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# Ebstein's anomaly in children and adults: multidisciplinary insights into imaging and therapy

Giulia Pasqualin <sup>1,2</sup>, Antonio Boccellino,<sup>3</sup> Massimo Chessa <sup>1,2,4</sup>,  
Giuseppe Ciconte <sup>3,4</sup>, Cecilia Marcolin,<sup>4</sup> Emanuele Micaglio <sup>3</sup>,  
Carlo Pappone <sup>3,4</sup>, Francesco Sturla <sup>5,6</sup>, Alessandro Giamberti<sup>7</sup>

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/heartjnl-2023-322420>).

For numbered affiliations see end of article.

## Correspondence to

Dr Giulia Pasqualin, Pediatric and Adult Congenital Disease Heart Centre, IRCCS Policlinico San Donato, San Donato Milanese, Italy; [Giulia.Pasqualin@grupposandonato.it](mailto:Giulia.Pasqualin@grupposandonato.it)

Received 16 January 2023

Accepted 20 June 2023

Published Online First

24 July 2023

## ABSTRACT

Although survival has significantly improved in the last four decades, the diagnosis of Ebstein's anomaly is still associated with a 20-fold increased risk of mortality, which generally drops after neonatal period and increases subtly thereafter. With increasing age of presentation, appropriate timing of intervention is challenged by a wide spectrum of disease and paucity of data on patient-tailored interventional strategies. The present review sought to shed light on the wide grey zone of post-neonatal Ebstein's manifestations, highlighting current gaps and achievements in knowledge for adequate risk assessment and appropriate therapeutic strategy.

A 'wait-and-see' approach has been adopted in many circumstances, though its efficacy is now questioned by the awareness that Ebstein's anomaly is not a benign disease, even when asymptomatic. Moreover, older age at intervention showed a negative impact on post-surgical outcome.

In order to tackle the extreme heterogeneity of Ebstein's anomaly, this review displays the multimodality imaging assessment necessary for a proper anatomical classification and the multidisciplinary approach needed for a comprehensive risk stratification and monitoring strategy. Currently available predictors of clinical outcome are summarised for both operated and unoperated patients, with the aim of supporting the decisional process on the choice of appropriate therapy and optimal timing for intervention.

## FROM BENCH TO BEDSIDE

### Embryology and anatomy

Ebstein's anomaly (EA) is a congenital valvular and ventricular dysplasia of the right-sided heart, frequently associated with left-sided heart anomalies.<sup>1,2</sup> EA results from incomplete delamination of the tricuspid valve (TV) from the right ventricular (RV) endocardium, which occurs between the 7th and 12th week of intrauterine life.<sup>3</sup> During this process, the innermost layer of the ventricular wall separates from the underlying tissue, forming TV leaflets and tendinous chordae. Genetics and environmental factors supposed to be involved in EA pathogenesis are provided in online supplemental material (section A, table 1).

Impaired fibrous transformation from the muscular precursor results in adherence of TV components to the RV wall, thus causing an apical displacement of the septal leaflet (SL) hinge point.<sup>1</sup>

The same pathological process may involve the posterior leaflet (PL) while less frequently the anterior leaflet (AL), due to a supposed different embryology.<sup>1,3</sup> Leaflets may adhere to the endocardium either directly, through linear (figure 1A, C and D; online supplemental video 1) or focal attachments (online supplemental video 2), or indirectly, through accessory fibrous chordae or muscular stumps (figure 1C and D; Online supplemental video 1).<sup>1</sup>

Leaflets adherence to RV wall determines two key EA anatomopathological features: (1) the TV effective orifice separates from the anatomical annulus and rotates towards the right ventricular outflow tract (RVOT) of a degree which depends on the extension of the delamination defect (figure 1C and D)<sup>4</sup>; (2) the myocardial wall above the effective TV orifice is 'atrialized' (figure 1A, C and D), thus rendering EA a 'RV myopathy' beyond a valve disease.<sup>1,5</sup>

The atrialized RV (aRV) lacks of myocardial fiber concentration and presents reduced wall thickness (figure 1A, C and D). The part of RV responsible for stroke volume (SV) generation is the functional RV (fRV), which extends from the effective TV orifice to the pulmonary valve (figure 1B, C and D).<sup>1,5</sup> The combination of aRV and fRV identifies the anatomical RV (ARV).

### Multimodality imaging

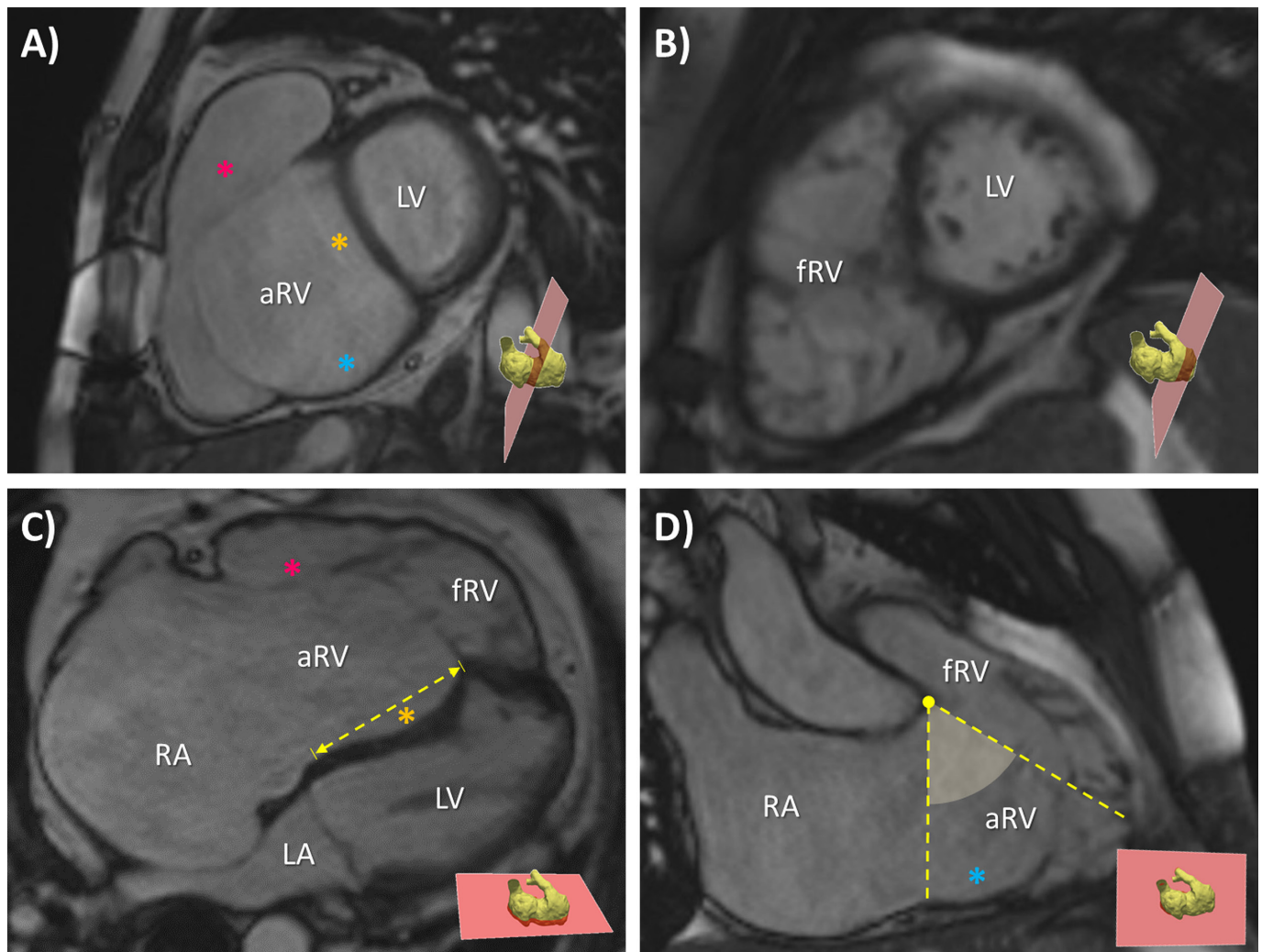
The quantitative criterion for EA diagnosis is an apical displacement of the SL hinge point by at least 8 mm/m<sup>2</sup> from the anterior mitral leaflet insertion, assessed in four-chamber view<sup>1,6</sup> (figure 1B). An absolute distance in atrioventricular valves offsetting of 15 mm in children and 20 mm in adults is also considered diagnostic.<sup>7</sup> Multimodality imaging is pivotal not only for anatomical and functional assessment of TV and right-sided chambers but also for identifying associated lesions (online supplemental material, section B)

Transthoracic echocardiography (TTE) is usually the first diagnostic tool. Second-line imaging includes transoesophageal echocardiography (TOE) and cardiovascular magnetic resonance (CMR), the former with particular usefulness in TV assessment, the latter in right-sided chamber volumes calculation and myocardial characterization. CMR is superior to TTE in the detection of PL and extracardiac abnormalities, while TTE reveals small septal communications more frequently.<sup>6</sup> Echocardiography and CMR are both recommended for



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**To cite:** Pasqualin G, Boccellino A, Chessa M, et al. *Heart* 2024;**110**:235–244.



### Tricuspid valve leaflets: \* Anterior \* Septal \* Posterior

**Figure 1** Magnetic resonance cine-SSFP images in a patient with Ebstein's anomaly in short axis (A, B) and long axis (C, D) views at end-diastole, highlighting the orientation of each cine-SSFP slice. Focusing on the tricuspid valve, apical displacement of the septal leaflet and rotation angle are reported in horizontal long-axis (C) and vertical long-axis views (D), respectively. RV, right ventricle; SSFP, steady-state free precession .

evaluating unoperated patients, informing on progressive disease and anatomies suitable of repair, as well as for monitoring operated patients, revealing surgical results and possible complications (figure 2).<sup>8,9</sup>

TOE is the fundamental imaging technique in the operation theatre. Cardiac computed tomography may be considered instead of CMR in cases of contraindications or major artefacts in the magnetic field, as well as before planning redo surgeries or 'valve-in-valve' replacements.

Over time, various classifications of EA severity had been proposed (figure 3). In patients older than 10 years, the CMR-derived total right/left-volume index showed higher association with clinical decompensation compared with Celermajer index and fRV to left ventricle (LV) ratio (figure 3), but revealed no correlation with the occurrence of major cardiovascular events (MACEs).<sup>10-12</sup> Imaging parameters predictive of adverse outcome in EA are reported in online supplemental tables 2 and 3.

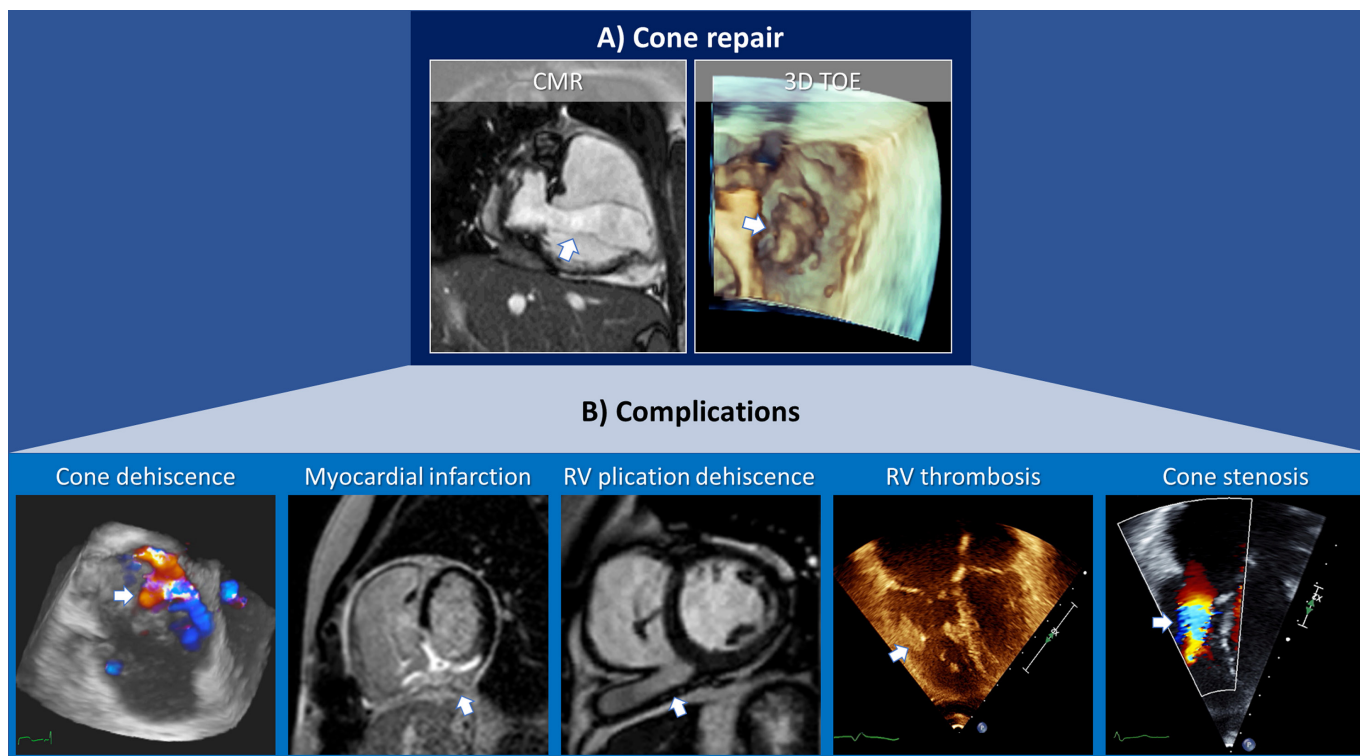
#### Tricuspid valve

TV is usually incompetent in EA, being occasionally stenotic.<sup>1</sup> Failure of delamination is responsible for a restrictive movement

of the affected leaflet or its functional absence (online supplemental videos 1 and 2).<sup>1,6</sup> AL may present fenestrations which contribute to tricuspid regurgitation (TR) as well as fibromuscular attachments which cause RVOT obstruction.<sup>1,6</sup>

Comprehensive echocardiographic examination relies on multiple TV views, often obtained by tilting the TTE probe from conventional axis (figure 4) or adapting the TOE transducer to different orientations (online supplemental figure 1).

CMR allows a cross-reference between short-axis and long-axis views in the post-processing analysis, as illustrated in figure 1. Cine steady-state free precession (cine-SSFP) and gradient-echo sequences are used to evaluate TV leaflets' morphology and motion. During a CMR examination, SL is detectable along the IVS. The other leaflets are visualised along the free wall: in a short-axis stack, PL is located next to the inferior wall and AL is adjacent to the lateral wall, while, in a para-axial stack from the diaphragm to the semilunar valves, PL and AL are detectable in bottom and top slices respectively (online supplemental figure 2). A vertical RV long-axis view explores both RV inflow and outflow, allowing the evaluation of PL delamination defects and possible RVOT obstruction; additionally, the degrees of



**Figure 2** Cone repair assessed through multimodality imaging during diastole (A): vertical long axis view of cine-SSFP sequence from CMR imaging and en face view by 3D-TOE (ventricular perspective). White arrows indicate the cone-shaped valve. (B) Structural complications of cone repair, as highlighted by a white arrow: (I) en face neo valve view with dehiscence of the antero-septal region by colour flow Doppler 3D-TOE; (II) phase-sensitive inversion recovery reconstruction (PSIR) sequence of a mid-ventricular short-axis view, showing myocardial infarction in the territory supplied by the right coronary artery, as represented by transmural late gadolinium enhancement of the inferior wall, inferior septum and RV diaphragmatic wall; (III) cine-SSFP mid-ventricular short-axis view of right ventricular plication dehiscence; (IV) colour flow Doppler 2D TTE of neo-subvalvular acceleration in a four-chamber view. CMR and TTE images are courtesy of Boston Children's Hospital, Department of Cardiology. CMR, cardiovascular magnetic resonance; 3D-TOE, three-dimensional transesophageal echocardiography; RV, right ventricle; SSFP, steady-state free precession; TTE, transthoracic echocardiography.

the effective TV orifice rotation can be quantified in this view (figure 1D).<sup>4</sup>

An 'en face' reconstruction of TV is retrievable from multiple long-axis views using three-dimensional (3D) TTE (online supplemental video 3) and TOE (online supplemental figure 1).

In mild disease, the TV offset from the anatomical annulus is modest and multimodal TR quantification is based on current recommendations. In case of significant TV orifice rotation from the anatomical annulus, regurgitant jets are generally better appreciated in long-axis rather than short-axis views. In these settings, TR echocardiographic evaluation is often qualitative, while CMR-based quantification is possible by subtracting total pulmonary antegrade flow from RV SV rather than using through-plane phase-contrast sequences orthogonal to the TV annulus.

TR is proportionally associated with decreased functional capacity in unoperated patients and its progression is accompanied by right-sided chambers volume overload and decreasing proportion of the left-sided chambers.<sup>11 13</sup>

#### Right atrium

RA is typically enlarged in EA and presents decreased either reservoir, conduit and booster pump function.<sup>14</sup> Fibrosis is predominantly observed in the free wall and showed an association with atrial tachycardia onset.<sup>15</sup> RA function is impaired in EA patients with heart failure (HF) and progressive disease.<sup>14 16</sup>

#### Right Ventricle

Although variability exists among different EA severity grades (figure 3), fRV is frequently enlarged and presents reduced systolic function when compared with normal subjects.<sup>14 17</sup> Differently from echocardiographic techniques, CMR allows an unrestricted view on right-sided heart chambers. In volume quantification, the para-axial cine-SSFP stack boundaries tracking showed a higher reproducibility than short-axis cine-SSFP stack (online supplemental figure 2).<sup>18</sup> Late gadolinium enhancement is typically revealed in the site of TV leaflet delamination defects.<sup>15</sup>

In regard to fRV function, the transverse rather than longitudinal component of contraction proved to be predominantly impaired in unoperated EA, even in the presence of preserved ejection fraction (EF).<sup>17</sup>

In general, data related to right-sided heart volumes mainly reflect cardiac decompensation and increased arrhythmic risk.<sup>11 12 14</sup> Specifically, aRV volume proved to be a marker of exercise intolerance and QRS fractionation, which is a known predictor of arrhythmic events.<sup>13 19 20</sup> Concomitantly, indexes of fRV systolic function revealed an association with MACEs, as detailed in online supplemental table 2.<sup>12 16</sup>

#### Left ventricle

The evidence that biventricular systolic impairment confers a ninefold increase in the risk of MACEs enlightens the impact of EA on left-sided heart.<sup>12</sup>

Qualitative evaluation Carpentier classification <sup>44</sup>		Quantitative indexes		
		Index	Calculation	Reference values
<b>Type A</b> - displaced SL (*) - AL (*) free motion - small aRV - adequate fRV volume		$\frac{\text{RA} + \text{aRV}}{\text{fRV} + \text{LA} + \text{LV}}$ <b>Celermajer index</b>	 TTE: area <sup>10</sup> CMR: area <sup>11,18</sup> CMR: volume <sup>11</sup>	<b>grade 1:</b> < 0.5 <b>grade 2:</b> 0.5-0.99 <b>grade 3:</b> 1.0-1.49 <b>grade 4:</b> > 1.5
<b>Type B</b> - displaced SL (*) and PL (*) - AL (*) free motion - large aRV - small fRV				
<b>Type C</b> - SL (*) and PL (*) markedly displaced - restrictive AL (*) motion - large aRV - small and dysfunctional fRV		$\frac{\text{fRV}}{\text{LV}}$	 CMR: volume <sup>13</sup>	<b>normal:</b> 1.1 ± 0.1
<b>Type D</b> - complete SL (*) and PL (*) adherence to RV wall - partial AL (*) adherence to RV wall - aRV markedly enlarged - fRV limited to infundibulum		$\frac{\text{RA} + \text{aRV} + \text{fRV}}{\text{LA} + \text{LV}}$ <b>Total right/left-volume index</b>	 CMR: volume <sup>11</sup>	<b>normal:</b> 1.1 ± 0.1

**Figure 3** Classification of Ebstein's anomaly from imaging. For the quantitative indexes, each term of the formula is highlighted in yellow when it is part of the numerator and in red when it is part of the denominator. AL, anterior leaflet; aRV, atrialised right ventricle; CMR, cardiac magnetic resonance; fRV, functional right ventricle; LA, left atrium; LV, left ventricle; PL, posterior leaflet; RA, right atrium; RV, right ventricle; SL, septal leaflet; TTE, transthoracic echocardiography.

When compared with healthy subjects, LV shows reduced volumes, systolic and diastolic function.<sup>14 21 22</sup> LV impairment in EA is multifactorial and principally triggered by: (1) inter-ventricular dependency (aRV–LV and fRV–LV interaction); (2) reduced LV preload due to decreased forward RV SV; (3) shape anomalies including LV basal narrowing and apical dilation; (4) myocardial alterations, including features of cardiomyopathy (i.e. non-compaction, hypertrophic) and myocardial fibrosis (both focal and diffuse)<sup>2 21 23 24</sup> (figures 5 and 6, online supplemental video 1 online supplemental file 5).

#### Clinical manifestations and outcome in unoperated patients

EA is a rare disease, counting 1–2.6 cases per 200 000 of live births (<1% of congenital heart disease).<sup>1 25</sup> Clinical presentation after neonatal period has a more favourable outcome than cases diagnosed in earlier life.<sup>26</sup> Subjects growing up to adulthood exhibit less severe anatomical abnormalities and, due to high right chambers compliance to volume overload, are usually asymptomatic for a long time.<sup>25 27 28</sup> Mean age at diagnosis is around 14 years among children and 20–35 years in adults.<sup>25 26</sup> New York Heart Association (NYHA) class I or II characterises the majority of adult patients at diagnosis.<sup>28</sup> Arrhythmias are the most common clinical manifestation both in children and in adults, being a possible cause of NYHA class deterioration.<sup>25 28</sup> Typical electrocardiographic and arrhythmic profiles of patients with EA are detailed in online supplemental material (sections C and D, respectively).

Right-to-left shunt may lead to chronic hypoxia and exertional cyanosis, while rest cyanosis is more common during infancy.<sup>26</sup> Cerebrovascular embolic events, as assessed in around

8%–10% of cases, are attributable to either paradoxical embolization or atrial fibrillation occurrence.<sup>26 28</sup> Endocarditis is rare and favoured by device implantation or surgery.<sup>26 29</sup> Figure 5 illustrates distinctive EA symptoms and their physiological substrates.

Contemporary survival at 10 years from the diagnosis or at an age of 60 years old is assessed ≥80% among unoperated subjects.<sup>25 30</sup> Causes of death are principally related to HF (40%) and arrhythmias (20%).<sup>28 30</sup> In a cohort of unoperated adults, sudden death (SD) had been reported in 23% of cases.<sup>28</sup> Clinical and instrumental features associated with unfavourable clinical outcome are reported in online supplemental table 2.

#### MULTIDISCIPLINARY CLINICAL MANAGEMENT

A clinical follow-up is recommended at least yearly in patients with EA, although the monitoring strategy is tailored according to patient's specific features.<sup>9</sup> HF, arrhythmias and cyanosis are the main clinical manifestations with known prognostic impact in EA (online supplemental table 2) and can be tackled by a multidisciplinary approach of monitoring, prevention and treatment (figure 7). Sports and pregnancy are both practicable but require preliminary assessment (online supplemental material, section E). Current achievements and knowledge gaps in EA multidisciplinary management are summarised in online supplemental table 4.

#### Drugs and HF treatment

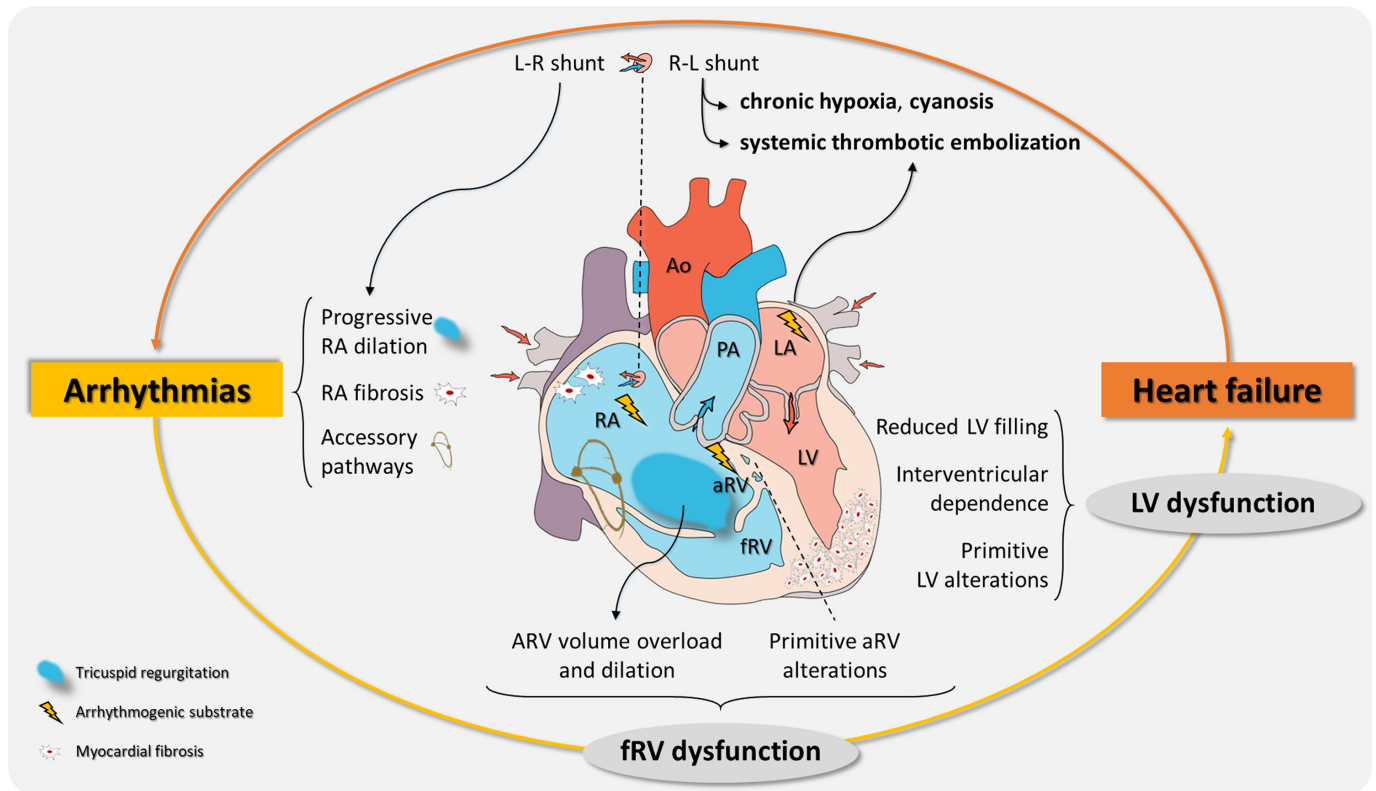
The effect of medical therapy on patients with EA has not yet been solidly investigated.<sup>31</sup> β-blockers and digoxin are used

View	Object of evaluation	Images	
		Carpentier type A EA	Carpentier type C EA
PLAX	RA aRV fRV inflow  <i>TV leaflets:</i> AL (*) adjacent to FW + SL (*) if IVS is seen + PL (*) if CS is seen		
PSAX	IAS RA aRV fRV ± Pas  <i>TV leaflets:</i> PL (*) adjacent to FW AL (*) /SL (*) adjacent to Ao		
APICAL 4CH	IAS, RA, aRV, fRV, IVS, left chambers  <i>TV leaflets:</i> SL (*) adjacent to IVS, AL (*) /PL (*) adjacent to FW		
RIGHT OBLIQUE SUBXIFOID VIEW	RA aRV fRV inflow fRV apex RVOT  <i>TV leaflets:</i> PL (*) adjacent to FW SL (*) /AL (*) contralateral		

**Figure 4** Main transthoracic echocardiographic views in EA. PLAX view was acquired with inferior tilt of the probe from conventional PLAX window. Right oblique subxifoid view was acquired with counterclockwise rotation of the transducer head from the four-chamber view. 4CH, four-chamber view; Ao, aorta; AL, anterior leaflet; aRV, atrialised right ventricle; ASD, atrial septal defect; CS, coronary sinus; EA, Ebstein's anomaly; fRV, functional right ventricle; FW, free wall; IAS, interatrial septum; IVS, interventricular septum; LA, left atrium; LV, left ventricle; Pas, pulmonary arteries; PL, posterior leaflet; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RA, right atrium; RVOT, right ventricular outflow tract; SL, septal leaflet; TV, tricuspid valve leaflets.

to reduce tachycardia-induced ventricular dysfunction.<sup>31–33</sup> Class IC and III anti-arrhythmic drugs may help to control the arrhythmic burden, however, there is general agreement to avoid sotalol and amiodarone as long-term therapy due to their known proarrhythmic risk and side effects.<sup>32–33</sup> In case of accessory

pathways (APs), the use of atrioventricular node blockers should be avoided. Oral anticoagulation may be appropriate in case of atrial fibrillation and right-to-left shunt.<sup>32</sup> Diuretics are used to relieve congestion, while a complete HF drug regimen may be justified in case of LV functional impairment.<sup>9–31</sup> Cardiac



**Figure 5** Clinical manifestations and pathophysiological substrates of Ebstein's anomaly. The interplay between arrhythmias and heart failure is highlighted. RA dilation promotes the occurrence of intra-atrial re-entries and the presence of accessory pathways may be the substrate for atrioventricular re-entries; aRV is vulnerable to trigger ventricular arrhythmias. Fast-conducted arrhythmias may contribute to ventricular dysfunction and reduced filling time. Adverse myocardial remodelling may enhance the arrhythmic substrate. Increased RA pressures favour right-to-left shunt in the presence of atrial communications, thus worsening hypoxia. Systemic embolisation is favoured by occurrence of atrial fibrillation or paradoxical thrombosis. Ao, aorta; ARV, anatomical right ventricle; aRV, atrialised right ventricle; LA, left atrium; L-R, left to right; LV, left ventricle; PA, pulmonary artery; R-L, right to left; RA, right atrium.

resynchronisation therapy can be applied in case of bundle branch block and either LV or RV dysfunction.<sup>32,34</sup> Both temporary mechanical cardiocirculatory supports implantation and heart transplantation had been performed in EA.<sup>29,35</sup> In end-stage HF, a biventricular assistance device may be successfully implanted, while LV assistance alone showed to deteriorate TR and fRV function.<sup>36,37</sup> Pre-surgical LV dysfunction demonstrated an increased risk of death after EA repair compared with patients with preserved LV function, thus suggesting the need of a careful evaluation before excluding heart transplantation candidacy in selected cases.<sup>33</sup>

#### Ablation and life-threatening arrhythmias prevention

Catheter ablation (Cabl) reports a long-term success of about 80% for atrioventricular re-entrant tachycardia and cavotricuspid isthmus-dependent atrial flutter, up to 100% for intra-atrial re-entrant tachycardias, and 92% for ventricular tachycardias (VTs).<sup>38,39</sup> Principal challenges include an atrioventricular junction less demarcated than other anatomies, multiple and broad APs, abnormal activation potentials, RA and aRV dilation, and impaired catheter stability. Moreover, each patient with EA may undergo different arrhythmogenic substrates during a lifespan.<sup>38</sup> Cabl procedural steps are illustrated for an emblematic case of multiple APs in online supplemental figure 3.

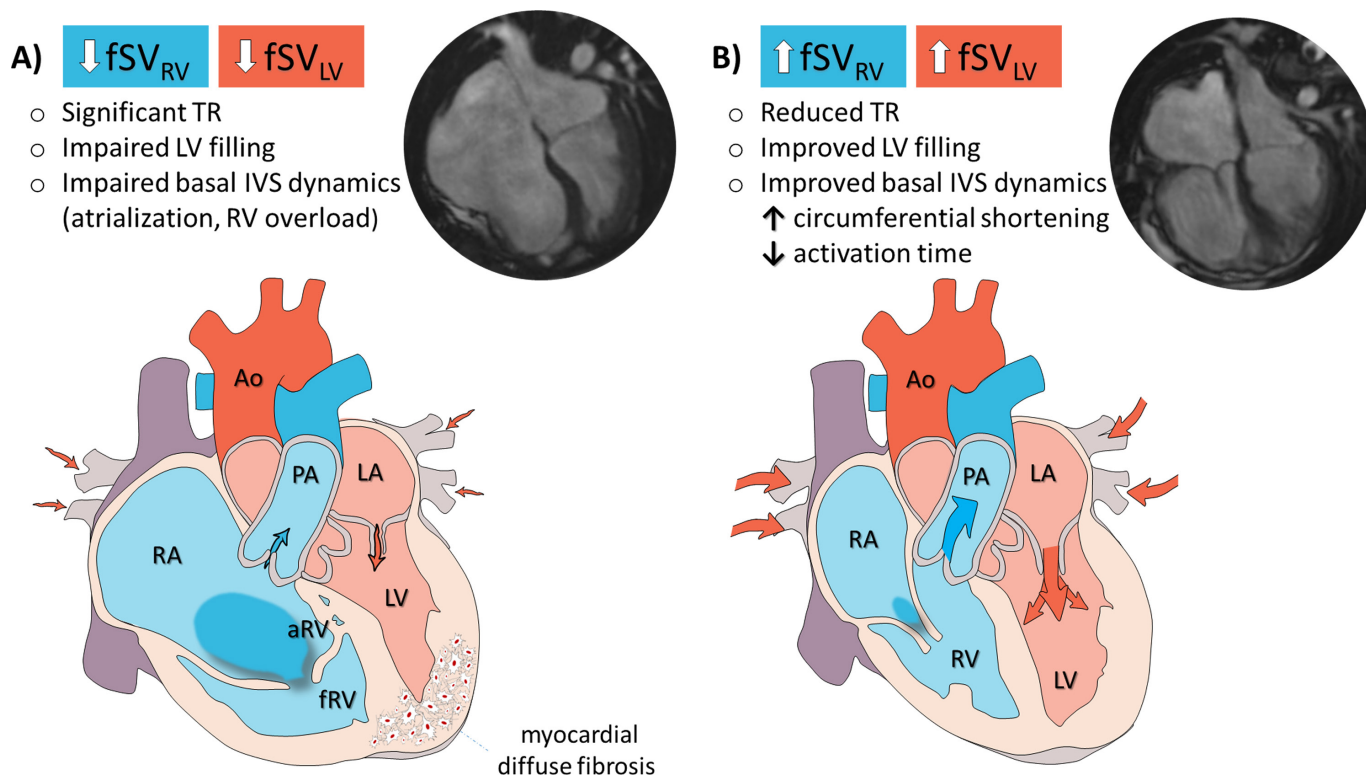
In a large cohort study on subjects with or without surgical history, SD incidence was detected in up to 5.1 per 1000 patient-years.<sup>40</sup> VTs, pulmonary stenosis, haemoglobin >15 g/dL, syncope

and previous cardiac surgery on TV proved to be independent SD predictors.<sup>40</sup> Potential proarrhythmic effects of surgery include ventriculotomy and cut-and-sew Maze.<sup>40</sup> A preoperative electrophysiological study (EPS) may reduce post-surgical SD risk. Current guidelines recommend EPS in patients with known APs or a history of arrhythmias but an arrhythmogenic substrate in the absence of these criteria was demonstrated.<sup>8,9,41</sup> Moreover, SD occurrence showed only a weak association with APs, while a significant association was demonstrated with atrial tachycardias and an even greater with VTs, both spontaneous and induced.<sup>40</sup> Current indications to implantable cardiac defibrillator in EA are not defined, but features associated with SD include syncope, spontaneous or induced VTs, QRS complex duration  $\geq 180$  ms, QTc interval >500 ms (online supplemental table 2).<sup>40</sup>

#### Cardiac catheterization

Interventional cardiac catheterization with closure of an inter-atrial communication (IAC) may alleviate cyanosis and prevent paradoxical embolisation.<sup>8,9,42</sup> A RA pressure  $\leq 18$  mm Hg without signs of low cardiac output is considered a safe cut-off for IAC closure. Right-to-left shunt in EA is favoured by the streaming of TR jet rather than right-sided filling pressures, which are elevated mostly in cases of RVOT obstruction.<sup>42</sup>

Transcatheter IAC closure is a valuable option in selected patients, having proved to be associated with increased pulse oxygen saturation and exercise tolerance.<sup>8,9</sup> The evidence that increased haemoglobin levels are a SD risk factor in EA



**Figure 6** Structural and functional cardiac alterations in Ebstein's anomaly (A) and changes after cone repair surgery (B). Also, a cine SSFP CMR sequence (horizontal long-axis view at end-diastole) is reported in the same patient before (A) and after cone repair (B). Ao, aorta; aRV, atrialised right ventricle; CMR, cardiovascular magnetic resonance; fRV, functional right ventricle; fSV, forward stroke volume; IVS, interventricular septum; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SSFP, steady-state free precession; TR, tricuspid regurgitation.

questioned if the closure of IAC itself may contribute to improve outcome in EA. The positive impact on functional capacity demonstrated after surgery may be at least partially related to IAC closure, while robust data focusing on surgical outcome in patients without IAC are lacking.<sup>43</sup>

### Surgery

Monocusp reconstruction for surgical treatment of EA had been used for many years (online supplemental table 5).<sup>44</sup> Nonetheless, there is nowadays a general consensus on adopting a more anatomical form of repair, described by da Silva *et al*<sup>45</sup> in 2007 (figure 8, online supplemental videos 4 and 5).

The concept of da Silva's cone repair (CR) is to perform a surgical delamination of all the rescuable leaflets in order to obtain a 360° TV annulus in anatomical position.<sup>45</sup> Plication, or triangular resection, of both the dilated aRV and atrioventricular junction is often necessary to adapt the cone-shaped neo valve to the anatomical annulus (figure 8). In this process, caution should be paid in avoiding right coronary artery damage (figures 2 and 8). During the neo-valve attachment, the suture line of the septal region is generally performed just below the anatomical annulus in order to avoid conduction tissue injuries. Such manoeuvre renders the septal area particularly vulnerable to post-surgical dehiscence, as shown in figure 2.

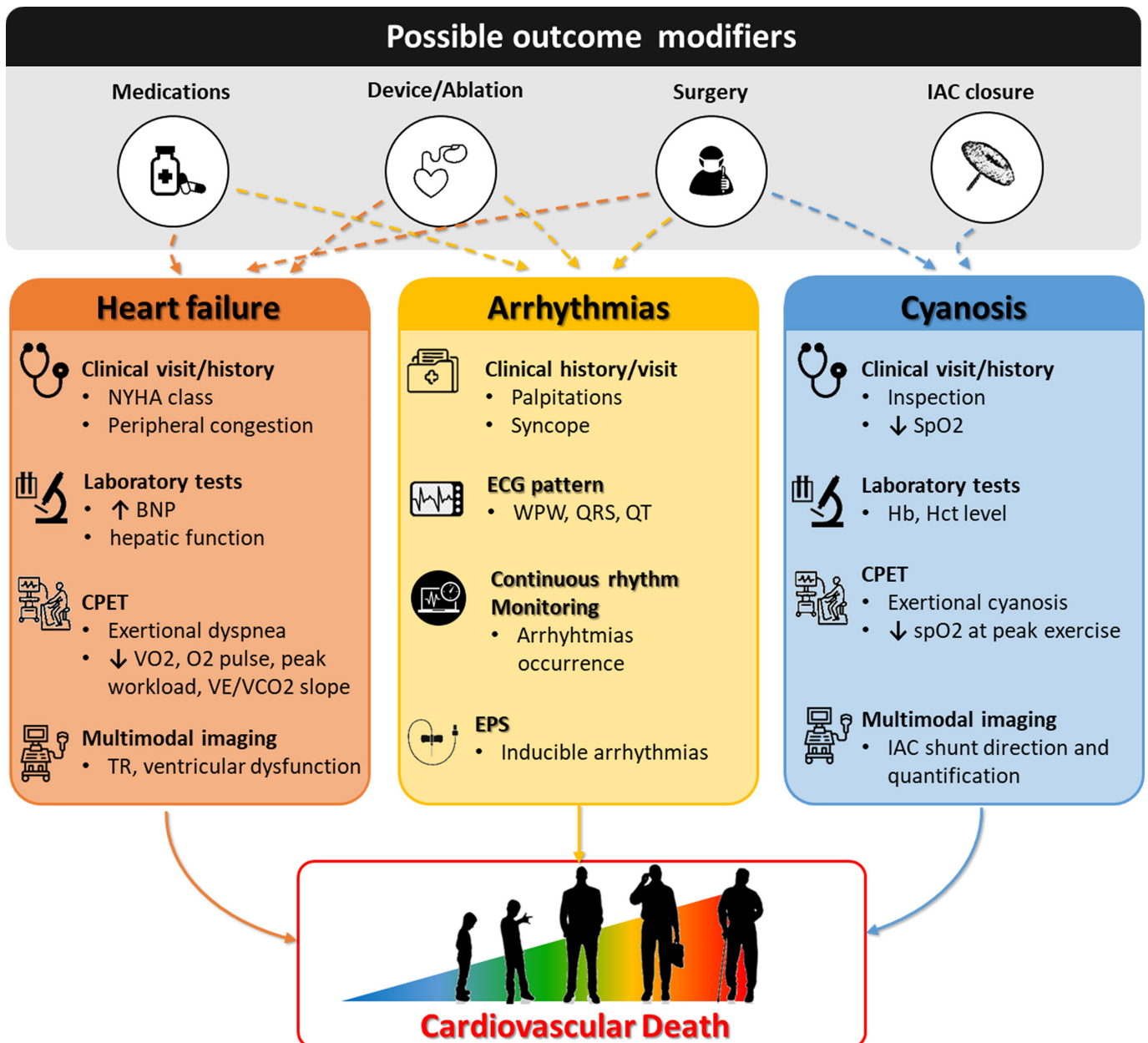
In case of inadequate fRV function, impossible weaning from cardiopulmonary by-pass or neo-valve stenosis, an associated bidirectional superior cavo-pulmonary anastomosis is generally performed ('one-and-a-half repair').<sup>46</sup> Glenn anastomosis showed to enhance LV filling and decrease fRV preload, thus reducing postoperative peripheral congestion.<sup>46</sup> When fRV size is reduced, a fenestrated rather than complete closure of

the atrial septal defect can be considered.<sup>9</sup> Possible additional surgical modifications include TV annuloplasty, pericardial patch enlargement of AL, and the so-called 'Sebening stitch' to mobilise the anterior papillary muscle toward the IVS, improving coaptation.

CR proved to be feasible in most of EA anatomies, as shown by online supplemental videos 6 and 7. The presence of a great functional TV rotation angle or fRV dilation showed to increase the probability of surgical breakdown (online supplemental table 3). In cases of extended deficit of delamination involving leaflets other than septal, the rescuable tissue may be scant and TV replacement might be considered.<sup>47</sup> Bioprosthetic rather than mechanical valves are preferred thanks to their acceptable durability, no need for anticoagulants, and the possibility of subsequent transcatheter 'valve-in-valve' procedures.

### Clinical outcome in operated patients

When compared with previous repair techniques, CR showed better results in terms of residual TR, freedom of re-operation and life expectancy.<sup>45 48</sup> Advantages of CR include growth potential and durability of the native tissue, no need for long-term anticoagulation therapy, and a more physiological TV and RV geometry.<sup>48</sup> CR demonstrated a favourable impact on RV and LV remodelling (figure 6), patient's clinical status and exercise capacity.<sup>23 29 48 49</sup> LV SV and peak oxygen consumption are parameters associated with adverse outcome in unoperated patients that showed to improve after CR. Nonetheless, biventricular EF has still shown no significant changes postoperatively, possibly due to the preload dependency.<sup>12 23 29 49</sup> Online supplemental table 3 provides an overview on the existing identified predictors of post-surgical outcomes in EA.



**Figure 7** Possible outcome modifiers and monitoring strategy for the key clinical manifestations of Ebstein' anomaly, namely heart failure, arrhythmias and cyanosis. BNP, brain-natriuretic peptide; CPET, cardiopulmonary exercise test; EPS, electrophysiological study; Hb, haemoglobin; Hct, haematocrit; IAC, interatrial communication; NYHA, New York Heart Association class; O<sub>2</sub>, oxygen; spO<sub>2</sub>, peripheral oxygen saturation; TR, tricuspid regurgitation; VE/VCO<sub>2</sub>, minute ventilation/carbon dioxide production; VO<sub>2</sub>, oxygen consumption; WPW, Wolf-Parkinson-White pattern.

Current indication to surgical intervention is severe TR with symptoms or, in the absence of symptoms, with progression in either right-sided heart dilation or frRV systolic dysfunction.<sup>8 9</sup> However, there is evidence that aerobic capacity is affected even in asymptomatic children and deteriorates rapidly before adulthood.<sup>50</sup> Furthermore, without symptoms, a long 'wait and see' may be needed to demonstrate right-sided heart disease progression.<sup>28 51</sup> In younger patients, cumulative data suggest better structural results and more effective clinical impact of surgical repair than in older adults.<sup>4 43 47 51</sup> Probability of re-operation or need for TV prosthetic replacement is greater with increasing age at intervention.<sup>4 51</sup> Furthermore, exercise capacity and functional class showed to be adequate in patients who received a repair during childhood or adolescence, while not every patient operated older than 50 years revealed a clinical improvement.<sup>43 47 51</sup>

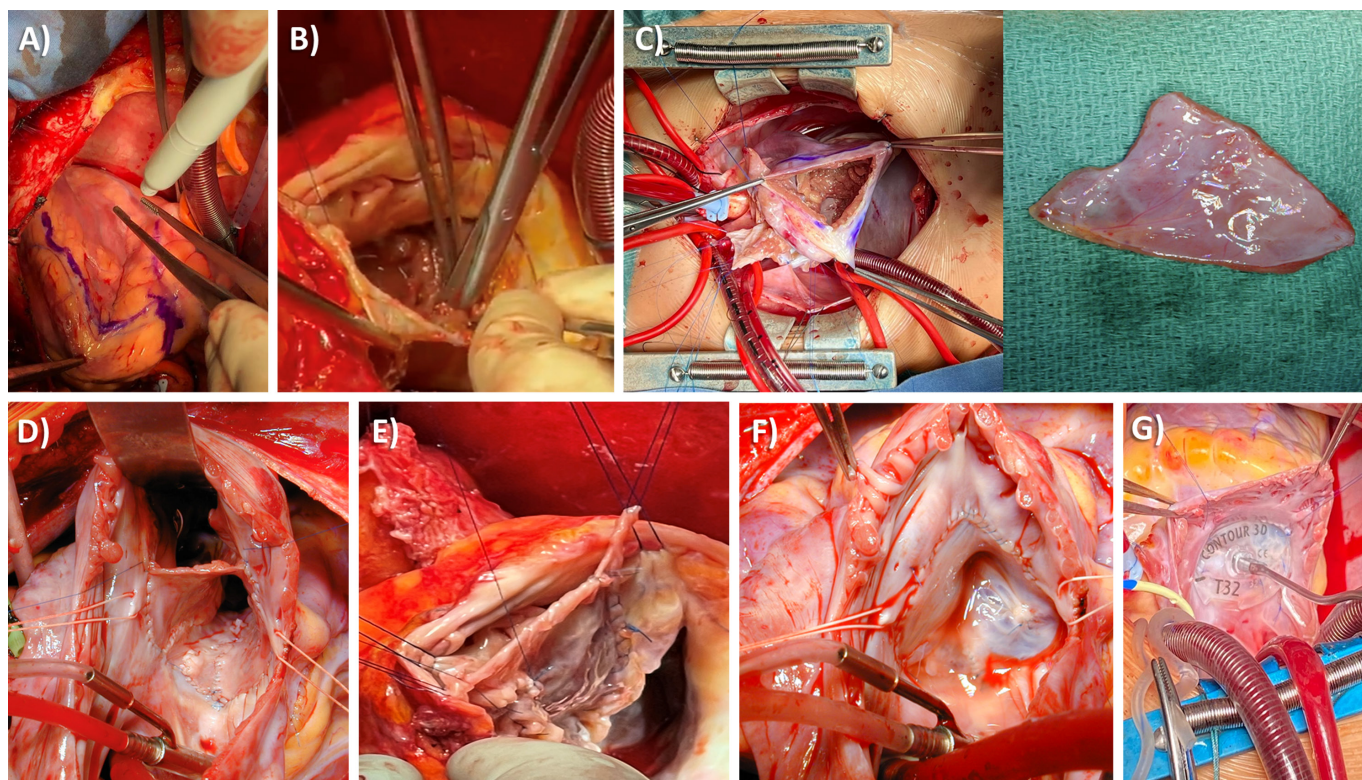
The latter patient subset showed lower long-term survival than younger patients and lower life expectancy compared with age-matched general population.<sup>43 47 51</sup>

Nonetheless, the surgical mortality risk for younger patients is not negligible even in experienced centres and, in the absence of randomized control studies, whether an early operation may effectively prevent complications of EA natural history is still debated.<sup>29 47 52</sup>

## CONCLUSIONS

EA diagnosis or diagnostic suspect should guide patient's referral to a specialised multidisciplinary team. EA spectrum of heterogeneous anatomical and clinical features requires a patient-tailored monitoring strategy. Large cohort studies are needed to assess





**Figure 8** Cone repair surgery is realised through a median sternotomy in cardiopulmonary by-pass with standard aortic and bicaval cannulation, left vent and cardioplegic cardiac arrest. After careful inspection and marking of the coronary arteries' anatomy (A), transverse RA incision is performed in the direction of the cavotricuspid isthmus. After a complete detachment and mobilisation of the delamination defects (B), part of the aRV is plicated or resected (C), and the neo valve, generally slightly rotated clockwise, is sutured into the anatomical annulus (D). The result is a cone-shaped valve with the vertex fixed at the RV apex (E); the valve is tested for competency (F), and then, if needed, stabilised with ring annuloplasty (G). RA, right atrium; RV, right ventricle.

the impact of medical treatment and to identify the best interventional approach, which should rely on time of presentation to medical attention as well as on indicators effectively correlating with clinical outcome.

#### Author affiliations

<sup>1</sup>Pediatric and Adult Congenital Disease Heart Centre, IRCCS Policlinico San Donato, San Donato Milanese, Italy

<sup>2</sup>European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart: ERN GUARD-Heart, Amsterdam, Netherlands

<sup>3</sup>Arrhythmia and Electrophysiology Department, IRCCS Policlinico San Donato, San Donato Milanese, Italy

<sup>4</sup>Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milano, Italy

<sup>5</sup>3D and Computer Simulation Laboratory, IRCCS Policlinico San Donato, San Donato Milanese, Italy

<sup>6</sup>Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milano, Italy

<sup>7</sup>Department of Congenital Cardiac Surgery, IRCCS Policlinico San Donato, San Donato Milanese, Italy

**Twitter** Giulia Pasqualin @g\_pasqualin and Cecilia Marcolin @marcolin.cecilia@hsr.it

**Acknowledgements** This work was partially supported by Ricerca Corrente funding from Italian Ministry of Health to IRCCS Policlinico San Donato. The authors are thankful to Professor Ashwin Prakash (Boston Children's Hospital, Boston, Massachusetts, USA), Professor Eustachio Agricola, Dr Francesco Ancona, Dr Stefano Stella and Dr Giacomo Ingallina (Cardiovascular Imaging Unit, Cardio-Thoracic-Vascular Department, IRCCS San Raffaele Scientific Institute, Milan, Italy) for their valuable support in providing part of the cardiovascular imaging enclosed in the present review.

**Collaborators** Not applicable.

**Contributors** GP conceptualised the review and drafted the initial manuscript, coordinating the revision process. MC, GC, EM, CP and AG contributed to sections of the review and implemented content according to the specific expertise of each author. GP, MC, CP, FS and AG critically reviewed the intellectual content of the manuscript. GP, CM, AB and FS designed, drafted and revised all figures, tables and videos. AG contributed to funding acquisition. All authors revised the final version of the review, reading and approving the submitted version.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Commissioned; externally peer reviewed.

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#### ORCID iDs

Giulia Pasqualin <http://orcid.org/0000-0002-3362-4501>

Massimo Chessa <http://orcid.org/0000-0001-7432-4815>

Giuseppe Ciconte <http://orcid.org/0000-0001-7886-5467>

Emanuele Micaglio <http://orcid.org/0000-0002-8298-7800>

Carlo Pappone <http://orcid.org/000-0002-0901-6135>  
 Francesco Sturla <http://orcid.org/0000-0001-7317-304X>

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