

## Managing Ebstein's Anomaly of the Tricuspid Valve: Impact of Cardiovascular Magnetic Resonance

Olga Hösch, Sophie Charlotte Alt, Thomas Paul, Joachim Lotz, Michael Steinmetz, Andreas Schuster

Olga Hösch, Sophie Charlotte Alt, Thomas Paul, Michael Steinmetz, Department of Pediatric Cardiology and Intensive Care Medicine, Georg-August University, Göttingen, Germany

Joachim Lotz, Institute for Diagnostic and Interventional Radiology, Georg-August University, Göttingen, Germany

Joachim Lotz, Michael Steinmetz, Andreas Schuster, German Centre for Cardiovascular Research, Germany

Andreas Schuster, Department of Cardiology and Pneumology, Georg-August University, Göttingen, Germany

Michael Steinmetz and Andreas Schuster Both contributed equally to the article.

Correspondence to: Andreas Schuster, MD, PhD, FESC, Department of Cardiology and Pneumology, University Medical Center Göttingen, Georg-August-University, Robert-Koch-Str. 40, D-37075 Göttingen, Germany.

Email: [andreas\\_schuster@gmx.net](mailto:andreas_schuster@gmx.net)

Telephone: +49551/39-6315 Fax: +49551/39-22026

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### ABSTRACT

Ebstein's anomaly (EA) is a congenital malformation of the tricuspid valve and right ventricle, with a highly variable morphology and clinical presentation. Recent technological developments in cardiovascular magnetic resonance (CMR) have resulted in a better understanding of the uncommon *in vivo* heart anatomy and function of EA. CMR has evolved into the preferred method for cardiac morphology and physiology assessment. Its feasibility and benefits for the assessment and management of EA have been demonstrated. Accurate volumetric and functional data can be obtained for the right and left side of the heart thereby enabling accurate evaluation of the severity of the disease and clinical decision-making. It furthermore contributes to the planning and timing of interventions. This article aims to review available CMR techniques and their impact on diagnosis and management of patients with EA with an emphasis on future developments and their potential clinical implications.

**Key words:** Congenital heart disease; Cardiovascular magnetic resonance imaging; Ebstein's anomaly

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### INTRODUCTION

Ebstein's anomaly (EA) of the tricuspid valve (TV) is a rare and complex congenital cardiac malformation firstly described by Wilhelm Ebstein in 1866<sup>[1]</sup>. It is defined as a myopathy of the right ventricle (RV) with embryologic failure of delamination of the TV leaflets from the endocardium<sup>[2]</sup>. This leads to a highly variable apical TV displacement, severe tricuspid valve regurgitation (TR), an atrialized portion of the RV (aRV) and right ventricular dysfunction<sup>[3-5]</sup>. It occurs with an incidence of about 1 to 200,000 live births, accounts for 0.3-0.5 % of all patients with congenital heart disease (CHD) and constitutes about 40% of congenital TV malformations<sup>[6,7]</sup>. Cardiovascular magnetic resonance (CMR) can help to quantify the severity of the disease and the associated severity of heart failure and contributes to the difficult decision-making process regarding the types and timing of interventions. This review aims to review the role of CMR in the assessment of the complex cardiac anatomy and the clinical management of patients with EA.

### EBSTEIN'S ANOMALY

#### Pathophysiology

The exact cause of EA is still largely unclear. Studies have demonstrated mutations in the sarcomere protein gene MYH7 as a cause in combination with left ventricular non-compaction<sup>[8]</sup>. Lithium given to mothers with mania is another firmly established etiology<sup>[9]</sup>. The degree of TV and RV morphological changes varies in patients with EA<sup>[5,10]</sup>. The main features comprise TV dysplasia and apical displacement of more than 8 mm/m<sup>2</sup> in the end-diastolic four-chamber view (4CV)<sup>[11]</sup>. This results in a division of the RV into a basal atrialized (aRV) and a functional portion (fRV) including the outflow tract<sup>[12]</sup>. The septal and posterior TV leaflets are often

dysplastic and displaced whereas the anterior leaflet is rarely affected<sup>[13]</sup>. There is commonly TV regurgitation with further right atrial (RA) dilation due to volume overload depending on the degree of TV malformation. The aRV functionally belongs to the RA, but contracts with the fRV. The myocardium of the inlet part in this area is often quite thin and atrophic or fibrotic<sup>[14]</sup>. A lack of muscle fibers in the aRV suggests disruption of the myofibril continuity between the free wall and inferior septal region<sup>[10]</sup>. With regard to the RV global ejection fraction (EF) seems mainly predicted by the extent of circumferential rather than longitudinal shortening<sup>[10]</sup>.

The dysmorphe RV also influences the shape and function of the left ventricle (LV). Thirty-nine percent of patients with EA show abnormalities of the left heart, which concern the myocardium or the valves<sup>[15]</sup>. Goleski *et al* observed that although LV end-diastolic volume (EDV) in CMR often remains preserved, morphological changes including basal narrowing, apical dilation and global hypokinesis lead to mildly impaired LV EF<sup>[16]</sup>.

The most common associated malformations with EA are first atrial septal defect (ASD) of the ostium secundum type and second patent foramen ovale (PFO) which are present in most cases<sup>[17]</sup>. Other well-known associated pathologies are Wolff-Parkinson-White syndrome<sup>[18]</sup>, pulmonary stenosis or atresia, ventricular septal defects and transposition of the great arteries<sup>[13]</sup>. The clinical symptoms of patients with EA are variable according to the diverse severity of the disease. They range from symptomatic neonate to asymptomatic adults<sup>[19]</sup>. Progressive right heart failure and impaired physical exercise capacity affect many patients at a quite early stage in their life. It is unknown which aspect of the changed anatomy, morphology, function and electrophysiology cause deterioration of cardiac function and subsequent heart failure. According to therapeutic possibilities TV reconstruction or replacement are common, but optimal timing and long term success are difficult to predict<sup>[10]</sup>. Indications for surgery are progressive cardiomegaly (increased cardiothoracic ratio), cyanosis and heart failure<sup>[20]</sup>.

### Hemodynamics

There are two significant hemodynamic effects in EA. First, most patients suffer from at least moderate TR. Second, the effective RV size reduces the blood volume capacity which results in increased filling resistance and elevated RA pressure up to venous congestion<sup>[21]</sup>. The TR leads to dilatation of the RA and the TV annulus resulting in volume overload and functional limitation of the fRV<sup>[22]</sup>. This causes chronic pulmonary hypoperfusion, reduced preload of the LV and therefore decreased left ventricular cardiac output. These anatomical changes of the heart are paralleled by modified mechano-kinetics of all cardiac chambers. The basal septum of the LV is bordered by a low pressure system (aRV) which in systole represents a weaker abutment compared to a contractile RV. This causes dyskinesia of the basal interventricular septum<sup>[10]</sup>. All of the individual changes have an influence on cardiac contractility and therefore the overall cardiac function.

## MR IMAGING OF EBSTEIN'S ANOMALY

CMR is particularly well suited as a diagnostic method for evaluating cardiac function and is a routine examination in patients with CHD<sup>[23-25]</sup>. It has emerged into the Gold standard for quantification of cardiac physiology<sup>[26]</sup>. The RV plays an important role in these patients and CMR has become the imaging method of choice for its assessment<sup>[24,27]</sup>. In patients with EA, CMR provides routine clinical information regarding ventricular volumes and function,

muscle mass, valve morphology, fibrosis and dyssynchrony when echocardiography is inconclusive or technically not feasible<sup>[28,29]</sup>.

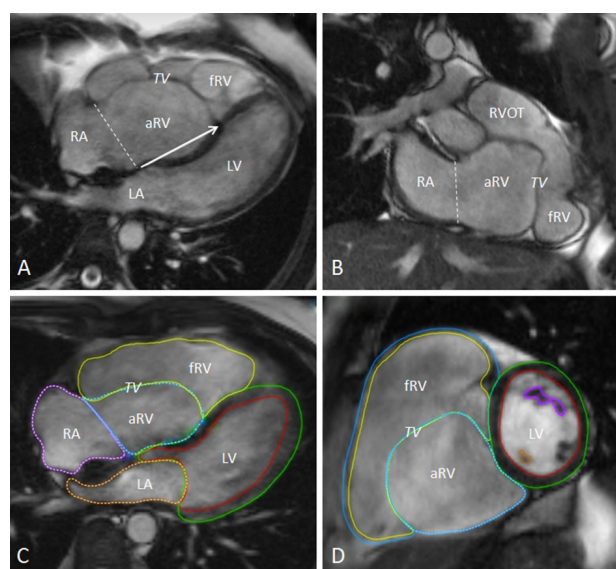
Although transthoracic echocardiography still remains the first-line cardiovascular imaging modality in patients with CHD, CMR can provide precious information especially in adults with suboptimal ultrasound windows<sup>[5,30-32]</sup>. This advantage stems from the fact that the images acquired using CMR are not limited by acoustic windows, as they are with traditional echocardiography. Furthermore, the potential for a larger field of view allows a comprehensive, segmental, anatomical approach to the patients<sup>[29]</sup>.

Importantly this is not exclusively limited to children or grown up patients with CHD. There is also evidence to suggest that CMR imaging may be a useful tool in the prenatal period. With regard to prenatal diagnosis, attempts have been undertaken to classify the severity of EA by combining fetal echocardiography and fetal CMR. This combination offers corroborative and in some instances additional information that may help in the decision-making process in fetuses where pulmonary hypoplasia might be present<sup>[33]</sup>. Further clinical investigations are needed to implement this in clinical routine.

### Conventional CMR techniques

The CMR protocol for EA should include stacks of multislice-multiphase steady state free precession (SSFP) cine images in transversal or ventricular short-axis orientation with a field of view covering all cardiac structures and great vessels. Furthermore 4CV, oblique coronal (RV vertical long-axis) cine images (Figure 1) and 2D through-plane phase contrast (PC) flow measurements in the ascending aorta and pulmonary trunk should be obtained as outlined in current guidelines<sup>[24,30]</sup>.

SSFP cine images should be used for the assessment of valve morphology rather than spin echo images<sup>[28]</sup>. Measurements of ventricular volumes, function and mass are performed using cine images in ventricular, transversal or short-axis orientations. LV and



**Figure 1** EA CMR in 4CV (A), oblique coronal (B), transversal (C) and short-axis (D) view in end diastole. The arrow indicates the extent of apical displacement of the septal TV insertions (A). The dotted lines demonstrate the original TV annulus, which marks the border between the RA and aRV. The segmentation to evaluate volumes and function are shown in transversal (C) and short-axis view (D). LA, left atrium; LV, left ventricle; RA, right atrium; aRV, atrialized right ventricle; fRV, functional right ventricle; RVOT, right ventricular outflow tract; TV, tricuspid valve.

left atrium (LA) segmentation in short-axis orientation follow the AHA standards set by Cerqueira *et al.*<sup>[34]</sup>. Currently there are no standards for determining the right-sided volumes and functions, as the segmentation procedure has not been clearly defined in EA. Some groups used arbitrary lines to define RA, aRV and fRV. The border demarcating the aRV from the fRV is then defined as a line connecting the anterior original TV annulus (the free wall attachment of the anterior TV leaflet) and the septal attachment of the apically displaced leaflet<sup>[35]</sup>. Others recommend to trace the malformed TV in detail<sup>[22,36]</sup> (Figure 1). This is more tedious but describes the anatomy of EA more accurately. However since the RV is difficult to define, one must also raise the question whether volumetric fRV EF is actually a reliable functional dimension and may be even more hampered by TR of various degrees. Similar to Doppler echocardiography, a qualitative assessment of TR is possible with CMR<sup>[28]</sup>. However the classification of the degree of TR using flow measurements at the level of the TV can be challenging due to the anatomical variability and often multiple leaflet fenestrations. A regurgitation jet cross-section of 6×6 mm or more, reflecting the regurgitation defect, can be regarded as severe<sup>[27]</sup>.

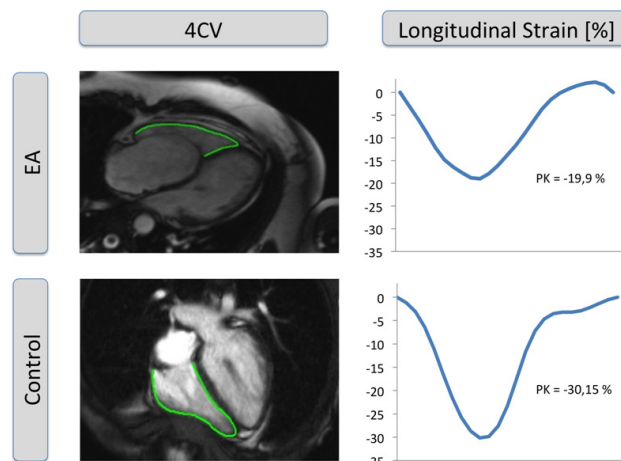
Hösch *et al* demonstrated that CMR can help to quantify the disease severity in general and the associated severity of heart failure by a CMR derived Total Right/Left-Volume-Index. For this purpose, the sum of the right-sided cardiac end-diastolic volumes (RA+aRV+fRV) is divided by the left-sided volumes (LA+LV) without the necessity of the laborious segmentation of the TV, aRV and fRV, since RA, aRV and fRV can be segmented as a whole<sup>[36]</sup>.

#### Future applications with CMR

There are also emerging future techniques such as T1-Mapping pre and post Gadolinium and CMR Feature Tracking (CMR-FT) entering the clinical arena that may offer great potential in the future but have yet to be fully validated in the clinical context.

Measurement of myocardial T1 times using the modified look-locker inversion recovery (MOLLI) sequence with and without gadolinium-enhanced inversion recovery-prepared sequences may be of potential use for the depiction of diffuse myocardial fibrosis<sup>[37]</sup>. However at present there is no data available demonstrating the feasibility of this approach in patients with EA, which should be investigated in future clinical research.

CMR-FT is a novel method for quantification of LV and RV myocardial deformation<sup>[38,39]</sup> which has also been successfully applied to patients with CHD<sup>[40-42]</sup>. The conditions studied so far include tetralogy of Fallot and coarctation of the aorta. Similar to echocardiographic speckle tracking myocardial velocity, displacement, strain and strain rate can be derived by tracking tissue voxel motion in any desired plane from routine 2-dimensional SSFP cine images<sup>[43,44]</sup>. Values can be derived as global parameters or for each cardiac segment according to established cardiac segmentation<sup>[34]</sup> (Figure 2). Recently intra- and interventricular dyssynchrony within and between the cardiac chambers have been studied in patients with EA using CMR-FT by quantitating the differences in time to peak strain duration within the LV and RV and between the two chambers respectively demonstrating RV intraventricular dyssynchrony<sup>[45]</sup>. Whilst these results are certainly interesting one need to consider despite similar reproducibility of CMR-FT at 1.5T and 3T<sup>[46]</sup> that reproducibility is generally better on a global rather than on a segmental level which is required to study dyssynchrony. It is also important to keep in mind that RV global and segmental reproducibility is lower as compared to the LV, probably due to the thinner RV myocardial wall<sup>[46]</sup>. Whilst Padiyath *et al*



**Figure 2** CMR feature tracking showing the fRV border tracking at an end-diastolic SSFP still frame in 4CV orientation of an uncorrected EA case (upper row) compared to a healthy control case (lower row). Quantitative global longitudinal strain curves are illustrated to the right of the anatomical images showing lower strain in the EA case as compared to the healthy control. PK, peak strain.

demonstrated reasonable to moderate inter-study agreement between CMR-FT and echocardiographic speckle tracking<sup>[42]</sup>, Wu *et al* found that particularly segmental CMR-FT strain results suffer from lower reproducibility<sup>[47]</sup> when compared to global results<sup>[48]</sup>. Future research will need to better define the clinical importance of CMR-FT derived dyssynchrony analysis and its possible therapeutic implications.

#### Impact on Patients' Management and Prognostic Potential

Several publications demonstrated that measurements of left and right heart size and systolic function can be reliably performed using CMR imaging in patients with EA<sup>[22,49]</sup>. It has been shown that the SSFP cine CMR can be used for pre- and postoperative evaluation of the morphology and function of the fRV, LV and TV in case of insufficient assessability of the fRV and the TV on echocardiography. Echocardiography and CMR provide complementary data for some aspects of EA such as for visualization of the posterior TV leaflets and quantitative assessment of size and function of the fRV (CMR is preferable), while echocardiography is better for detecting small interatrial shunts or tiny ventricular septal defects. Appropriate risk stratification requires both CMR and echocardiography before cardiac surgery<sup>[29]</sup>.

Whilst many changes are frequently observed the severity classification of EA still remains a challenge. Carpentier *et al* classified the severity visually from a surgical point of view using the valve's morphology from type A (mild form: small contractile aRV with a mobile anterior leaflet) up to type D (severe form: the leaflet forms a continuous pouch which adheres to the dilated fRV)<sup>[50]</sup>. For neonatal age a distinction in four grades of severity according to Celermajer *et al* is applicable: In the echocardiographic end-diastolic 4CV, the area above the TV (RA+aRV) is divided through the sum of the areas of fRV, LA and LV. According to the area ratio (RA+aRV)/(fRV+LA+LV) the disease severity is classified as follows: <0.5 there is grade I, between 0.5 and 0.99 grade II, 1.0 to 1.49 grade III and > 1.5 grade IV<sup>[19]</sup>. However these two classifications are not used in clinical practice where rather the TV displacement seen on echocardiography is used to determine the clinical significance within a given case. Until now all three methods showed little to no association with functional and heart failure parameters.

Evaluation of right and left heart volumes and function by CMR

is preferably performed using axial imaging since this provides better inter- and intraobserver variability<sup>[22,35]</sup>. In patients with EA greater TV apical displacement (i.e. less shared ventricular septum) is associated with larger fRV EDV<sup>[51]</sup> and decreased fRV EF<sup>[52]</sup>. According to Lai *et al* this supports the approach to reposition the TV annulus in surgical repair, which may result in an improvement in the LV contribution to RV workload<sup>[52]</sup>.

Regarding the fRV size some studies demonstrated reduced fRV size<sup>[13]</sup> while others showed increased fRV size using echocardiography<sup>[3]</sup>. Fratz *et al* have assessed the fRV volume using CMR in patients with unrepaired EA and have found large fRV volumes in 90 % of cases, with 2.5 times larger volumes compared to the LV. There was also a strong correlation of the fRV volumes with TR<sup>[22]</sup>. However at present the prognostic implications of these findings have yet to be defined.

Delayed and prolonged depolarization of the RV is common in EA. QRS duration has been shown to be a marker of RV enlargement and dysfunction and is associated with a greater total RV (aRV+fRV) volume. A preserved surface ECG identifies a subset of patients with EA with mild morphological and functional abnormalities associated with better cardiopulmonary exercise capacity<sup>[53]</sup>.

Reduced exercise capacity is frequently observed in EA<sup>[54,55]</sup>. Tobler *et al* related CMR derived ventricular and atrial measures to exercise capacity data. The aRV EDV appears to be correlated to peak oxygen uptake (VO<sub>2</sub>)<sup>[51]</sup>. Peak VO<sub>2</sub> is an independent predictor of outcome in patients with EA<sup>[55,56]</sup>. Therefore a decrease in exercise capacity may be taken as one of the relative indications for surgery, but outcomes may be better if surgery is performed before the heart dilates and the clinical status deteriorates<sup>[57]</sup>.

The Total Right/Left-Volume-Index correlates well with established clinically employed biomarkers of heart failure including peak VO<sub>2</sub>, allowing an accurate quantification of the disease severity<sup>[36]</sup>. Clinical biomarkers are useful as surrogate measures of reduced pulmonary perfusion with increased plasma BNP levels and hematologic parameters (hemoglobin, hematocrit, red blood cell count) correlating with impaired fRV functional data from CMR as well as with reduced cardiopulmonary exercise capacity<sup>[49]</sup>. These parameters may therefore help finding the optimal time-point to intervene and be useful for disease monitoring. Up to date, information from CMR is not routinely employed for the decision when to operate, to replace or reconstruct the TV or to apply a Glenn anastomosis, but should be used more in the future.

There are also some limitations of CMR that need to be kept in mind. These include limited availability, problems in the presence of arrhythmias or claustrophobia, implants like pacemakers or implantable cardio-defibrillators and a lower temporal resolution compared with echocardiography. TV leaflets are often very thin and difficult to visualize by CMR, they may not appear as sharply depicted as they do on echocardiography<sup>[29,35]</sup>. Although imaging methods to investigate EA have continuously evolved, standardization of assessment protocols e.g. for valve demarcation by CMR is required. Furthermore due to the low incidence of EA and associated small patient numbers, most CMR studies report an average of about 25-30 patients. Therefore the statistical power is often limited and prospective longitudinal multi-center studies are needed to better define the role of CMR in the management of EA.

## CONCLUSIONS

CMR is the cardiovascular imaging method of choice for the assessment of patients with EA and contributes to the decision-making process

regarding the types and timing of interventions. Accurate morphologic, volumetric and functional data can be obtained for the right and left side of the heart to quantify the severity of the disease. Although standardization of assessment protocols e.g. for valve demarcation by CMR is still required, a detailed CMR examination should be regarded as a necessary facility of a center specializing in the care of patients with EA. Novel techniques for fibrosis and deformation quantification may be of great potential in the future but have yet to be fully validated fully in the clinical context.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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**Peer reviewers:** John A St.Cyr, Jacqmar, Inc., VP R & D, 10965 53rd Avenue North, Minneapolis, MN 55442, USA; Ilaria D'Angeli, Private Clinic Villa Stuart, Department of Cardiology, Via Trionfale 5952, 00136, Rome, Italy; Elhadi Hussein Aburawi, Department of Pediatric, College of Medicine and Health Sciences, UAE University, P. O. Box 17666, Al Ain, Abu Dhabi, UAE.