Editorial

Ventricular arrhythmias and sudden death in patients with Ebstein anomaly: insights from a retrospective cohort study

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Ebstein anomaly accounts for <1% of all congenital heart defects (CHDs), with a prevalence of ~1 per 200,000 live births. In 1866, Wilhelm Ebstein described "A very rare case of insufficiency of the tricuspid valve, caused by a severe congenital malformation". He reported the pathological findings of a 19 year-old cyanotic male, Joseph Prescher, who complained of shortness of breath and palpitations since childhood and subsequently died from heart failure. Ebstein's meticulous description of the malformed tricuspid valve was complemented by the drawings produced by his colleague, Dr. Wyss, shown in *Figure 1* (1). Ebstein anomaly is characterized by (I) adherence of septal and posterior tricuspid valve leaflets to the underlying myocardium, (II) downward (apical) displacement of the functional tricuspid annulus, (III) dilation of the "atrialized" portion of the right ventricle (RV), (IV) redundancy, fenestrations, and tethering of the anterior tricuspid valve leaflet, and (V) dilation of the right atrioventricular junction (2).

Despite major improvements in the care and outcomes of patients with Ebstein anomaly over the past decades, ventricular arrhythmias and sudden death remain feared complications. The incidence of life-threatening arrhythmias is poorly defined and the risk profile understudied, considering that the literature is largely limited to small retrospective studies. Within this context, Attenhofer Jost presented an analysis of their impressive single-center retrospective cohort of 968 consecutive patients with Ebstein anomaly managed at the Mayo Clinic between April 1972 and December 2015 (3). Patients were 25 years of age on average at first presentation, and 41.5% were male. Sustained ventricular arrhythmias [ventricular tachycardia (VT) or fibrillation (VF)] were combined with resuscitated cardiac arrest and sudden death into a composite outcome that the authors labeled "sudden death". This outcome occurred in 65 patients during a follow-up that averaged 13.2 years, with 31 witnessed sudden deaths, 10 sustained VT/VFs, 10 resuscitated out-of-hospital cardiac arrests, and 14 unwitnessed deaths with autopsy reports or death certificates consistent with sudden death. When assessed from birth, corresponding 10-, 50-, and 70-year rates of ventricular arrhythmias/sudden death were 0.8%, 8.3%, and 14.6%, respectively.

Attenhofer Jost *et al.* are to be commended for undertaking the largest study to date on the incidence and predictors of ventricular arrhythmias/sudden death in patients with Ebstein anomaly. Assuming a linear risk, the estimated incidence of the combined outcome was ~0.2% per year, a finding consistent with prior reports (4,5) and within the range of CHD substrates associated with an increased risk for sudden death, such as tetralogy of Fallot (6,7). There are, however, numerous challenges to calculating incidence rates from retrospective studies. One important issue in estimating survival from birth in a predominantly adult cohort (i.e., average age 25 years at presentation) is so-called immortal-time bias. "Immortal-time" refers to a span of time during which it is impossible for at least one of the components of the outcome to have occurred. If a child with Ebstein anomaly died suddenly prior to presentation at the Mayo Clinic, that patient would

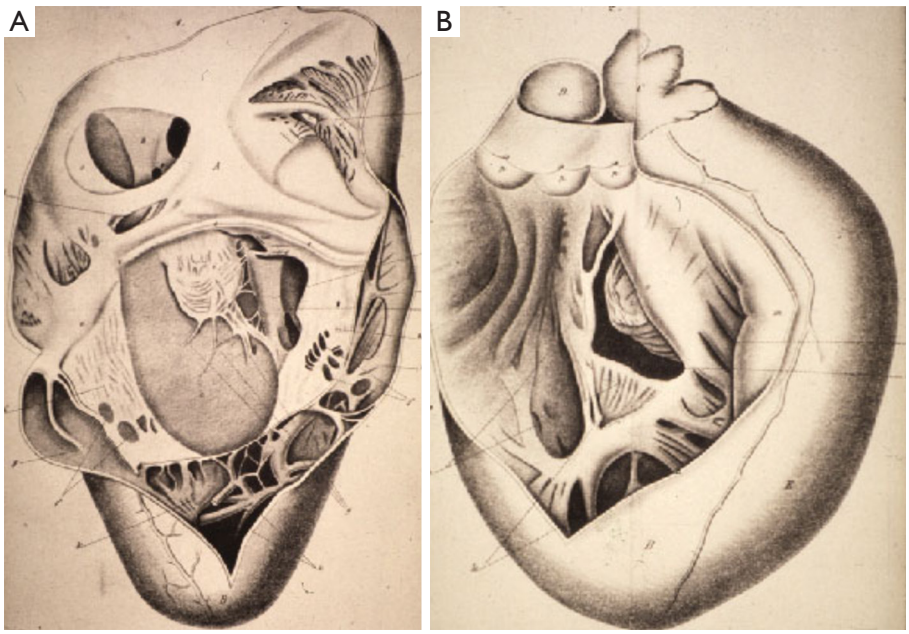

Figure 1 The original drawings by Dr. Wyss, complementing the autopsy description of Joseph Prescher's anomaly of the tricuspid valve as described by Dr. Wilhelm Ebstein. Reproduced with permission from (1).

have escaped detection. It is, therefore, not possible for a study patient to have died suddenly between birth and enrollment such that, statistically, selected individuals were "immortal" during this time frame. Not accounting for this bias can result in an under-estimation of the incidence of sudden death. Validated techniques to address immortal-time bias include Manel-Byar and landmark methods.

Conversely, an analysis of malignant ventricular arrhythmias and sudden death based on the experience of a single quaternary center with world-renowned expertise can result in an over-estimation of risk owing to the fact that more complex patients are preferentially referred. For example, most adults with Ebstein anomaly have mild forms and do not require surgery. In contrast, 80% of patients in Attenhofer Jost *et al.*'s study had severe Ebstein anomaly with tricuspid valve surgery performed in 83%. Given the potential for this referral bias to have a major impact on the estimated incidence of sudden death, results should not be extrapolated to the larger lower-risk population (3). This is particularly relevant to the issue of relying on such sudden death risk estimates in selecting appropriate candidates for primary prevention implantable cardioverter-defibrillators (ICD). Unlike tetralogy of Fallot for example (8), expert consensus recommendations have yet to specifically address primary prevention ICDs in Ebstein anomaly (9). In Attenhofer Jost *et al.*'s study, 24 (2.5%) patients had ICDs, 14 for secondary and 10 for primary prevention. Seven of 14 (50%) patients with secondary prevention ICDs received appropriate shocks. In contrast, no patient with a prophylactic ICD had appropriate anti-tachycardia pacing or shocks, a finding that precludes the identification of factors associated with ventricular arrhythmias and sudden death in primary prevention ICD recipients.

Despite such limitations, the study provides valuable insights. In an analysis that considered factors collected at the time of the first encounter at the Mayo Clinic, multivariable predictors of the composite outcome were history of VT [hazard ratio (HR) 6.0], heart failure (HR 5.7), tricuspid valve surgery (HR 5.9), syncope (HR 2.0), pulmonary stenosis (HR 3.4), and hemoglobin >15 g/dL (HR 2.1) (3). In exploratory analyses, additional factors associated with ventricular arrhythmias and sudden death not incorporated in the multivariable model included increased QRS duration, QTc interval >500 ms, left ventricular non-compaction, mitral regurgitation, and atrial arrhythmias. Despite the low prevalence of coronary artery disease (5.9%) in this young population, it was also significantly associated with the composite outcome (HR 2.4). This observation highlights the prognostic importance of acquired diseases in the aging population with CHD.

In general, much has been learned about the RV and its association with ventricular arrhythmias and sudden death by studying patients with CHD. In Attenhofer Jost *et al.*'s study, neither the anatomic severity of Ebstein anomaly nor degree of RV enlargement or tricuspid regurgitation was predictive of ventricular arrhythmias and sudden death, which contrasts with previous reports (5,10,11). It is difficult to know to what extent under-representation of patients with mild forms of Ebstein anomaly may have influenced these findings. RV systolic dysfunction did, however, exhibit a dose-dependent relationship with the composite outcome. While reasons underlying disparities between RV structural and functional parameters are unclear, the authors speculated that they may be due, in part, to limitations of conventional echocardiography, which may not adequately assess the shape of a crescentic RV that is dependent on left ventricular (LV) septal motion. It remains to be determined whether a more reliable determination of RV size and function provided by advanced imaging modalities, such as three-dimensional echocardiography or cardiac magnetic resonance (CMR), would result in consistent associations between RV metrics and ventricular arrhythmias and sudden death. Rydman *et al.* recently reported that CMR-derived indices of RV and LV function and volumes carried prognostic information regarding major adverse cardiovascular events in adults with unrepaired Ebstein anomaly (12). In addition, while the mean LV ejection fraction was normal in Attenhofer Jost *et al.*'s study (58.3%±8.3%), LV systolic dysfunction has been associated with poorer survival in other cohorts (13).

Prior reports have suggested that earlier presentation and diagnosis of Ebstein anomaly is associated with coexisting cardiac defects and poorer outcomes (10,14,15). The high event rate observed in Attenhofer Jost *et al.*'s study, in which most patients required surgical intervention, is concordant with these observations. Importantly, the authors observed a higher incidence of ventricular arrhythmias/sudden death in patients who underwent tricuspid valve surgery (3). A causal association cannot be established from a retrospective observational study where residual confounding remains a plausible alternative explanation. Nevertheless, Attenhofer Jost *et al.* raised the possibility that tricuspid valve surgery may itself have a proarrhythmic effect and called into question the need for and appropriate timing of surgical intervention (3). While tricuspid valve surgery has been shown to improve functional outcomes in selected patients with Ebstein anomaly (16), surgical proarrhythmic effects associated with ventriculotomy incisions and patches are well recognized in other forms of CHD, and ventricular arrhythmias have been reported after surgical repair of Ebstein anomaly (4). It could be hypothesized that the atrialized portion of the RV is particularly vulnerable to such proarrhythmic effects considering that, in our experience, ventricular arrhythmias can be induced by non-aggressive programmed stimulation at this site. The authors also reported that a bi-atrial Maze was strongly associated with ventricular arrhythmias and sudden death in comparison to a right-sided Maze (HR 18.4). Given the non-randomized study design, it is likely that the arrhythmia burden, a marker of poorer prognosis, was higher in patients with bi-atrial versus right-sided Maze procedures. While it is reasonable to consider concomitant atrial arrhythmia surgery in adults with Ebstein anomaly undergoing cardiac surgery, a left atrial Cox Maze III procedure should generally be avoided in the absence of documented atrial fibrillation (9,17).

Finally, over the inclusion period that spanned four decades, substantial refinements in management and surgical approaches occurred that could impact risk assessment (18), as appropriately acknowledged by the authors. Forty percent of operated patients in the present cohort had tricuspid valve repair (3). While few details are provided regarding the valve reconstruction techniques used, investigators at the Mayo Clinic have pioneered technical modifications that have been incorporated over time (11). Most recently, the cone procedure, described by da Silva and colleagues, has emerged as a more anatomical approach whereby septal leaflet mobilization allows circumferential 360° leaflet reattachment, resulting in superior leaflet-to-leaflet coaptation when compared to earlier monocuspid valve repairs (19). These considerations underscore the difficulty of risk assessment in adults with CHD who constitute a "moving target", as they are subjected to, and benefit from, continued improvements in surgical and medical care over the years. From an arrhythmia perspective, there is some data to suggest that an aggressive diagnostic strategy that includes preoperative electrophysiological testing can contribute to lowering the risk for sudden death in patients with Ebstein anomaly undergoing the cone procedure (20).

In conclusion, Attenhofer Jost and colleagues provided much needed data in an important subgroup of patients with CHD. As the largest study of its kind, it confirms that ventricular arrhythmias and sudden death are major contributors to long-term morbidity and mortality in patients with Ebstein anomaly. The study raises important questions regarding potential proarrhythmic effects of

surgical interventions and paves the way for future research addressing risk reduction strategies, including the selection of suitable candidates for primary prevention ICDs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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