Chasing a moving target: outcome and risk stratification in patients with transposition of the great arteries after atrial switch operation

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This editorial refers to ‘The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years’, by J.A.A.E. Cuypers et al., on page 1666

Before the advent of the atrial switch operation, hardly any infant born with complete transposition of the great arteries (TGA) survived beyond the first year of life. In the 1950s and 1960s, two operations introduced by Senning and Mustard, respectively, revolutionized the outcome of the condition, allowing patients to survive well into adulthood.1,2 However, ongoing long-term complications, as well as increased morbidity and mortality remain an issue even five decades later. This type of physiological repair has now been largely replaced by the arterial switch procedure.3 Today it continues to be reserved only for highly selected cases and has, thus, become part of medical history more than being a viable treatment option.

Late complications and risk stratification in patients after Mustard or Senning repair

Patients after Mustard or Senning (M/S) repair are afflicted by three main problems: (i) loss of sinus rhythm and arrhythmias; (ii) right (systemic) ventricular dysfunction leading to heart failure; and (iii) problems with baffle obstruction or leaks. These complications add to morbidity and induce excess mortality in this population.4 Since the introduction of surgical correction, cardiac surgeons, paediatric cardiologists, and later adult congenital cardiologists continue to study these problems. This has led to a considerable and growing body of literature delineating the prevalence of complications and trying to predict future problems based on surgical and/or medical history. Since 1990, > 20 studies, including over 3500 patients, have dealt with these issues (Table 1). However, risk stratification remains an unsolved problem in this population. Late mortality appears to be due to two main problems: (i) sudden cardiac death; and (ii) heart failure-related mortality.5,6 Both remain problematic but create challenges at different levels: while the first is in principle addressable by implantable cardioverter-defibrillator (ICD) therapy, patient selection and the considerable risk of device-related complications or inadequate therapies remain of concern. The latter, in turn, poses challenges mainly in terms of treatment (as no convincing treatment option exists). Table 1 presents an overview of published risk predictors in this population. It illustrates that there is disagreement regarding the prognostic impact even of simple characteristics such as the type of operation and the complexity of the underlying condition. Furthermore, the prognostic value of electrocardiogram (ECG) parameters or demographics has not been unequivocally established. Table 1 also shows that little information exists on the predictive value of novel biomarkers or advanced imaging parameters. In fact, almost all studies concentrated on widely available surgical/medical history or demographic parameters.

The changing spectrum of disease in the ageing Mustard or Senning population and need for ongoing studies

As shown in Figure 1A, the age distribution of M/S patients is changing. This is estimated based on birth numbers for Germany and survival probabilities derived from the literature.7–9 The figure illustrates that all surviving M/S patients have now entered adulthood. It is to be expected that, with increasing age, the majority of patients will continue to deteriorate symptomatically and present with increasing complications. After the stormy early years of life with evolving and high-risk surgical procedures, the majority of surviving patients benefited from a relatively low annual risk of death during the following 2–3 decades.10 These relatively stable patients have been part of

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many previous studies evaluating the natural cause of the disease. However, as M/S patients enter the fourth and fifth decade of life, the rate and spectrum of complications is set to change and this will create new challenges for risk stratification and therapy. Therefore, the study by Cuypers and colleagues is a timely contribution to the literature, describing contemporary complications and outcome in a cohort of M/S patients followed for nearly 40 years. The authors describe a group of 91 patients followed since the
Figure 1  (A) Estimated age distribution of Mustard/Senning (M/S) patients in Germany based on birth numbers and survival probabilities from the literature.\textsuperscript{7,8,10} Details on the analysis are available upon request from the author. To estimate approximate numbers for the EU-15 countries, multiply by 4.75. (B) Kaplan–Meier survival curve based on the data provided by Cuypers et al.\textsuperscript{11} In addition, the expected survival for the general population is shown (dotted black line). The figure illustrates that M/S patients are likely increasingly to enter a phase of accelerated decline and increasing complications/mortality.
1970s/1980s. This is the third in a series of papers characterizing this population over time.\textsuperscript{12,13} Patients were assessed prospectively every 10 years and complications were documented. The current report and its predecessors highlight the burden of disease, with an event-free survival of only \~20\% at 35 years of follow-up. The authors also document how the focus has shifted from early surgery-related complications to late morbidity such as right ventricular dysfunction and tricuspid valve regurgitation. In addition, the study introduces state of the art imaging and measurement of biomarkers, not available in previous reports. This is particularly relevant as risk stratification based on conventional clinical findings and historical data is unsatisfactory, as described above. It is hoped that advanced imaging modalities, brain natriuretic peptide (BNP) levels, as well as objective exercise capacity may aid in identifying patients who could benefit from evolving therapeutic techniques. Together with other recent reports investigating the prognostic value of cardiopulmonary testing and strain imaging,\textsuperscript{14,15} this approach could help to overcome some of the limitations of previous reports. However, risk stratification in M/S patients remains challenging. This is mainly due to the heterogeneity of the population. The current dilemma of inadequate risk stratification is illustrated by a recent study\textsuperscript{5} showing that out of 23 M/S patient identified as high-risk patients on clinical grounds and provided with an ICD for primary prevention, only one received an appropriate ICD shock over a median follow-up time of 3.5 years.

Future therapeutic options: not all is lost

While the right ventricle (RV) may not be designed to sustain systemic pressure over a lifetime and certain (patho-)physiological adaptations occur, it is questionable whether increased RV afterload per se is sufficient to cause cardiac failure with time.\textsuperscript{16,17} Rather, one must assume that cofactors, including volume overload due to tricuspid regurgitation and potentially systemic mediators, may trigger heart failure in this setting.\textsuperscript{16} There are also important anatomic and pathophysiological differences between patients post-M/S and those with congenitally corrected TGA, contesting the pathophysiological concept of the patient with a ‘systemic RV’. These involve the different aetiology of tricuspid regurgitation, conduction system abnormalities, the spectrum of associated malformations, and the effect of the atrial baffles on ventricular filling.\textsuperscript{5} M/S patients in particular present with diastolic dysfunction and inability to increase stroke volume on exercise. Moreover, even within the M/S cohort, the spectrum of complications is different between post-Sennening or post-Mustard repair patients and also depends on the presence of associated problems (i.e. complex disease). To make things worse, the clinical condition encountered in adulthood ranges from asymptomatic patients with preserved RV function, without relevant tricuspid regurgitation and arrhythmias, to severely impaired patients with depressed RV function, tricuspid regurgitation, arrhythmias, and overt signs and symptoms of heart failure. As shown by the study by Cuypers et al., systemic ventricular dysfunction is an increasing problem in this ageing population and is significantly associated with tricuspid regurgitation. In this study only one patient (i.e. 2\%) showed a normal RV function on echocardiography. Therefore, as illustrated in Figure 18, the M/S cohort beyond the third decade of life is likely to enter a period of accelerated decline with heart failure symptoms and ultimately death. As a consequence, novel treatment strategies are required to improve symptoms and outcome in this population. It is unlikely that simply extrapolating concepts and therapies from acquired heart failure will be successful. Of course standard heart failure drugs can be administered with low risk in M/S patients but the effect is probably also only marginal, as demonstrated by previous negative trials.\textsuperscript{16} Rather than copying heart failure strategies—ignoring the underlying physiology—new tailored treatment approaches should be explored specifically in this population. As the window of opportunity for M/S takedown and arterial switch operation has now passed in these adult patients, pulmonary arterial banding (potentially combined with tricuspid valve procedures) could provide a treatment option for selected patients.\textsuperscript{16} However, important unsolved issues remain: the optimal timing for intervention is unclear and the mortality of tricuspid valve operations may be prohibitively high in patients with a failing RV. In addition, the potential of innovative pacing devices (especially cardiac resynchronization systems) deserves further study. Ultimately, these patients may have to be listed for transplantation ± assist device bridging if required.

In summary, the number of M/S patients will decrease over the next decades, but complications will continue to increase. These patients are likely increasingly to require particular medical attention. Risk stratification continues to be challenging and this is of particular relevance for predicting sudden cardiac death. Further studies (with multicentre case—control studies arguably representing the most promising strategy), including state of the art imaging, exercise parameters, and laboratory measures, are required to improve risk prediction. Treatment options for cardiac failure are limited. It is unlikely that further heart failure medication studies will be successful given the limited number of patients, the relatively low event rate, and the particular physiology of M/S patients. Rather, tailored approaches, including aggressive electrophysiological interventions and innovative surgical procedures, may be required. M/S patients still alive today continue to be a testimony to the remarkable ingenuity of the pioneers of cardiac surgery and cardiology, and should remind us that even in times of increasing regulation, government intervention, and threat of litigation, innovation has—at times—to be revolutionary rather than evolutionary to allow patients with congenital heart disease to fulfil their full potential.

Conflict of interest: none declared.

References


