Extrasystoles in grown-ups with congenital heart disease - treatment options

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Introduction

The prevalence of congenital heart disease (CHD) is estimated at almost one in hundred newborns, with >90% of patients with CHD surviving into adulthood due to medical and surgical advances over the last decades.¹ While ventricular premature beats (VPBs) are quite common in patients without underlying structural heart disease, they occur even more often in patients with underlying CHD, due to the underlying anatomical substrate and surgical modifications and altered loading conditions of the ventricles².

Rationale for treatment of VPBs

The rationale for treatment of VPBs in the general population without underlying structural heart disease is mainly based on the presence of symptoms, and/or the risk for developing VPB-induced cardiomyopathy in patients with very frequent VPBs. In CHD, the same general principles are valid, but the clinical picture is often more complicated due to the presence of symptoms and/or systolic dysfunction due to the underlying heart disease itself. In these patients, the causative role of the VPBs in the development of systolic dysfunction, heart failure and symptoms of exercise intolerance are often not clear. Furthermore, in certain populations as tetralogy of Fallot, there is an increased risk of ventricular arrhythmias in relation to corrective surgery and residual cardiac lesions. In this sense, the role of VPBs as a trigger for ventricular arrhythmias in CHD remains unclear. As there are many uncertainties, treatment decisions should always be taken in a multidisciplinary approach involving CHD physicians and electrophysiologists alike.

Prognostic significance of VPBs in CHD

Sudden cardiac death due to ventricular arrhythmias is a major concern in the CHD population, although its incidence in the entire CHD group is relatively low (<0.1% per year).³⁻⁵ Among the CHD substrates, tetralogy of Fallot and transposition of the great arteries after atrial switch procedures, with a systemic right ventricle, pose the greatest risk for ventricular arrhythmias and sudden cardiac death, and risk stratification in these patients remains challenging.

In patients with tetralogy of Fallot, a much lower rate of VPBs was present on routine electrocardiograms in patients without arrhythmic events compared to patients experiencing sudden death². In this group of 488 patients with repaired tetralogy of Fallot, asymptomatic VPBs were found in 13% of them on routine electrocardiogram. Ventricular arrhythmia on routine electrocardiogram occurred in 100% of those who later died suddenly compared with 12% of those who did not die ($p < 0.01$). In another study of 359 patients with repaired tetralogy of Fallot, spontaneous VPBs were present on 24-hour ambulatory holter recording in 48%.⁶ In this study, induced sustained ventricular tachycardia during electrophysiology study was related to spontaneous VPBs on 24-hour holter recording. VT was not induced in asymptomatic patients who had normal 24-hour holter recordings and normal right ventricular systolic pressures. Late sudden death occurred in five patients (1.4%), most of whom had spontaneous VPBs on ambulatory monitoring (in 4/5) and right ventricular diastolic pressure > 8 mmHg (in 4/5). However, the relationship between asymptomatic ventricular arrhythmias on 24-hour holter recordings and development of subsequent clinical ventricular arrhythmias or sudden cardiac death was not confirmed in another multicenter cohort study in 793 tetralogy of Fallot patients, 346 of whom underwent 24-hour holter recordings.⁷ Therefore, the data on the prognostic significance of VPBs or more complex asymptomatic ventricular arrhythmias in tetralogy of Fallot remain conflicting, whereas symptomatic non-sustained ventricular tachycardia has been associated with worse outcome.⁸

While intra-atrial repair of transposition of the great arteries is associated with a significant incidence of cardiac arrhythmias and an increased risk of sudden death^{9,10}, the risk of significant ventricular arrhythmias after arterial switch procedures seems low. In a study on 92 patients with transposition of the great arteries, there was a relatively low incidence of ventricular arrhythmias pre-operatively with 12% of patients showing isolated VPBs on 24-hour holter recordings, and without any cases of arrhythmic death or symptomatic ventricular arrhythmias during a mean follow-up of 3.1 year after anatomical.¹¹ In addition, the role of ventricular arrhythmias as a cause of sudden cardiac death in intra-atrial repaired transposition of great arteries patients is also controversial. In this sense, an observational study of a cohort of these population with cardiac defibrillators showed that in patients with appropriate shocks, intracardiac electrograms documented supraventricular tachycardia preceding or coexisting with ventricular tachycardia in 50%¹².

As for other forms of CHD, relevant data on the frequency and prognostic significance of VPBs are currently not available.

Medical treatment for VPBs

Beta-blockers are the first line medical treatment for CHD patients with VPBs, although no dedicated studies are available on the use of beta-blockers or anti-arrhythmic drugs in patients with CHD for this indication. The medical management of arrhythmias in CHD is largely adapted from the studies that are available in acquired heart disease. Beta-blockers suppress the frequency of VPBs and the subjective feeling of palpitations associated with the VPBs, although there is large variability in response and patient tolerance.

Class I anti-arrhythmic drugs, which may be very efficient in the suppression of VPBs, can be harmful in case of diseased ventricles and should be avoided in patients with systolic dysfunction or ventricular scar. Sotalol has little additional effect compared to beta-blockers

on the suppression of VPBs and has a pro-arrhythmogenic potential, so is generally to be avoided for long-term treatment of VPBs in CHD.

Amiodarone is the most potent anti-arrhythmic drug and can be used to suppress VPBs, though its use is limited by the potential severe side-effects and adverse reactions when used for chronic treatment. We sometimes use it as a temporary treatment in patients with VPBs and systolic dysfunction to evaluate the effect on the symptoms of the patient and on systolic function. However, it must be considered that side effects of Amiodarone are even more frequent in CHD patients than in general population (Ref: Koyak Am J Cardiol 2013). The treatment response can guide the decision to go to a possibly complex ablation procedure in CHD patients.

Catheter ablation for VPBs in CHD

Catheter ablation has evolved in recent years as an important treatment modality for cardiac arrhythmias, generally showing superior efficacy over medical treatment for most types of arrhythmias. In the recent guidelines for management of adult CHD¹, catheter ablation received a class Ic indication for the treatment of ventricular tachycardia as an adjunctive therapy to ICDs, and a IIa indication for the treatment of symptomatic monomorphic sustained ventricular tachycardia in patients for whom medical therapy is not desired, provided that the procedure is performed in experienced centers. There is a paucity of data, however, on the use and efficacy of catheter ablation for the treatment of VPBs in patients with CHD, and therefore this indication was not explicitly mentioned in the guidelines.

However, technological advances in recent years have led to improved methods for ablation even in complex underlying anatomical substrates, with possibilities for image fusion between 3D imaging modalities and electro-anatomical mapping systems during the procedure. Therefore, ablation of VPBs is often possible with high success rates even in patients with

complex CHD. Careful pre-procedural planning is of key importance to determine the optimal way of vascular access. Previous surgical reports should be available to understand the underlying anatomical substrate and location of scar regions, and presence of prosthetic materials such as pulmonary homografts which can impede ablation in the covered regions. Two examples of VPB ablation in CHD patients are detailed below.

Case 1: ablation of right ventricular outflow tract VPBs in a patient with repaired tetralogy of Fallot

A 38-year old male patient with repaired tetralogy of Fallot was referred because of very frequent VPBs. Although he did not experience any symptoms, a 24-hour holter recording showed >10000 VPBs and transthoracic echocardiography showed a gradual decrease in his systolic left ventricular function (LVEF 50%) and mild dilation of the left ventricle (LVEDD 61 mm). There was only a mild pulmonary stenosis (peak gradient 24 mmHg) and minimal pulmonary insufficiency. Because of suspected adverse remodeling due to the frequent VPBs despite treatment with bisoprolol, catheter ablation of the VPBs was scheduled.

The procedure was performed with the Carto 3D electro-anatomic mapping system. Before mapping the origine of the VPBs, a biplane angiography of the right ventricle was performed which showed mild dilation of the RV with a global preserved RV contractility. The angiographic image was imported in the 3D mapping system to serve as anatomical reference before activation mapping of the VPBs was performed. Activation mapping of the VPBs showed an origin in the posteroseptal right ventricular outflow tract, where the local electrogram preceded the surface QRS onset by 40 ms. Ablation at this location with a power of 30W eliminated the ventricular ectopy without recurrence during the procedure. Although the procedural endpoint was successfully reached, further evaluation was performed given the underlying anatomical substrate in this patient. A ventricular stimulation protocol with 2

ventricular extrastimuli from the right ventricular apex and outflow tract did not induce sustained or nonsustained VT. However, a substrate map acquired during sinus rhythm showed a low-voltage scar regions at the location of the ventricular septal defect patch, with a narrow isthmus of slow conduction between this patch and the pulmonary valve. This isthmus of slow conduction, described as isthmus 3 by Zeppenfeld et al.¹³, is known to be pro-arrhythmogenic and the cause of macro-reentrant ventricular tachycardia in patients with repaired tetralogy of Fallot when conduction velocity over the isthmus is lower than 0.50 m/sec. The substrate map further showed that the origin of the previously eliminated VPB was at the border zone of the scar region, and the ablated region bordered the slow conducting isthmus. Given the possible future pro-arrhythmogenic potential, an ablation line connecting the pulmonary valve with the VSD patch was created to block this isthmus of slow conduction, and a new substrate map demonstrated block of conduction over the isthmus. This case illustrates the importance of the underlying substrate in CHD patients, where the VPBs originated in the border zone of low-voltage scar tissue and further mapping and ablation was warranted to close a possible arrhythmogenic conduction isthmus.

Case 2: Ablation of PVC and VT in a patients with complex anatomy

A 32 year-old male with complex CHD was referred to our center because of VPBs and ventricular tachycardia. He underwent a correction surgery of transposition of the great vessels, ventricular septal defect (VSD) and double outlet of right ventricle with arterial switch and VSD closure at 2 months of age. Due to progressive aortic regurgitation he underwent a Bentall-Bono surgery with a mechanical aortic valve prosthesis when he was 13 years old and ICD implantation and VT ablation for secondary prevention after monomorphic sustained VT when he was 25 years old. Despite antiarrhythmic drugs several VT were treated with antitachycardia

pacing in the next years requiring 3 more ablations that failed. He was finally sent to our hospital with frequent PVCs that triggered VTs with the same morphology (inferior axis, RBBB and early transition).

A cardiac magnetic resonance (CMR) with late gadolinium enhancement and wide band sequence was performed to define the arrhythmogenic substrate. The CMR images were processed with a dedicated software (ADAS 3D, Barcelona) and integrated into the navigation system (Fig 3). A channel of border zone tissue (yellow) was seen inside an anteroseptal scar (red) and below the prosthetic valve. The ablation procedure was done with the Ensite Precision system (Abbott Medical, USA) and high definition catheter (HD Grid, Abbot Medical, USA) with transseptal access and a deflectable sheath to access and map the left ventricle. An anteroseptal scar (grey) and border zone channel (red) were found in the same area that was detected with CMR. Late potentials were seen in that area. During voltage mapping VPBs triggered incessant VT that was also mapped. (Fig 4). Clockwise activation between the anteroseptal scar and aortic valve using the previously detected channel and ablation at that point finished the VT. After completing focal substrate ablation at that point VT could not be induced anymore neither VPBs were observed. This case illustrated the usefulness of preprocedural imaging and high density mapping in patients with CHD and complex anatomies.

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Disclosures

None.

References

1. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, Lung B, Kluin J, Lang IM, Meijboom F, Moons P, Mulder BJM, Oechslin E, Roos-Hesselink JW, Schwerzmann M, Sondergaard L, Zeppenfeld K. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J* 2020.
2. Garson A, Jr., Randall DC, Gillette PC, Smith RT, Moak JP, McVey P, McNamara DG. Prevention of sudden death after repair of tetralogy of Fallot: treatment of ventricular arrhythmias. *J Am Coll Cardiol* 1985;6:221-7.
3. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol* 2000;86:1111-6.
4. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, Budts W, Zwinderman AH, Van Gelder IC, Mulder BJ. Sudden cardiac death in adult congenital heart disease. *Circulation* 2012;126:1944-54.
5. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulos K, Gatzoulis MA. Survival Prospects and Circumstances of Death in Contemporary Adult Congenital Heart Disease Patients Under Follow-Up at a Large Tertiary Centre. *Circulation* 2015;132:2118-25.
6. Chandar JS, Wolff GS, Garson A, Jr., Bell TJ, Beder SD, Bink-Boelkens M, Byrum CJ, Campbell RM, Deal BJ, Dick M, 2nd, et al. Ventricular arrhythmias in postoperative tetralogy of Fallot. *Am J Cardiol* 1990;65:655-61.
7. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet* 2000;356:975-81.
8. Koyak Z, de Groot JR, Bouma BJ, Van Gelder IC, Budts W, Zwinderman AH, Mulder BJM. Symptomatic but not asymptomatic non-sustained ventricular tachycardia is associated

with appropriate implantable cardioverter therapy in tetralogy of Fallot. *Int J Cardiol* 2013;167:1532-5.

9. Scott L, Saalouke M, Shapiro S, Rios J, Perry L. Sudden unexplained death following Mustard's procedure for d-transposition of the great arteries (abstr). *Circulation* 1976;54:II-89.
10. Flinn CJ, Wolff GS, Dick M, II, Campbell RM, Borkat G, Casta A, Hordof A, Hougen TJ, Kavey RE, Kugler J, Liebman J, Greenhouse J, Hees P. Cardiac Rhythm after the Mustard Operation for Complete Transposition of the Great Arteries. *New England Journal of Medicine* 1984;310:1635-8.
11. Martin RP, Radley-Smith R, Yacoub MH. Arrhythmias before and after anatomic correction of transposition of the great arteries. *J Am Coll Cardiol* 1987;10:200-4.
12. Khairy P, Harris L, Landzberg MJ, Fernandes SM, Barlow A, Mercier L-A, Viswanathan S, Chetaille P, Gordon E, Dore A, Cecchin F. Sudden Death and Defibrillators in Transposition of the Great Arteries With Intra-atrial Baffles. *Circulation: Arrhythmia and Electrophysiology* 2008;1:250-7.
13. Zeppenfeld K, Wijnmaalen AP. Clinical Aspects and Ablation of Ventricular Arrhythmias in Tetralogy of Fallot. *Card Electrophysiol Clin* 2017;9:285-94.

Figure Legends:

Figure 1:

Mapping of the origin of VPBs in a patient with repaired tetralogy of Fallot. The local activation map shows the timing of local electrograms of the VPBs in the right ventricular outflow tract, with the red colour showing the region of earliest activation. Ablation at this point (marked as VPB origin) eliminated the VPBs. The local electrogram at the VPB origin is shown on the left and preceded the onset of the surface QRS with 40 ms. The voltage map on the right shows the region of low voltage marked as the red coloured area (where voltage is <0.5 mV), corresponding to the area of the patch at the ventricular septal defect. This substrate map, acquired during sinus rhythm, demonstrates that the VPB origin was in the borderzone of the low voltage area. Both for the local activation and voltage map, 3D mapping data are projected over a previously acquired angiographic image of the right ventricle, projected in an 'inverse RAO' projection looking towards the right ventricular septum. (EGM: electrogram, RV: right ventricle, VSD: ventricular septal defect, VPB: ventricular premature beat)

Figure 2:

Activation map showing the propagation of electrical activation over the isthmus between the VSD patch and the pulmonary valve. The yellow arrow on the left image shows the area of slow conduction across isthmus 3, with activation timing going gradually from early to late as marked by gradual progression of orange (early) over green to blue (late) colour. After a linear ablation lesion from the pulmonary valve to the VSD patch area, this slow conducting isthmus is closed (red 'x') and no conduction across the isthmus can be demonstrated. The white line shows the region of block, and there is no gradual progression of early to late activation across the isthmus. Both activation maps are projected over a previously acquired angiographic image of the right ventricle, projected in an 'inverse RAO' projection looking towards the right ventricular septum. (PA: pulmonary artery)

Figure 3:

Left panel: Voltage map showing scar in the anteroapical area below the aortic mechanical prosthesis (grey, <0.1 mV) and voltage channel of border zone (yellow/orange, <1.5 mV) inside the scar. Late potentials can be seen in that area. Right panel: Cardiac MRI image after

postprocessing with dedicated software (ADAS) with scar (red) in anteroseptal region below aortic mechanical prosthesis and area of border zone inside (yellow/white) as a possible conducting channel.

Figure 4:

Activation map during VT showing a clockwise circuit below the aortic mechanical prosthesis using the conducting channel visualized both in voltage map and in cardiac MRI as a diastolic pathway. Diastolic potentials can be seen in that channel during VT,

Figure 1

Figure 2

Figure 3

Figure 4