child is one month of age. The patients in this study are similar to other populations of TGA with a male:female ratio of 2:1. Most patients had an atrial communication made shortly after birth either with the Rashkind procedure or the Blalock-Hanlon operation. The frequency of Mustard/Senning procedures performed in this Danish and Swedish population was 35 per million which is similar to the incidence reported by Moons and co-workers from Belgium (34 per million), suggesting a similarly high pre-operative mortality in children with TGA in that population. For almost two decades, the ASO has replaced the atrial switch operations, which means that the patient population with a Mustard or Senning repair will disappear over the next 40 years. The main reason for studying the Mustard and Senning population in the 21 century is to determine what predicts mortality in this the current adult Mustard- and Senning population, and it is also an opportunity to study right ventricle in the systemic position. We found that the perioperative mortality was 20% which is much higher than revealed in most reports. We could find only one recent report of similar high mortality which is also a population based study, and not a report from tertiary center. We speculate that the historic reports of low perioperative mortality could be explained by patient selection in tertiary centers and publication bias, and we suggest that population based studies better reflect the risk for a patient with a congenital heart defect. There is also a learning curve for complex
surgery and postoperative care, and studies form the 1980s, late in the Mustard- and Senning era, show very low perioperative mortality\textsuperscript{16,17}. That there was a higher perioperative mortality in smaller centers like those in Denmark and Sweden compared to the large international high output surgical centers was undoubtedly also the case. It is unlikely that such differences in perioperative mortality would have been tolerated today.

The primary findings in this study is that several factors, normally considered important for long term survival: operation type (Mustard vs. Senning), age at operation, institution where the operation was performed, operation early or late in the era, associated defects such as VSD and LVOTO, is not statistically significantly associated with long term survival. In the early part of the Mustard- and Senning era patients were operated late. It has been suggested that longstanding preoperative hypoxia might be an important risk factor for poor long-term outcome, but we did not find any evidence for that. There are several reports describing the advantages of the Senning procedure relative to the Mustard procedure\textsuperscript{12,18}. This study could not show any statistically significant difference in long-term survival between patients operated with the Senning or Mustard procedure (figure 3). Long-term survival appears to be primarily determined by how well the right ventricle and the tricuspid valve tolerates systemic afterload and blood pressure. Patients with congenitally corrected transposition (ccTGA) has a long term survival similar to patients operated with the Mustard and Senning procedures, even though many patients with ccTGA have never undergone cardiac surgery\textsuperscript{19-21}.

Cardiac function necessitating implantation of a pacemaker is associated with an increase in mortality (HR 1.90, 95% c.i. 1.05-3.46, \textit{p}=0.04), this could be because the need for a pacemaker is a sign of other impending problems, or it could be that pacing has a deleterious effect on the systemic right ventricle.
The risk of reoperation was not associated with the type of surgery or the presence of additional defect, but was associated with who did the surgery. Denmark had a statistically significant higher number of reoperations after atrial repair compared to Sweden (table 3). A less than perfect Mustard- or Senning repair, does not damage the right ventricle but will increase the risk of needing a re-operation on the atrial baffles. However, reoperation was not found to be associated with a statistically significant effect on long term survival.

This study suggests that, when caring for survivors after Mustard- and Senning repair, then the clinical focus should be on the function of the right ventricle and tricuspid valve. Operation notes will be less helpful in providing information useful for predicting long-term survival. Special attention should be given to Mustard and Senning patients with pacemakers because they have increased mortality.

The population of Mustard- and Senning patients will disappear over the next forty years, but cardiologist will always have to treat patients with ccTGA where knowledge of how the right ventricle tolerate systemic afterload could be helpful. In future comparisons with ASO one should keep in mind that one of the major advantages of the ASO procedure is, that the ASO is performed very early (2-6 weeks post partum)(ref), because many children with TGA died before the atrial switch operation. Today atrial correction could also be performed in the neonatal period and most likely with similar pre- and perioperative mortality as the ASO. The importance of physiological correction of TGA is supported by the observation that 25 years of perfecting the Mustard- and Senning surgery did not significantly change the long term survival.

An other observation relevant to future studies of congenital heart disease, is that the predictors of perioperative survival can be very different from what determines long term survival, and survival plots without the perioperative mortality could some times be more
clinically relevant in adult congenital heart disease.

Limitation of the study

23 patients who underwent a Mustard/Senning procedure were not found in the death registry and they were presumed to have died early postoperatively before they were given the national 10-digit personal number in the national population registry system. If they are assumed to be dead but if they are actually still alive, the perioperative mortality is overestimated by 5% and long-term follow-up rate is reduced to 95%.

The reported number of patients with PM insertion might have been underestimated since all patients were not followed by dedicated center’s and PM could have been inserted at the local hospital and not found in the medical records.

Conclusion

We identified all 468 TGA patients operated with Mustard or Senning operation in Sweden and Denmark. The 30 days perioperative mortality was high (20%). Perioperative mortality was statistically significantly correlated with the presence of LVOTO and/or VSD, and whether surgery was performed before or after 1980. None of the factors important for perioperative mortality had any influence on long term mortality. Implantation of a pacemaker was the only factor identified to have an adverse effect on long term mortality.

Clinical impact of this study

It is often discussed what is important for long-term survival in patients palliated with the atrial switch procedures. This study finds that type of operation; time of operation; even institution of operation, does not predict long term survival and need for transplantation. Long-term survival is good in adulthood, and the “knee” on the Kaplan Meier plot probably is the result of censoring.
Only the need for implantation of a pacemaker is associated with poorer long-term survival. This study also suggests that in adult congenital heart disease survival curves that only looks at survival in adulthood could be more relevant for clinical practice.

**Conflict of Interest Disclosures:** None.

**References:**


**Table 1.** Baseline characteristics and demographics.

<table>
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<tr>
<th></th>
<th>Denmark, n= 193</th>
<th>Sweden, n= 275</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>61 (32%)</td>
<td>88 (32%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Mustard op., n (%)</td>
<td>186 (96%)</td>
<td>124 (45%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Age at operation, mean (years)±SD</td>
<td>1.6 ± 2.1</td>
<td>2.1 ± 2.8</td>
<td>0.03</td>
</tr>
<tr>
<td>VSD, n (%)</td>
<td>64 (33%)</td>
<td>70 (25%)</td>
<td>0.07</td>
</tr>
<tr>
<td>LVOTO, n (%)</td>
<td>14 (7%)</td>
<td>22 (8%)</td>
<td>0.77</td>
</tr>
<tr>
<td>LVOTO and VSD, n (%)</td>
<td>5 (3%)</td>
<td>15 (6%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

VSD= ventricular septal defect, LVOTO= left ventricular outflow tract obstruction, SD=standard deviation

**Table 2.** Multivariable logistic regression testing factors associated with perioperative death. Only early surgery (early in the Mustard- and Senning era) and associated defects (LVOTO and VSD) was found to influence perioperative death significantly. This analysis is from the time of surgery.

<table>
<thead>
<tr>
<th></th>
<th>Univariable analyses</th>
<th>Multivariable analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Estimated odds ratio</td>
<td>P</td>
</tr>
<tr>
<td>Age at operation (pr year)</td>
<td>1.01 (0.92-1.10)</td>
<td>0.90</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.09 (0.67-1.77)</td>
<td>0.73</td>
</tr>
<tr>
<td>Surgery performed in Denmark</td>
<td>1.23 (0.80-2.04)</td>
<td>0.31</td>
</tr>
<tr>
<td>Surgery performed after 4 November 1980</td>
<td>0.40 (0.25-0.65)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mustard surgery</td>
<td>1.02 (0.62-1.67)</td>
<td>0.94</td>
</tr>
<tr>
<td>Associated heart defect(s)</td>
<td>2.04 (1.28-3.24)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

VSD= ventricular septal defect, LVOTO= left ventricular outflow tract obstruction.
**Table 3.** Reoperation. In a multivariable analysis only surgery performed in Denmark was associated with an increased risk of redo of the Mustard- and Senning repair.

<table>
<thead>
<tr>
<th></th>
<th>Univariable analyses</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age at operation (pr year)</td>
<td>0.92 (0.75-1.12)</td>
<td>0.38</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.77 (0.49-1.22)</td>
<td>0.27</td>
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<tr>
<td>Surgery performed in Denmark</td>
<td>7.77 (2.93-20.58)</td>
<td>&lt;0.01</td>
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<tr>
<td>Surgery performed after 4 November 1980</td>
<td>0.96 (0.42-2.23)</td>
<td>0.93</td>
</tr>
<tr>
<td>Mustard surgery</td>
<td>5.25 (1.24-22.30)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Associated heart defect</td>
<td>1.91 (0.89-4.12)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

CI=confidence interval

**Table 4.** Univariable and multivariable analysis of death and HTX.

<table>
<thead>
<tr>
<th></th>
<th>Univariable analyses</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age at operation (pr year)</td>
<td>0.98 (0.92-1.04)</td>
<td>0.44</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.02 (0.87-1.20)</td>
<td>0.76</td>
</tr>
<tr>
<td>Surgery performed in Denmark</td>
<td>1.02 (0.76-1.38)</td>
<td>0.88</td>
</tr>
<tr>
<td>Surgery performed after 4.10.1980</td>
<td>0.68 (0.50-0.92)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mustard surgery</td>
<td>0.93 (0.67-1.28)</td>
<td>0.64</td>
</tr>
<tr>
<td>Associated heart defect</td>
<td>1.60 (1.18-2.15)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

In the multivariable analysis only surgery performed after 4 November 1980 and associated heart defect stayed in the model. This analysis is from the time of surgery

CI=confidence interval

**Figure Legends:**

**Figure 1.** HTX-free survival after surgery. Kaplan-Meier plot with 95% confidence interval.

Perioperative mortality was over 20%. The “knee” on the curve is very likely the result of censoring.

**Figure 2.** Re-operation free survival. The survival curves starts at 30 days, to show the survival that is not directly dependent on the preoperative mortality. (a). Re-operation free survival in the
early and late era. (b) Re-operation free survival for Mustard and Senning patients. (c) Re-
operation free survival with and without additional lesions (VSD and/or LVOTO). A
multivariable Cox regression analysis shows that none of these factors are significant (table 4).
VSD= ventricular septal defect, LVOTO= left ventricular outflow tract obstruction.

**Figure 3.** Kaplan Meier curves for HTX free survival. These survival curves starts from the time
of surgery and also reveal the perioperative mortality. (a). HTX free survival in the early and late
era. (b) HTX free survival for Mustard and Senning patients. (c) HTX free survival with and
without additional lesions (VSD and/or LVOTO). A multivariable cox regression analysis shows
that none of these factors are significant. HTX= heart transplantation, VSD= ventricular septal
defect, LVOTO= left ventricular outflow tract obstruction.
Figure 2A
Figure 2C
Figure 3B
Figure 3C
Long-Term Outcome of Mustard/Senning Correction for Transposition of the Great Arteries (TGA) in Sweden and Denmark

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