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Satoshi YASUKOCHI
Nagano, Japan
it is our great honour and pleasure to welcome you at the occasion of the 7th annual scientific meeting of the ESC-working group on adults with Congenital Heart Disease. It is worth mentioning, that this year the DACH-Symposium, a GUCH-meeting of the German-speaking Central European countries, has been integrated into this congress.

The combined effort – cardiological and surgical – to treat adults with congenital heart disease is a story of success. Today an increasing number of patients, even with very complex congenital heart disease, survive to adulthood with a good quality of life. However, since true „correction“ of a congenital cardiac lesion is rarely achievable, these patients need lifelong expert medical surveillance and close collaboration of health professionals in many medical sub-specialities.

The first day of the current meeting is concentrating on the right ventricle in patients with congenital heart disease. Diagnostic modalities, indication for treatment and treatment options are presented and discussed. The second day is focuses on different clinically relevant topics for this group of patients. We believe the meeting will be attractive not only for adult – or pediatric cardiologists and surgeons, but also for cardiac anesthesiologists, intensivists, nurse specialists and other health professional caring for GUCH patients.

We hope that, besides an excellent scientific meeting, you will enjoy Bavarian hospitality and a stimulating atmosphere here in Munich. It is an opportunity not only to share scientific thoughts but to promote personal relationships.

Last but not least, we would like to sincerely thank “Actelion Pharmaceuticals Germany GmbH”. Without their support it would not have been possible to provide you with the companion volume of this meeting.

In addition, a printable pdf version of the booklet is also available (see: www.dhm.mhn.de/de/kliniken_und_institute/klink_fuer_kinderkardiologie_u.cfm).
Over the last couple of generations, the number of adult patients with congenital heart defects has greatly increased, and numerous ACHD clinics have opened. Perhaps you are thinking of starting one. Let’s have a look at the things you should be thinking about and planning for in order to ensure that your clinic is successful, and that your patients get excellent care.

The first consideration has to do with understanding where your patients are going to come from. Will pediatric cardiologists send a lot of patients to you? Are you depending on adult cardiologists doing so? Primary care physicians? Patients and families finding you from their communities? What will be the trajectory of new graduates from pediatric cardiology practices? If the pediatric cardiologists are willing to refer their graduates to your ACHD program, that is welcome news. If not, that spells trouble.

How many patients are needed to build a strong ACHD program? In order to build a strong multidisciplinary ACHD program, I believe if you need approximately 250 new referrals a year or a base of at least 1500 patients in order to develop and maintain team skills, to train fellows, and to provide adequate volumes for both diagnostic and interventional services.

Another issue has to do with an agreed age to transfer from pediatric to adult care. In Canada, this occurs at age 18. Most Western European countries have an agreed age of transfer. To me, this is a critical factor in growing successful ACHD programs. In the USA, there is no agreement on any age of transfer, and this is a key factor in weakening ACHD care in the USA. A notable exception is at Emory University in Atlanta, where patients are routinely transferred at age 21 to the adult facility.

Another process that needs to be monitored virtually from birth and the diagnosis of congenital heart defects is the issue of attrition or loss to care of patients with moderate and complex congenital heart conditions (s). Attrition of patients who would benefit from ongoing lifelong care is a widespread problem that will result in avoidable morbidity and mortality for some of these patients. Accordingly, a determined effort to identify these patients and keep them in care in the pediatric institutions or practices would be very valuable for all concerned. If appointments are missed, the family/patient should be contacted and a follow-up made unless it is known that patients are receiving appropriate care elsewhere.

For those patients who remain in pediatric cardiac care...
after age 11 or 12, a consistent progressive patient and family education program is in order. This is often called “transition”, but I don’t like the word. At least in the USA, pediatric cardiologists hear the word “transition” and assume that we are going to try to steal their patients. Unfortunately, I haven’t found a suitable replacement. In dealing with adolescents and young adults, we need to remember that our brains don’t mature until approximately age 25. A transition program should include teenagers and young adults and should be aimed at encouraging young people to take appropriate responsibility for their own health. Healthy attitudes and behaviors are encouraged. The lifelong care message is emphasized for most patients. Education should include career planning, lifestyle choices, insurance planning, and reproductive counseling. Young people who make good lifestyle choices are more likely to take responsibility for their own health and lives, so healthy lifestyles should be strongly encouraged.

Some patients are expected to be at low risk of adverse outcomes over the course of their lifetime. Such patients, such as those with closed secundum ASDs at a young age, small VSDs, and repaired pulmonary stenosis, need to learn of our favorable expectations for them at a young age so they can lead a normal life and not think of themselves as “heart patients”. The same facts need to be conveyed to their parents. Transfer of such patients from pediatric care is usually easy since good primary care physicians and cardiologists can usually provide appropriate care. The medium to high risk patients need expert lifelong surveillance. Expert care has been shown to have a survival advantage for these patients (2). Group life expectancy is clearly reduced in a lesion-dependent fashion (3). Many of these patients will have limitations of their exercise capacity and lifestyle. Examples of moderately complex patients are arterial switch patients, repaired tetralogy, moderate to severe pulmonary valve lesions, repaired AV septal defects, aortic coarctation, and Ebstein anomaly. Examples of very complex patients include Fontan patients, severe pulmonary hypertensive patients, Mustard/Senning patients, patients with conduits, truncus arteriosus repairs, and cyanotic patients. It is critically important that such patients remain within expert care whether in the pediatric clinic or, after a certain age, in an ACHD clinic. These patients need to know not only the lifelong care message, but how to identify expert care and where to find it (4).

Part of the education process includes teaching the patient and family the basics. What is the name of the condition the patient has? What treatment has he or she received? What are future expectations? Are there any threats that can be anticipated, or any precautions that should be taken? What symptoms should be watched for? How frequently should the patient be seen, and by whom and where?

A multidisciplinary ACHD clinic needs to be based in an institution or at least a large multidisciplinary ambulatory practice. Your ACHD clinic will need the support of the institution or practice group. Is there a long-term commitment to build and maintain the program, and to provide excellent care for ACHD patients? There needs to be an agreement on goals, objectives, financial considerations, and other matters.

If you have a choice, should the program be located in an adult hospital or a children’s hospital? There is no best answer to the question. The ideal situation would be one in which both adult and pediatric services are provided in the same institution. There is evidence that successful transfer to adult care is more effective and successful when the patient can be transferred within the same facility (5, 6). The availability of both adult and pediatric subspecialty providers improves your potential flexibility in identifying the right resources for your patient. In my experience having an ACHD clinic in an adult hospital means that you may lose the opportunity to keep complex CHD children and adolescents in care unless you have remarkable support from your pediatric cardiology colleagues. Having an ACHD clinic in an adult hospital means you may not be able to negotiate the smooth transfer of complex CHD patients to adult care, especially in the USA. On the other hand, having an ACHD clinic in a children’s hospital means you may avoid the loss to care of complex CHD children and adolescents and help effect a smooth transfer to adult care. Caring for ACHD outpatients is fairly straightforward and can occur in either a pediatric or adult clinic location. On the other hand, the care of ACHD inpatients is a much more difficult challenge. Adult inpatients are not welcome in children’s hospitals. ACHD inpatients in adult hospitals may be cared for by teams not familiar with their conditions or how best to treat them.

There are important cultural differences between adult hospitals and children’s hospitals. Team members with an adult background will align most easily with an adult envi-

Figure 1: Key members of a multidisciplinary ACHD team
environment and team members with a pediatric background will align best with a pediatric environment. The reverse also applies, and alignment may be painful. A related issue has to do with the need for separate and distinct protocols for adult patients in any environment as regards echocardiography, exercise testing, cardiac catheterization, cardiac surgery, and other diagnostic procedures and therapies. Extension of pediatric protocols to adult patients is not appropriate, even though it is widely done. In countries with national healthcare, the importance of engaging the governmental health department’s interest and support cannot be underestimated in helping to establish and maintain a well-organized service. You must commit yourself and your program to excellent patient care. This will reduce the number of times you do things you shouldn’t because of pride or self-interest. Honoring this principle will help you build and maintain your credibility.

You and your program should aim to be able to address the needs of any patient that comes through your door. You may not be able to do everything in your own institution or community. If not, you need to make sure that services of high quality are available to your patients, and you should refer them to the best available resources. The members of a multidisciplinary ACHD care team are many. Moreover, you don’t just want to have one person in each of your key categories. You must at least duplicate key skills.

You need at least two ACHD cardiologists. These can come either from an adult cardiology or a pediatric cardiology background. If from pediatric cardiology, that person needs to practice differently when dealing with adults than when dealing with children and their parents. The script used needs to be fundamentally different. Life is theater, and this is a good example of where changing roles and responsibilities and customers are needed. Ideally, both types of cardiologists will have received specific training in ACHD. If not, there is at least the need for a clear career commitment to become an excellent ACHD cardiologist and to grow and maintain one’s skills.

As a rule, we believe it’s important to have both adult-trained and pediatric-trained cardiologists in an ACHD clinic. Each brings hopefully offsetting strengths and weaknesses to the table.

As you begin building your program, you’ll need to identify potential consulting team members. Once done, you will need to develop and improve the capabilities of your consulting team in a constructive ongoing way. You definitely need an excellent echocardiography service. This includes both physicians and sonographers. High-quality echo work is critically important to the success of an ACHD clinic. Adult echoes and pediatric echoes are very different and are reported differently. Adult approaches are needed for adult patients. A full range of echo services for adult patients needs to be provided. Excellent nursing support adds value to the team. Whether nursing team members should come from an adult or pediatric background can be debated. A long-term commitment to ACHD care will improve their knowledge and abilities. Access to excellent congenital heart surgery is essential. This does not need to be in your own institution, but it certainly needs to be accessible. This includes the entire surgical team and intensive care personnel. The most common ACHD surgical procedure is pulmonary valve replacement. In my opinion, these are best handled by congenital heart surgeons. Indeed, there is evidence that there is a survival advantage for ACHD patients being operated on by congenital rather than adult cardiac surgeons (7). There are other patients that can be handled by adult cardiovascular surgeons skilled at aortic, mitral, aortic valve surgery, coronary artery bypass, etc. If your ACHD program is going to include patients with Marfan syndrome, there needs to be 24/7 availability of emergency surgical services to deal with anticipated aortic dissections. If your program is going to include cardiac patients who are pregnant, appropriate resources must be available 24/7.

Access to excellent diagnostic and interventional catheterization services is also imperative. Again, they don’t need to be in the same building, but they need to be accessible. The cardiologists doing these procedures usually come from a pediatric cardiology background, although adult cardiologists with training and experience in structural heart disease a well be capable of managing many of these catheterization cases. In either case, the interests of the patient should be primary. The procedure should be done by someone with appropriate expertise and experience and whose equipment and resources offer the patient the best possible chance of an excellent outcome. Is a biplane facility required? Does the lab have enough adult-sized catheters and devices to manage contingencies?

Access to excellent electrophysiology services are also very important. EP issues are very prevalent amongst ACHD patients. Pediatric EP cardiologists do very different work from adult EP cardiologists, so selecting a consultant may depend on the needs of the individual patient. Heart failure and transplant services will also need to be available. Heart failure is becoming an increasing issue in ACHD programs. Access to pulmonary hypertension resources will also be needed. Many ACHD programs now include team members with pulmonary hypertension expertise. Reproductive services also need to be available locally. This begins with the ability to counsel women of childbearing age regarding contraceptive options and their pregnancy risks. Some women should not use an estrogen-containing preparation. Risk factors for pregnancy should be evaluated...
according to several standard scales. One or more interested gynecologists may well make a valuable contribution to the family planning aspects of your ACHD clinic. A good primary care physician might provide many of the same services. The availability of maternal fetal medicine services is also vital. The ACHD program should provide the cardiac component of surveillance and treatment planning in collaboration with one or more obstetrical teams. Imaging services beyond echocardiography are also essential. Excellence in MRI is particularly vital, and CT angiography will need to be available. Specific training and experience in congenital heart disease and/or ACHD is essential to maximize value and minimize errors.

A number of other people might be important from time to time. If you have Fontan patients, you should have a knowledgeable hepatologist available. Many ACHD patients have chronic kidney issues, so nephrology support and involvement would be important. The availability of a geneticist and a genetics counselor may also be very important to the assessment and management of some patients. Hematology involvement may be required at times. Mental health resources are an important part of a comprehensive service.

In starting a new ACHD program, you need to have the essential elements in place before you open the doors. Once you do open the door and patients come in in sufficient numbers, your team will gain additional clinical experience and will become even more talented than they were at the outset. The team would be well advised to focus on quality outcome metrics in order to ensure themselves that they are maintaining standards and following published guidelines to ensure the best care of their patients (8–10).

The Adult Congenital Heart Association in the USA has created accreditation metrics for American ACHD clinics. This information should, in my opinion, be accessed from all jurisdictional services. The Adult Congenital Heart Association in the USA has created accreditation metrics for American ACHD clinics. This information should, in my opinion, be accessed from all jurisdictions since it provides important reminders regarding the many elements of high-quality ACHD patient care.

ACHD services need to be designed separately from pediatric cardiology services and from adult cardiology services. This applies to a wide range of activities including echocardiography, exercise testing, heart catheterization, and inpatient care. This is a difficult process, but extending pediatric services into the adult age range is not a formula for success, nor is the extension of acquired heart disease services into the congenital heart population likely to be successful. Parallel systems in all these dimensions should be created.

If you want to build a strong ACHD program, you will need: lots of suitable patients; a supportive institution; supportive colleagues; a talented team; a commitment to excellent patient care; educated patients and families; an effective transition/education process; and a clear transfer/graduation policy. You will need to focus mainly on medium risk to high-risk ACHD patients, and will work to keep them in care and to meet whatever health needs they may develop. You may need to decide in what type of institution to locate your program. Most of your care will be ambulatory, and you will need to establish suitable and different diagnostic and management protocols for the ACHD patients regardless of whether you are in a pediatric institution or an adult institution. If you are based in a children’s hospital, the admission of adult patients will be trying until you develop an appropriately adult trained care team to take the load off the pediatric practitioners. You will need to keep the interests of the patient uppermost in your planning and will need to be clear what services you will be able to provide locally, and which services will need to be accessed elsewhere.

You will be challenged to develop your multidisciplinary care team and this will take both persistence and patience. Collaboration of at least one pediatric trained cardiologist with at least one adult trained cardiologist is a good foundation for a program. An excellent echocardiography service is essential, and will need to be different from both pediatric echo services and adult acquired heart disease echo services. Success will not be easy, but there are an ever increasing number of patients who are depending on you to get the job done, and to get it done well.

References

KEY POINTS

Significant improvement has been achieved in assessing RV function using conventional and advanced ECHO techniques. Despite high sensitivity to loading conditions, many ECHO measures and indices can be applied to clinical practice for their high predicting value, particularly in conditions where RV is exposed to high afterload.

Echocardiographic (ECHO) assessment of RV function is complex and no single functional parameter is generally accepted in clinical practice. Several cross-sectional imaging parameters have been tested and validated and many article published suggesting advantages and limitations. Major limitation of all of them is more or less load dependency; however, many of them are giving insight in understanding of mechanism of RV failure and should be routinely used in clinical practise (1–4.). Parameters used for assessment of RV function are based on conventional ECHO methods (fractional area change - FAC/%, M-mode derived fractional shortening – FS/%), Doppler derived E/A ratio, S/D ratio, change of the pressure over the time (+dP/dt max/mmHg-s), tricuspid annular plane systolic excursion (TAPSE/mm), or based on Tissue Deformation Imaging techniques (tissue Doppler velocity and colour coded and 2D Strain imaging measures) for assessing myocardial velocities (S’, E’, A’), measuring myocardial performance index (MPI), Strain (S/%) or Strain rate (SR/-1), or isovolemic acceleration index (IVA), perhaps least load dependent but strongly heart-rate dependent parameter. Real-time 3D ECHO appeared to be alternative to MRI in assessing RV function. Twenty-three studies including 807 subjects however showed that 3D ECHO significantly underestimates RV enddiastolic volumes as well as RV ejection function (5).

Right ventricle exposed to high preload (atrial septal defect – ASD, tetralogy of Fallot with postoperative pulmonary regurgitation – TOF/PR, Ebstein anomaly – EA): In ASD patients, longitudinal deformation measured conventional and TDI showed in general normal or supra-normal functional parameters. Significant increase was found in the apical segment by using 2D Strain technique (6), apical strain correlated with shunt-ratio, RV end-diastolic area, and
RV stroke volume (7). Reduced functional parameters after surgical closure as compared to preoperative finding and post-catheter closure are related to reduced preload, cardiopulmonary bypass procedure and pericardial constrain. In TOF/PR, functional parameters are compounded by several factors such as type and time of initial surgical interventions, degree of residual pulmonary regurgitation and stenosis and QRS time. Several studies (8, 9, 10) confirm reduced overall longitudinal deformation but more significantly in the more apical segments of the RV free wall and the interventricular septum but predictive value of these changes is still not clearly identified. Higher pulmonary regurgitation volume and larger RV end-diastolic volume can also be associated with decreased LV radial strain (11) due to apical RV dilatation. In our study (12) we confirmed that the increase in early LV diastolic filling post percutaneous pulmonary valve implantation correlated with the reduction in RV to LV mechanical delay and change in septal curvature. Abnormally delayed septal contraction can be often explained by electromechanical dyssynchrony due to QRS prolongation (13, 14). Early septal activation leads to early pre-stretch and late contraction of the RV basal lateral segments that are hallmarks of electromechanical dysynchrony similar to LV dysfunction and LBBB resulting in mechanical inefficiency. Diastolic dysfunction is also well described in these patients, potentially preceding systolic functional impairment, concept of Doppler derived pre-systolic atrial antegrade flow in pulmonary artery suggestive of restrictive RV physiology (15) has been routinely used in clinical practise. Our study however suggested that RV physiology is influenced by degree of PR and this Doppler flow pattern can resolve once PR is eliminated (16).

In EA, the RV is chronically exposed to high preload (significant TR±ASD) and low afterload (low PVR). Despite the TR and large atrialised portion of the RV together with under-filled LV, this physiology can be tolerated well even for years. Successful cone operation eliminates TR and incorporates atrial RV into functional RV. This acute change leads to rather dramatic RV dysfunction documented by ECHO.

Figure 1. Clinical information (A) and RV echocardiographic indices (B-D.) before and after cone operation for Ebstein anomaly. NYHA = New York Heart Association, TAPSE = tricuspid annular plane systolic excursion, RV FAC = right ventricular fractioning area change

Figure 2. Conventional LV echocardiographic indices (A-B), 2D Strain (C.) and dyssynchrony assessment (D) before and after cone operation for Ebstein anomaly. LVEF = left ventricular ejection fraction, TTP = time-to-peak, HR = heart rate
MRI or catheter derived data (21). Simple measure of RV longitudinal function TAPSE is associated with survival in patients with PAH (22), however this parameter analyses very small part of the RV. Other ECHO predictors of prognosis include pericardial effusion, indexed right atrial area, the degree of septal shift toward the left ventricle in diastole, pulmonary vascular capacitance, and RV myocardial performance index (MPI, Tei index) (23, 24). Relatively simple methods such as Doppler derived systolic/diastolic index (25) might be used effectively as well as rather sophisticated RV myocardial strain (26).

In patients with ccTGA, in TGA after intra-atrial baffling, and in HLHS, the morphological RV is the systemic ventricle. Several studies in patients with ccTGA and TGA after Mustard or Senning operation showed that quantitative echocardiographic assessment of global systemic RV function such as MPI highly correlates with RVEF obtained by CMR and can be used in clinical practice (27). Speckle tracking derived global longitudinal strain is lower especially in the apical segment, and tended to be lower in TGA-Mustard than ccTGA patients (28) and is related to adverse clinical outcome (29).
References


Advanced echocardiographic modalities in the assessment of right ventricular function

Satoshi Yasukochi, MD
Heart Center, Nagano Children’s Hospital
Toyoshina, Azumino, Nagano, Japan

The right ventricular (RV) structure and function have been found to be an important determinant of prognosis and the outcome of the treatment in congenital heart disease. Currently, echocardiography and cardiac magnetic resonance are the two major imaging modalities to visualize the structure and functions of the RV.

The newer echocardiographic technology provides more information to dissect out the detailed contractile mode and intra-cardiac flow dynamics of RV, besides the complexity of its geometrical shape and structure. The contractile mode and morphology of anatomical RV is different in case of pulmonic ventricle from that of systemic ventricle. The 3D morphology of pulmonic RV is
crescent while that of systemic RV is ellipsoidal. (Figure 1)
The contractile mode of pulmonic RV shows peristaltic from inlet to outlet, which means dominant longitudinal strain with less circumferential strain. On the other hand, the systemic RV contracts more like a systemic left ventricle which means more circumferential and longitudinal strain. However, both pulmonic and systemic RV DO NOT have a torsion or twist which a normal systemic LV does have. (Figure 1)
The systemic RV in hypoplastic left heart syndrome (HLHS) demonstrates lower 3D peak strain and longer time-to-peak strain, compared to those in normal LV. Recently, the intra-blood flow kinetics could be analyzed by novel imaging modality using color Doppler to calculate “blood flow kinetic energy loss” (EL, mW) from the reconstructed velocity vector components transformed into Cartesian coordinate system as previously reported by K. Itatani et al., 2013.

The EL data were indexed by measuring a ratio of EL to the inflow kinetic energy (KEin) through systemic atrioventricular valve in diastole. EL/KEin in diastole of HLHS is higher than that of normal LV. This means systemic RV of HLHS may lose intracardiac blood flow kinetic energy besides impairment of chamber and wall kinetics. (Figure 2)

References
Assessment of RV function with pressure-volume loops – impact on treatment indication for a volume-loaded RV

Prof. Dr. Christian Apitz
Division of Pediatric Cardiology
University Children’s Hospital Ulm
Ulm, Germany

The assessment of right ventricular function is aggravated by the complex anatomy of the right ventricle and the variable effects of abnormal loading conditions. Pressure-volume loop analysis by conductance catheters is extensively used in experimental studies especially in models of acute and chronic right ventricular pressure or volume overload and is generally considered the most reliable way to quantify right ventricular contractile function. (1–6)

A conductance catheter is a specialised multi-electrode catheter which allows accurate measurement of ventricular volume and pressure continuously throughout the cardiac cycle. A variety of physiological parameters can be derived from pressure-volume loops.

By recording a family of pressure-volume loops during reduction of preload, preferably achieved by temporary balloon occlusion of the inferior caval vein, the systolic ventricular function could be calculated by the slope of the endysystolic pressure-volume relation (Figure).

Main drawback for the routine use of pressure-volume loop analysis in clinical everyday practice is its invasive nature. Nevertheless, in individual cases it might be a helpful tool to support decision-making for change in therapy, RVOT intervention or reoperation, as well as monitor changes after treatment and as a predictor for outcome of patients with congenital heart disease and adverse RV loading condition.
References


Figure: Family of pressure-volume loops during reduction of preload achieved by temporary balloon occlusion of the inferior caval vein.
KEY POINTS

The right ventricle can easily be assessed by cardiovascular magnetic resonance. Right ventricular volumes, flow in the pulmonary artery and even through the tricuspid valve are measured and provide valuable data on ventricular function and information about tricuspid and pulmonary valve regurgitation.

Cardiovascular Magnetic Resonance (CMR) has become a valuable tool for assessment of right ventricular structures in routine follow-up of right ventricular disease. Anatomic reasons may limit assessment of the right ventricle by echocardiography. Is has been shown that right ventricular volumes and function can be assessed very precisely by CMR, since other methods tend to over- or underestimate right ventricular volumes. (1) The main conditions for patients grown-up with congenital heart disease to be referred to CMR assessment are situations after repair of tetralogy of Fallot for evaluation of right ventricular volumes, function and assessment of pulmonary regurgitation.

In patients after atrial switch operation for transposition of the great arteries failing of the systemic right ventricle is the main focus of the assessment in CMR. Additionally, tricuspid valve regurgitation can be evaluated. Evaluation of the ventricular myocardium to detect myocardial scars may be useful, but this issue is controversially discussed in patients with systemic right ventricle. (2, 3) Therefore we do not perform routinely late gadolinium enhancement for detection of myocardial scars in follow-up assessment of patients with systemic right ventricles. The assessment of the systemic right ventricular myocardium for scientific purpose includes e. g. T1 mapping. Most of the right ventricular disorders can be evaluated by CMR with scan times less than one hour. In patients after arterial switch the focus of the examination lies on the anteriorly positioned pulmonary artery that may become stenotic over time. The right and left pulmonary artery may also get stenotic mainly due to anatomic reasons and due to tension on the pulmonary arteries due
to relocation of the pulmonary artery anterior to the aorta. Further congenital cardiac conditions that are routinely evaluated in adulthood by CMR to evaluate the right ventricular situation are congenital corrected transposition of the great arteries, complex DORV situations, single ventricle performance and Ebstein’s anomaly.

In Ebstein’s anomaly right ventricular function and tricuspid regurgitation play a target role. Figure 1 shows a 68 years old woman with Ebstein’s anomaly with severe tricuspid regurgitation. Figure 2 shows the same patient after cone repair of the tricuspid valve. Generally, regurgitation of the tricuspid valve can be evaluated by two methods in CMR. It can be assessed by measuring directly the flow through the tricuspid valve. This measurement implements some technical problems since the tricuspid valve area is moving during the cardiac circle and therefore during flow measurement. The second method to assess tricuspid regurgitation is based on measuring the stroke volume of the right ventricle by evaluation of the end-diastolic and the end-systolic volume. The stroke volume is calculated and the flow in the main pulmonary artery is measured. Further the part of the stroke volume that is not running through the pulmonary artery is assumed to be regurgitated through the tricuspid valve. (Figure 3)

Major limitations for volume and flow assessment by CMR are rhythm abnormalities that do not allow sufficient triggering of the ECG signal. Therefore, atrial fibrillation, atrial flutter, many kinds of ectopic beats during the scan and also largely widened ECG complexes may cause problems. Most CMR scans need a stable ECG signal for averaging image information that has been measured over several heart beats. Bad ECG trigger may impair the quantitative analysis, but it may still be possible to qualitatively assess ventricular volumes and function in such conditions. Volume overloaded ventricles may also be detected and end-diastolic volume indices can be used, but with precaution. In such situations volume indices, structural assessment, size and function of the right ventricle by eyeballing and relation of size and function of the right ventricle to left ventricle parameters may be used.

References

KEY POINTS

- The right ventricle is inseparably connected with the venous system, that determines preload, and the pulmonary vascular bed, that determines afterload.
- Right ventricular function can only be judged when preload and afterload are taken into account.
- Understanding of both basics of the exercise physiology and the limitations in the non-invasive assessment of right ventricular function, helps in the assessment of right ventricular function in clinical practice.

Physiology of the circulation during exercise

During exercise, the metabolic demands of the body increase instantaneously. These increased demands should be met by an increase in cardiac output. This is achieved by the left ventricle, by increasing stroke volume and heart rate. The left ventricle can only do so, if supplied adequately by the right ventricle.

At the start of exercise, pulmonary vascular resistance drops, allowing the right ventricle to increase pulmonary perfusion with only limited rise of right ventricular pressure. There will be more pulmonary venous return to the left atrium and thus the left ventricle. In turn, the right ventricle can only increase pulmonary blood flow when provided with more systemic venous return. This is achieved by increase of the vascular tone in the capacitance vessels of the venous system, for which in increase of sympathetic nerve activity is responsible (1).

At rest, a large part of the circulating volume is in the venous compartment. The thin-walled and very compliant venous system holds approximately 10 times the volume that the stiffer and thicker-walled arterial system holds (2). In other words, the total systemic vascular capacitance (or blood-holding capacity) is predominantly dependent on the venous system. In this system, the biggest reservoirs are in the splanchnic system, in the spleen and in the liver. A small increase in vascular tone will directly lead to an increase in venous return towards the right atrium. A prerequisite is that right atrial pressures remain low at exercise. Only then, a higher systemic venous pressure will lead to a
higher pressure difference (gradient) between systemic veins and right atrium and consequently more systemic venous return towards the right atrium.

The main role of the right side of the heart during exercise is to accommodate substantially larger quantities of blood, without elevating right atrial pressure and to pump these larger quantities of blood into the pulmonary vascular bed. The instantaneous lowering of pulmonary vascular resistance during exercise will limit the increase of pulmonary artery pressures, despite substantial increase in pulmonary blood flow (3). In the large vessels of the pulmonary vascular tree, the pulmonary capacitance vessels, the antegrade flow takes place predominantly in systole, during ventricular contraction.

The relation between stroke volume and pulmonary pressure is the elastance of the pulmonary vascular bed. The pulmonary vascular elastance expresses to which extent the right ventricle and the pulmonary vascular bed work together at rest and during exercise: the ventricle-arterial coupling. A good elastance implies a limited increase in systolic pulmonary artery pressure during increase in stroke volume.

In healthy individuals this works well during not too vigorous exercise: the ventriculo-arterial coupling is intact. Pulmonary vascular resistance is dictated primarily by the pulmonary capillary bed. Beyond the pulmonary capillary bed is the pulmonary venous vascular bed and eventually the left atrium and left ventricle. At exercise, left ventricular systolic pressure rises substantially, since it has to pump more blood into the great arteries, which will have a higher resistance from the onset of the exercise, due to the increased sympathetic nerve activity.

When a ventricle is confronted with a sudden increase in afterload and/or a sudden increase in preload, we know from the work of Anrep and Frank Starling (4) from the early 19th century, that the ventricle dilates first: with an unaltered contractility – ejection fraction when translated in clinical practice - the stroke volume can only increase if the ventricular volume increases. This was called heterometric adaptation.

Within a few minutes, the contractility increase and ventricular volumes come down to the original size. This was Frank Starling’s observation, that contractility of a muscle fiber increases when stretched.

**Normal RV: hang-out interval**

2nd part systole: RV pressure lower than PA pressure

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**Figure 1:**

- PAP = pulmonary artery pressure
- RVP = right ventricular pressure
- PEP = pre-ejection period
- RVET = RV ejection time

(Figure used with permission of H. Hamer & E. Pieper)
This is referred to as homeometric adaptation. If increased loading condition are not chronic and do not last excessively long (extreme endurance sports), the right heart can deal with exercise, without damage being done to the myocardium (5).

Exercise almost always means physical activity, with skeletal muscles generating the physical activity. Specifically in the muscle that do the exercise, the vascular resistance will decrease, resulting in preferred blood flow towards that muscles that do the work. The higher metabolic need of these muscles is met this way. Due to increased muscle activity, the “muscle pump” (6) will enhance venous return towards the central venous system, which eventually contributes to the filling of the right heart.

Right ventricular function

In healthy individuals, all these mechanism work together in close harmony. When one of these factors in the whole chain that is necessary to augment cardiac output at exercise is affected, it will influence exercise capacity.

The role of the left ventricle is studied extensively. Cardiac imaging is well suited (especially designed) for assessment of its morphology and changes in shape during the cardiac cycle. Doing invasive assessment of left ventricular function, the rectangular shape of its pressure-volume curve will allow identification of end-systolic elastance, “the” marker of ventricular function.

All measurements of ventricular function depend on the loading conditions, but end-systolic elastance is considered to be the most stable marker of ventricular function: during changes in pre- or afterload, the end-systolic elastance remains remarkably stable.

The right ventricle is notoriously difficult to catch. Its complex geometry – crescent-shaped, curved around the high-pressure left ventricle – and its longitudinal, caterpillar-like contraction, starting at the inlet and ending in the right ventricular outflow tract, very different from the concentric contraction pattern of the left ventricle, make imaging and functional assessment based on imaging, very cumbersome.

Invasive studies of the right ventricular function, looking at pressure-volume relation, are also more complicated than on the left side of the heart. A pressure-volume curve of a human right ventricle was produced for the first time in 1988. (7) Only in the subsequent years/decades the understanding of right ventricular function became more profound. In a normal right ventricle, that is coupled with the low-resistant and very compliant pulmonary vascular bed, the pressure-volume relation is very different from that of the left ventricle. Its shape is triangular instead of rectangular. There is no real isovolumetric contraction and after peak-systolic right ventricular pressure, the propulsion of blood into the pulmonary artery continues, while right ventricular pressure is already declining. This is called the “hang-out period”. (see Figure 1) Simultaneous pressure recordings show that pulmonary artery pressures are actually higher than RV pressures in this phase. The hang-out interval is only possible because of the very low impedance of the pulmonary vascular bed. The consequence is that, in contrast to end-systolic elastance of the left ventricle, the elastance at end-systole, defined by pulmonary valve closure, is not a good representation of right ventricular function (but of pulmonary vascular impedance). Redington et al (8) showed that peak-systolic (not end-systolic) elastance was a good marker of ventricular function: despite substantial variations in pre-load, peak systolic elastance remained the same.

This marker, peak-systolic elastance, is the only measurement that truly represents right ventricular function. It is related with – or represents – contractile reserve. All other measurements of parameters that might represent right ventricular function, are (very) load-dependent. The problem is that RV elastance can only be measured invasively, in a research setting. It is considered the gold standard for RV function, but it cannot be used in clinical practice. We have to do with tools that we have in clinical practice, realizing their shortcomings.

If we talk about RV function in clinical practice, it is not well defined what is meant. RV ejection fraction, assessed with MRI, will come closest for most clinicians working in this field, but 2D echo and especially 3D echo are used too (9). RV dysfunction is not well defined either, but most will consider a measurement representing RV systolic function outside (below) the mean value minus > 2 standard deviations RV dysfunction (10, 11). The next problem is, that there are no consensus about what the normal ejection fraction is in humans. Only small series have been published, with values for EF ranging form 48 % to 60 %, with different standard deviations (9). A RV with an ejection fraction of 60 % will be normal, regardless the normal values one uses. A RV EF of 50 % is abnormal in one study, but normal in the other. The same is true for many other markers of RV function, being either echo- or MRI-derived. RV failure can be defined in different ways. Most clinicians will use the combination of clinically visible signs of venous congestion, RV dysfunction and complaints of early fatigue and exertional dyspnea.

RV dysfunction and exercise

We normally investigate patients at rest, either by echo or by MRI. Whatever you choose – tricuspid annulus planar systolic excursion (TAPSE, measuring the longitudinal movement of the RV lateral wall), TDI of this lateral wall (measuring the velocity of this displacement), RV dimensions, fractional area change (FAC) or currently RV strain or
strain rate determined with 2D speckle tracking—all these measurements provide data about how the RV functions in baseline condition, at rest, in supine or in left decubitus position. The same is true for MRI assessment of the RV. A completely normal RV function at rest—irrespective of how it is determined non-invasively—does not necessarily mean that at different loading conditions, during exercise, function will remain normal. A few studies looked at RV function at exercise, especially in pulmonary hypertension (12), showing that the degree of RV dysfunction can better be judged by doing measurements at rest and during exercise. Once the RV already has diminished systolic function at rest, it will not improve during exercise. From clinical studies is known that many adult patients with (repaired) congenital heart defect, will have a diminished exercise capacity (13). It is likely that in many patients RV dysfunction will contribute substantially to the reduced exercise capacity, but, in contrast to in pulmonary hypertension, very few studies have been done to understand the exact mechanisms of RV dysfunction in congenital heart disease.

Conclusion

Exercise physiology makes clear that all shackles in the chain in the circulation are interdependent and all are important when cardiac output has to increase during exercise. The right ventricle is inseparably connected with the systemic veins and the pulmonary vascular bed, but if hypothetically regarded is isolation, its specific function during exercise would be to increase blood flow to the lungs, while keeping right ventricular filling pressures, i.e. right atrial pressures, low. The best way to measure whether the RV is up to this task, is peak-systolic pressure-volume relation. This can only be measured invasively, in a research setting and is not useful in clinical practice. All parameters we use in clinical practice that reflect RV function, are very much load-dependent. If patients are studied at rest, which is almost always the case, one can only judge RV performance in these resting conditions. Testing the RV in various conditions, especially during exercise, will allow a better judgement of RV function than the usual testing in resting condition.

References

Indications for treatment in adults with tricuspid valve dysfunction due to a congenital cardiac anomaly

**Prof. Dr. Markus Schwerzm ann**
Zentrum für angeborene Herzfehler
Universitätsspital Inselspital
Bern, Switzerland

**KEY POINTS**

The tricuspid valve is frequently affected in adults with congenital heart disease (CHD). Valve failure can occur primarily or develop secondary to changes in the right ventricle caused by other defects. Quantitative echocardiographic assessment of tricuspid regurgitation is essential to predict prognosis. Treatment options vary depending on the underlying defect and right ventricular function. Surgical management of tricuspid valve disease is complex and evolving.

Tricuspid valve (TV) dysfunction in the setting of a congenital heart defect (CHD) consists most of the time of tricuspid regurgitation (TR).

Its clinical significance is underestimated and guidelines for management are less aggressive and more subjective than those of other valves (1). Quantitative grading of TR severity is in principle similar to the grading of mitral regurgitation, but less robust (2). It is nevertheless a powerful predictor of outcome and superior to standard qualitative assessment (3).

TR can be classified into primary and secondary TR (Figure 1).

In adults with severe TR due to valve dysplasia, symptoms in the absence of RV dysfunction or progressive RV dilatation and/or function deterioration in asymptomatic patients are indications for TV surgery (4).

In adults with secondary TR due to a volume loaded RV (e.g. due to an atrial septal defect or to severe pulmonary regurgitation after Fallot repair), TR is expected to regress after shunt closure or pulmonary valve replacement and does not preclude percutaneous interventions (5–8).

In patients with a systemic RV and a previous atrial switch procedure, TR is usually related to progressive RV failure. Akin to functional mitral regurgitation, TV replacement is not advised if there is significant systemic RV dysfunction. Medical therapy and consideration of mechanical support or cardiac transplantation are essential.

In adults with a systemic RV and congenitally corrected transposition (ccTGA), severe TR is more likely due to intrinsic TV disease and timely valve surgery is mandatory (9).
For best results, TV replacement is advised before systemic ejection fractions (EF) falls < 40 % or the subpulmonary ventricular systolic pressure rises to > 50 mmHg (10).

In ccTGA patients, pre-operative EF is the single most important predictor of post-operative EF.

References

Surgical techniques to improve tricuspid valve function in congenital heart defects

Victor Tsang FRCS, Henri Haapanen MD
Great Ormond Street Hospital for Children, Department of Cardiothoracic Surgery
London, United Kingdom

KEY POINTS

Also in adults with congenital heart disease and tricuspid valve (TV) anomalies the understanding of the physiological features of the valve anomalies and individualised technique selection are the keys to a good decision-making and a durable valve repair in selected cases.

Tricuspid valve (TV) anomalies form a wide spectrum of pathological defects in adults with congenital heart disease. The surgical techniques and additional concomitant procedures to improve the tricuspid valve function are well established, for example, tricuspid valve regurgitation (TR) after tetralogy of Fallot repair, right atrioventricular valve dysfunction after atrioventricular septal defect repair, and reimplantation of straddling TV in biventricular repair.

It may be worth emphasising the surgical approach to the very challenging Ebstein’s anomaly, which has been at its turning point during the last decade. There have been a “disproportionate” number of technical approaches introduced for the Ebstein’s anomaly, including Danielson and Carpentier’s techniques. In 2007, da Silva at al. described cone technique, which consequently improves the functional anatomy of RV inflow (1). The reconstructed anteriorsuperior leaflet and the remnants of the delaminated septal and posterior leaflets are rotated to form a cone with a RV apical connection (Figure 1). The cone repair has been shown to be effective technique for patients with severe regurgitation associated with Ebstein’s anomaly (2). However, the very highly variable tricuspid valve anatomy and the significant dilatation of the right heart cavity size and ventricular dysfunction in adults demand a very careful decision if a durable valve repair is possible and achievable.

Some important surgical details require further commenting, such as the adequacy of the tricuspid valve leaflet tissue for repair, the placation of the atrialised right ventricular cavity, the reinforced annuloplasty sutures, the proxi-
mity of the right coronary artery and the posterior descending artery, and the conduction tissue.

Moving further to the boundaries of adult congenital heart surgery, the management of tricuspid valve dysfunction in the context of systemic morphological right ventricle is difficult even for the experienced surgeons, including the emerging population of patients following univentricular palliation of hypoplastic left heart syndrome.

We have already described the range of surgical strategies to deal with the moderate to severe tricuspid valve regurgitation in the younger age group (3) but the intrinsic tricuspid valve dysfunction would be more substantial in adulthood. Similarly, based on limited data, the anatomic repair of atrioventricular discordance appears to provide better functional results in selected patients in terms of TV function (4), but at the expense of a long risky operation and a high burden of reoperations (5). A less definitive approach using pulmonary artery banding as a palliative strategy offers a reconfiguration of the ventricular septal shift leading to some regression of TR.

References


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When Tricuspid Valvuloplasty fails ... 
What is the best valve in tricuspid position?

Alessandro Giamberti, MD
Head Congenital Cardiac Surgery Unit
IRCCS-Policlinico San Donato – University Hospital
Milan, Italy

KEY POINTS

Tricuspid valve problems in ACHD are treated not rarely by valve replacement, especially in older patients. The use of bioprostheses is preferable in term of performance, results, freedom from complications and the possibility to perform transcatheter valve procedures.

Tricuspid valve (TV) replacement is a relatively infrequent surgical procedure and is reserved for those few occasions where repair of the TV is not feasible or attempts at repair have failed. For the TV replacement there is no specific prosthesis. The mitral ones are used but the choice between mechanical or biological prosthetic valve remains a controversial subject. The use of bioprostheses is today preferable in term of performance, results, freedom from complications and the possibility to perform transcatheter valve procedures.

Tricuspid valve problems, especially tricuspid regurgitation (TR), in adults with congenital heart disease (ACHD) can be associated with different anatomical or functional mechanisms. Different groups of patients have been identified including:

1) patients with Ebstein anomaly
2) patients with TV damaged by previous surgical operations, cardiac catheterizations or pacemaker (or ICD) placement
3) patients with a TV failing in its capacity as systemic atrio-ventricular valve (status post Senning or Mustard operation and congenitally corrected transposition of great arteries)
4) patients with functional TR related to right ventricular dilation or dysfunction (1).

Indications for surgery of the TV include symptoms, decreased exercise tolerance, structural valve abnormalities, progressive right ventricular dilatation, the onset or progression of atrial tachyarrhythmias, and need for concomitant cardiac surgery (1, 2).

When surgery for TV is indicated, TV repair is preferable and TV replacement is the second choice. TV replacement is a relatively infrequent surgical proce-
dure, approximately 2% of all valve replacement (3), especially compared with left-heart valve procedures, and is reserved for those few occasions where repair of the TV is not feasible or attempts at repair have failed. In ACHD TV replacement is much more performed than in pediatric patients (2) and usually used in 50% of adults with Ebstein anomaly (75% of patients over 50 years) (4, 5), in case of rheumatic disease, endocarditis, after repair failure, in patients that had undergone three or more previous sternotomies, and in patients where the leaflets are thicker and more rigid. TV replacement is not technically challenging and, in the absence of in-ter-cardiac communications, it is possible to perform the procedure in beating-heart without aortic cross-clamping.

There are three techniques most commonly used to suture the prosthetic valve along the circumference of the annulus:

- evert ing sutures
- non evert ing sutures, and
- c ontinuous suture.

To avoid injury of the conduction system it is better, in the septal portion of the valve, not to touch the annulus but to use the septal leaflet tissue to perform the suture (Figure 1). Otherwise it is possible to perform a supra-annular implantation of the prostheses leaving the coronary sinus and the AV-node on the ventricular side of the prosthetic valve (Figure 2). For the TV replacement there is no a specific prosthesis. The mitral ones are used but the choice between mechanical and biological prosthetic valve remains a controversial subject (6).

Tricuspid or mitral homografts have been proposed as alternative to prostheses (2, 8), but the experience is limited, technically not simple, and generally used in endocarditis or rheumatic disease. Biological valves do not need anticoagulant therapy but these valves will inevitably experience wear and degeneration requiring a second implant; mechanical valves, on the other hand, have potential unlimited duration but high risk of valve thrombosis, thromboembolic event, and bleeding complications correlated to the anticoagulation treatment. The use of a bioprosthesis is today preferable to a mechanical valve in tricuspid position. Previous reports (9) have shown that a bioprosthesis in the tricuspid position is more satisfactory than in mitral position and in the Ebstein anomaly (10) a bioprosthesis seems to be superior in term of freedom from complications and overall survival.

Other important advantage using bioprostheses in tricuspid position is the possibility to perform balloon valvuloplasty and future transcatheter valve replacement with the so called “valve-in-valve” procedure. This approach, first performed by Leen van Garse in 2011 (11), is actually used in selected cases both in acquired and congenital heart disease (12) and is another factor in favor of using bioprostheses in TV position.

References

Which valve is best in right ventricular outflow tract dysfunction?

**Autor**
Rüdiger Lange
Munich, Germany
Indications for pulmonary valve replacement in adults with congenital heart disease

Werner Budts MD, PhD
Congenital and Structural Cardiology, University Hospitals Leuven, and Department of Cardiovascular Sciences, Catholic University Leuven, Leuven, Belgium.

KEY POINTS

The right ventricular outflow in adult congenital heart disease requires lifelong attention. Patients with treated or untreated pulmonary valve stenosis, after repair of a tetralogy of Fallot, or after Ross or Rastelli repair might suffer from increasing right ventricular outflow tract obstruction or ongoing valve regurgitation. Not timely intervening on the persistent pressure or volume overload of the right ventricle might compromise outcome. Guidelines do suggest when and how to intervene on the right ventricular outflow tract. However, the shift from surgical interventions to the promising and evolving technique of percutaneous valve implantation raises the question whether much earlier intervention is needed to keep ventricular structure and function optimized.

The right ventricular outflow tract (RVOT) in adult patients with congenital heart disease deserves lifelong attention. The natural history of the underlying disease or the consequences of interventions in childhood exposes the RVOT to anatomic and functional changes.

Some patients evolve to a progressive outflow tract obstruction that leads subsequently to increasing pressure load of the right ventricle. This stenosis may occur at different levels of the outflow tract: subvalvular, valvular, and supravalvular. In other patients is the right ventricle exposed to persistent volume overload because of ongoing significant valve regurgitation. Congenital heart defects that require specific attention for the RVOT are mainly

- pulmonary valve stenosis (PVS),
- tetralogy of Fallot (TOF), and
- lesions for which Ross or Rastelli repair was performed.

Several, currently adult patients with PVS underwent pulmonary valvulotomy or balloon valvuloplasty in childhood. Unfortunately, the price paid to open (mainly surgically) a stenotic valve is evoking valve regurgitations. This valve insufficiency might require in its turn reavaluation of the outflow tract. Because the association with a relatively
large outflow tract leads to a surgical re-intervention and implantation of a homograft, a valved conduit, or a biological valve prosthesis.

The same is true for patients after TOF repair. The ventricular septal defect is closed and the RVOT enlarged. This RVOT enlargement may include infundibulectomy, pulmonary valvuloplasty, including valvulotomy, and relief of co-existing supravalvular stenosis.

Immediate implantation of a biological valve or a homograft is very rare, but in a substantial number of currently adult patients transannular patching was performed. Subsequently, this led to a severe pulmonary valve regurgitation and might require in its turn revalvulation. Similarly to PVS, the association with a large outflow tract requests mostly a surgical re-intervention and the implantation of a homograft, a valved conduit, or a biological valve prosthesis.

Finally, in a more complex congenital anatomy, as after Ross repair for aortic valve disease, or Rastelli repair for transposition of the great arteries with ventricular septal defect and pulmonary stenosis, or Rastelli repair for arterial trunk, the right ventricle is bypassed to the pulmonary trunk by the insertion of a homograft or valved conduit. Unfortunately, all these implanted valves degenerate subsequently over time so that a new intervention becomes imperative later in life (2, 3).

Both volume and/or pressure overload of the right ventricle open the question when and how to (re-)intervene. The ESC guidelines for the management of grown-up congenital heart disease are very helpful to decide when to intervene in patients with a native right ventricular outflow tract obstruction (table 1) or with a stenotic right ventricular to pulmonary artery conduit (table 2) (4).

Symptomatology and right ventricular pressures at rest are the main drivers for re-intervention that mainly consists of surgical or percutaneous valve replacement. Today, the growing expertise and the good results consider percutaneous pulmonary valve implantation (PPVI) as first choice of treatment where technically applicable (5). The shift of last years from a surgical to a more percutaneous approach raises the question whether no earlier interven-
tion than suggested by the most recent ESC guidelines is indicated. Indeed, longstanding pressure overload of the right ventricle might be not that harmless.

The ESC guidelines do also indicate when to intervene in case of pulmonary valve regurgitation (PR) (table 1 and 2) (4). However, optimal timing for pulmonary revalvulation remains challenging, but it is generally accepted not to exceed an end-diastolic volume index > 160 ml/m² (6).

The question raises whether no earlier intervention is needed in stead of waiting until the first signs of ventricular damage occur. Revalvulation for PR is mostly done surgically, although new percutaneous techniques and new valve designs might encourage a percutaneous approach (7–9).

However, long-term follow-up will find out whether PPVI will improve finally clinical outcome.
References

While percutaneous pulmonary valve implantation (PPVI) was the first transcatheter valve replacement which gained clinical importance with the introduction of the Melody valve in 2000, there is no such valve developed especially designed for tricuspid valve replacement.

With increasing experience in valve-in-valve procedures, however, it became obvious that many degenerated bioprosthesis can be overstented by transcatheter valves. (1–3) The procedure is analog to the pulmonary valve implantation, and in most cases even technically simpler because the tricuspid valve location is easier to reach and the bioprosthesis provides a clear landing zone, which is not always the case in PPVI.

Coronary compression is not an issue, but pacing leads and a small ring of the surgically inserted bioprosthesis may be so. Fortunately, pacing leads may be overstented without loss in function or can be exchanged across the transcatheter valve later.

In certain surgical bioprosthesis, the valve ring can be cracked with ultra-high pressure balloons in order to implant larger transcatheter valves. (4) Special cases are patients with Bjoerk-Fontan circulation. (5) They have either a patch or a biological conduit across the right atrial-ventricular junction. Coronary compression may play a role and pre-stenting is usually necessary, thus the procedure is more complex.

In patients with atrial switch operation, a tricuspid valve-in-valve procedure is possible, replacing the tricuspid valve in the systemic circulation. A trans-baffle approach is necessary, otherwise the intervention is comparable to a percutaneous tricuspid valve or mitral valve implantation, respectively.
References


Figure: Patient after atrial Switch Operation with bioprosthesis in tricuspid position. Injection in the superior caval vein (left). Placement of a transcatheter valve in the bioprosthesis via transbaffle access (middle). Valve after successful placement (right).
Transcatheter Percutaneous Pulmonary Valve-in-Valve Implantation

Dr Chessa Massimo, MD, PhD, FSCAI, FESC
Pediatric and Adult Congenital Heart Centre
IRCCS-Policlinico San Donato- University Hospital
San Donato M.se – MILAN, Italy

Transcatheter percutaneous pulmonary valve-in-valve implantation (TPVIV) is an effective and safe treatment for pulmonary bioprosthetic valve (BPV) dysfunction, both using the Melody or the Edward Sapien valve, improving freedom from surgical reintervention. Long-term studies will redefine the management of dysfunctional RVOT, either native or surrogate, including bioprostheses. Approximately 20% of newborns with congenital heart disease (CHD) have anomalies of the pulmonary valve (PV) or of the right ventricular outflow tract (RVOT) (1), traditionally requiring multiple surgical interventions during their lifetime due to recurrent RVOT dysfunction (2).

Surgical revision may employ valved conduits, homografts, mechanical or bioprosthetic valves (BPVs) that can be stented or stentless (Figure 1), which can degenerate, leading to pulmonary valve stenosis, regurgitation or both (PR) (3–4). BPVs are currently the most widely used devices for pulmonary valve replacement. They are readily available, easy to implant, do not need extensive dissection of the pulmonary arteries, and anticoagulation therapy is not necessary.

KEY POINTS

Transcatheter PVIV can be performed safely, and with high success rate, low procedure-related morbidity and excellent medium term results.

The new frontier will be to enlarge the population eligible to transcatheter implant of pulmonary valve in bioprosthesis, and to identify the best timing and clinical parameters on when to proceed.

The use of 3DRA is helpful defining the implantation site, and evaluating the relationship between the RVOT and the coronary arteries (FIGURE 2)
Surgical valves durability is attested at 10 years for more than 85% of patients (10).

Percutaneous pulmonary valve implantation has provided an option for non-surgical management of these bioprosthetic valve failed (5).

The TPViV is feasible, effective, and at a relative low risk. Gillespie et al. (6), reported the biggest series on TPViV, in a multicentric North American preliminary experience in which 104 patients underwent Melody pulmonary implantation within a variety of failed surgical BPsVs.

The experience of my Centre confirmed excellent results for those who received a Melody Valve and for the pts in which an Edward Sapien was implanted. No differences in terms of right chamber pressures and output were revealed, neither in terms of symptoms, thus suggesting that Sapien and Melody could be both equally useful to perform TPViV. The most significant difference between the two percutaneous valves (Melody and Sapien), are the larger available diameters and the smaller height of the last one, thus enlarging the number of patients suitable to TPViV.

References


KEY POINTS

Remarkable progresses in pediatric cardiac surgery and interventional procedures have led to the fact that more patients with moderate to complex congenital heart disease (CHD) are surviving into adulthood. Heart failure and progressive cardiopulmonary dysfunction occurs late after interventions, palliative and corrective surgery. Therefore heart, lung or combined heart-lung transplantation becomes a treatment option. Those patients who survive the first year have better longterm (5–10 years) outcome compared to non-CHD transplant patients. There is a need for international consensus to reconsider current criteria for urgent cardiac transplantation in patients with adult CHD (ACHD).

Due to progress in pediatric cardiac surgery on patients with congenital heart disease (CHD) this has led to a noticeable improvement in the life expectancy of these patients with CHD (1). Together with advances in surgical techniques, anesthesia, and intensive nurse care the mortality has dramatically decreased and approximately 85% of children with CHD are surviving to adulthood (2, 3). The most common cause of morbidity and mortality in adult congenital heart disease (ACHD) patients is late myocardial dysfunction that often occurs after palliative or corrective surgery, and heart failure it is the most common cause of decline and death in patients with CHD (1, 3, 4). Consequently, a growing number of patients with CHD presents with a progressive decline in cardiopulmonary function as an adult, at which point transplantation becomes the only treatment option. The outstanding surgical and medical challenges in adults with CHD (ACHD) who are in evaluation to heart transplantation (HT), lung transplantation (LT) or heart-lung transplantation (HLT) owing to their complex anatomy, multiple prior palliative and corrective procedures, frequently increased pulmonary vascular resistance (PVR) from longstanding congestive heart failure or cyanosis, and overall debilitated condition. ACHD may also require interventional procedures such as coil embolization of aortopulmonary shunts and collateral vessels, pulmonary artery angioplasty or stents for stenotic
pulmonary arteries, stenting of atrial baffle obstruction prior to the transplantation or additional reconstructive surgery during the transplantation (5). For these reasons and others, CHD is a significant risk factor for increased 1-year mortality in heart transplant recipients (6). The statistics vary, ranging from 16% to as high as a 50% 30-day to 3-month early mortality (7–12). But after the first year of transplantation, ACHD patients have improved survival: 5-year survival ranges from 69% to 80% compared with approximately 72% in non-CHD patients (6, 7, 13, 14), whereas 10-year survival is even better, ranging from 52.8% to 57.4% compared with 50.9% to 53.6% in non-CHD transplant recipients (7, 8, 11, 15). These findings may be related to lower recipient age, variable CHD diagnoses and fewer comorbidities at the time of transplantation (7).

To optimize the outcomes of ACHD transplantation there is a need of international consensus to reconsider current criteria for urgent cardiac transplantation rating those who require mechanical cardiac support (MCS) and inotrope support. But ACHD patients may be not appropriate candidates for MCS due to restrictive anatomy, limited venous access, abundant collateral vessels and the presence of scar tissue (16). At the time of listing ACHD patients are less likely to be dependent on inotropes but they are presenting with severe comorbidities like protein losing enteropathy, hepatic and renal dysfunction or coagulopathies (8). As pointed out in a recent publication by Goldenberg S. and colleagues some steps are necessary to redefine the listing criteria for ACHD (17). The definition of ACHD need to be standardized, with defined sub-groups, so that research will expand the understanding of prognostic characteristics and survival in this population.

Furthermore the characteristics of ACHD that increase waiting list and post-operative mortality need to be subsequently explored to determine whether they should be considered when determining listing status. In addition to it the effect of bystander organ dysfunction on waiting list and post-operative mortality need to be further researched and potentially incorporated in listing status criteria.

Finally a separate scoring system for United Network for Organ Sharing (UNOS) listing of ACHD transplant candidates, created by international consensus, is needed because current criteria do not always meet the needs of ACHD patients. If that happens we should be able to identify better transplant recipients, determine the appropriate time to list these patients, and optimize post-operative care and transplantation outcomes.

References

The John Hess Lecture – How to optimize ACHD patient care and future directions in physician education

Gary Webb, M.D.
Director
Cincinnati Adolescent and Adult Congenital Heart Center
Cincinnati Children’s Hospital
Cincinnati, USA

KEY POINTS

• Deliver the lifelong care message - repeatedly.
• Keep children and adolescents in care.
• Have methods to track and help prevent loss to care during childhood and adolescence.
• Work continuously with pediatric cardiologists as respected care partners.
• Encourage some pediatric cardiologists to take a career interest in ACHD care.
• Agree on a defined age of transfer to ACHD care.
• Minimize health insurance barriers to care.
• Educate and empower adolescents and young adults to become competent managing their own lives and health care - the so-called transition process.
• Provide such good patient care that patients know and respect its value.
• Commit yourself and your program to excellent patient care.
• The program’s mission should be to be able to address the needs of any patient that comes through the door.

You may not be able to do everything in your own institution. If not, you need to make sure that services of high quality are available to your patients, and you should refer them to the best available resources.
• Care must be 24/7.
• Provide patient care as conveniently as possible (Satellite clinics? Evening clinics? Telemedicine?)
• Make sure that ACHD team members are well-qualified or become well-qualified.
• Work to solidify sources of patients, whether from pediatric cardiologists, adult cardiologists, or primary care physicians.
• I believe you need a base of at least 1500 patients to develop and maintain team skills, to train fellows, and to drive adequate volumes in both diagnostic and interventional arenas.
• Make “following the guidelines” part of your team culture.
• Use the ACHA clinical accreditation criteria as the basis for your planning clinic accreditation and construction in your own jurisdiction.
• Encourage other and younger colleagues, especially in subspecialty areas, to make a career commitment to ACHD care. Build the future.

The future of ACHD professional education

• One-on-one instruction will always be valuable.
• If you make teaching in a digital environment, you can use it repeatedly, and share it endlessly.
• ACHD colleague should collaborate to create high-quality educational material that can be used by professional members of many teams.
• This material should be reused and repurposed as frequently as possible.
• Don’t just put in one place - put in lots of places repeatedly so people have a chance to see and use it.
• Get regular feedback, and replace or improve or update material on a continuing basis.
Brain natriuretic peptide (BNP) value is one piece of information which may reflect the actual condition of a patient with congenital heart disease. The importance in predicting major cardiac events depends on the underlying cardiac disease, however, in many complex diseases its usefulness remains questionable.

Given the heterogeneity of the underlying conditions (e.g., univentricular heart, right ventricular type of systemic ventricle, residual lesions with predominance of the stenotic and regurgitation component, pulmonary hypertension and cyanosis) heart failure in adult congenital heart disease (ACHD) differs from that of acquired heart disease. It seems that, also natriuretic peptides, as markers of volume and pressure overload behave differently in these clinical conditions. Patients with ACHD have higher levels of natriuretic peptides when compared with normal controls, however, their overall values do not reach such high levels as in acquired heart disease (1). The most commonly used natriuretic peptides in clinical practice is brain natriuretic peptide (BNP), or his N-terminal pro-hormone (NT-proBNP). These markers are considered to have greatly equivalent value, although some authors highlight important differences, showing that BNP might be a better indicator of a chronic clinical condition compared with NT-proBNP, which might be more useful in registering acute changes in the disease (2, 3, 9).
An important percentage of adult patients with ACHD are in heart failure, without being aware of it (4). In the presence of a chronic condition, a “slow” clinical deterioration may be subjectively missed by the patient. BNP may help in identifying ACHD patients at risk to deteriorate, and to adjust a therapeutic plan for them. Besides the BNP values as cross sectional data, limited data are available regarding longitudinal measurements and their role in predicting cardiac events, timing of a therapeutic intervention or heart transplant (1). In this short overview the most important clinical conditions where BNP has been extendedly studied will be highlighted.

**Tetralogy of Fallot post repair**

BNP elevation is determined mostly by the pulmonary regurgitation (PR) and right ventricular (RV) dilatation. Nevertheless the presence of left ventricular dysfunction or aortic regurgitation should be also considered. Higher NYHA class correlates with higher BNP values (there being a significant difference between BNP values in asymptomatic vs. mildly symptomatic patients), and an inverse correlation exists between BNP and peak oxygen uptake during exercise (5). In patients with a good clinical condition BNP does not seem to present correlations with RV size and PR (6), although in general there is a significant correlation among them.

Heng at al. (7) found that 70% of the asymptomatic patients had abnormal BNP values, and demonstrated that in stable patients BNP can be used as mortality predictor. In their median 10 year follow-up study a BNP above 52 pg/ml predicted a 5 fold increase in risk of death, and each 35 pg/ml increment resulted in 2 fold increase in risk of arrhythmia. The role of BNP in timing pulmonary valve replacement remains questionable, because most studies present only cross sectional data. There are some exceptions, where longitudinal studies found elevated BNP levels before pulmonary valve replacement (PVR), which decreased afterwards, though the BNP values differed so widely, that they were unable to conclude which cut-off value predicts a good timing for intervention (8).

**Transposition of the great arteries after atrial switch operation (TGA-ASO)**

Increases in BNP levels might be related to systemic RV-dysfunction, severity of tricuspid regurgitation, and abnor-
mal ventricular filling (the latter being seen more often after the Mustard type surgery).

BNP in TGA-ASO is higher than in normal controls even in asymptomatic patients (5). Positive correlation with NYHA class (9) or negative correlation with peak oxygen uptake has been demonstrated (5), although, there are studies questioning these facts (5, 10). In most of the studies BNP has a negative correlation with systemic RV ejection fraction (by CMR or echocardiography measurements) and a positive correlation with severity of tricuspid regurgitation (5). Haberg er et al. (9) in a study of 83 patients with TGA-ASO, showed that the BNP cut-off value for discriminating the risk for a major cardiac event was 85 pg/ml, with a sensitivity of 88 %, and specificity of 85 %. After Mustard type surgery there was a higher risk for a critical event compared with Senning type of surgery, but in this particular study there was no difference between simple or complex TGA.

Haberg er et al. (9) in a study of 83 patients with TGA-ASO, showed that the BNP cut-off value for discriminating the risk for a major cardiac event was 85 pg/ml, with a sensitivity of 88 %, and specificity of 85 %. After Mustard type surgery there was a higher risk for a critical event compared with Senning type of surgery, but in this particular study there was no difference between simple or complex TGA.

**Single ventricle**

In Classic Fontan there is an increased wall stretch in the systemic venous atria which explain why these patients have significantly higher levels of BNP compared with those who had undergone the TCPC procedure (total cavo pulmonary connection). Moreover, after completion of the Fontan procedure by TCPC, the BNP values of asymptomatic patients are comparable with healthy age-matched controls (11). In some studies ventricular morphology, namely the presence of an anatomically RV in systemic position has been showed to have a higher BNP compared with LV morphology (12); but others did not find this correlation. Overall, in Fontan patients strong positive correlations were found between BNP and NYHA class when all functional classes were studied (11). Data are not convincing regarding the correlation between BNP and oxygen saturation during rest, though a possible cause of increased BNP in single ventricle physiology has been attributed to the presence of cyanosis (5, 13). The relation between BNP and peak oxygen consumption during exercise was not conclusive as well (5). Prognostic value of BNP in these patients also remains questionable (1).

**Pulmonary arterial hypertension (PAH)**

Changes in BNP reflect the degree of increased RV wall stretching and subsequent deterioration in RV function caused by pulmonary vascular disease (14). Conflicting data
concerning the relationship between BNP and functional capacity exist (eg. NYHA functional class, 6-minute walk distance). This might be explained by the different oxygen carrying capacity of the blood and the degree of desaturation during exercise.

RV volume overload may be a stronger trigger of BNP production than chronic pressure overload, as stable patients with Eisenmenger syndrome (ES) had lower BNP values (14). BNP has been demonstrated to have prognostic value in predicting right heart failure or death in PAH patients.

Serial BNP predicts survival and/or hospitalization in ES, values >104pg/ml are associated with increased risk of death (15,16) and values <50pg/ml with better survival (17). A good response to specific PAH therapy can be demonstrated by decrease in BNP, as well.

Based on 2015 the ESC PAH guideline (18), generally speaking of PAH (not specified for ES) patients, BNP should be used at the first assessment for risk evaluation and further on for monitoring the effect of specific therapy.

References

Heart failure in ACHD: What is different from acquired heart disease?

Pedro Trigo Trindade, MD, FESC
Clinique Générale Beaulieu
Geneva, Switzerland

KEY POINTS

• The incidence of first heart failure admission has been reported at 1.2 per 1000 patient-years (CONCOR registry).
• Mortality amounted to 2.8% during a follow-up period of 24865 patient-years.
• Median-age at death from heart failure was 51 years (range: 20.3–91.2 years).
• Aetiology, pathophysiology and triggers of impaired ventricular function in ACHD patients are complex and diverse (Fig. 1, Table 1).
• Patients may not report symptoms even though systemic pump function is often reduced.
• As opposed to acquired heart disease different scenarios have to be envisaged: systolic failure of the morphological systemic left ventricle, - of the morphological systemic right ventricle, - of the morphological sub-pulmonary right ventricle, - of the single ventricle.
• There is a lack of randomized controlled trials to guide therapy in heart failure in adult congenital heart disease (Table 2).
  – The value of ACE-inhibitors, ARB’S and beta-blockers remains to be defined, and these drugs can even be harmful in certain patients.
  – Pulmonary arterial vasodilators may be helpful in certain conditions.
  – The role of CRT remains unknown.
  – Heart transplantation can be a therapeutic option.
1. Systolic dysfunction of the systemic morphological left ventricle
   - Pressure overload (sub-, supravalvular or valvular aortic stenosis, coarctation of the aorta)
   - Volume overload (aortic valve regurgitation, VSD, patent ductus arteriosus, or mitral regurgitation)
   - Myocardial injury (limited myocardial protection during bypass, ventriculotomy)
   - Altered myocardial architecture (non-compaction)
   - Altered geometry of the sub-pulmonary ventricle interfering with diastolic filling of the systemic ventricle (severe pulmonary regurgitation in TToF)

2. Systolic dysfunction of the sub-pulmonary morphological right ventricle
   - Volume overload (severe pulmonary regurgitation in TToF, atrial septal defect with large left-to-right shunt)
   - Pressure overload (severe RV outflow tract obstruction)

3. Systolic dysfunction of the morphological systemic right ventricle
   - Pressure overload (congenitally corrected transposition of the great arteries, dextro-transposition of the great arteries after atrial switch repair [Mustard or Senning])
   - Myocardial injury by functional ischaemia (single right coronary artery)

4. Systolic dysfunction of the systemic single ventricle
   - Volume under-load after initial volume overload (Fontan repair)
   - Myocardial injury (limited myocardial protection during bypass, ventriculotomy)
   - Myocardial architecture

5. Systolic dysfunction of the cyanotic systemic and/or sub-pulmonary ventricle with or without pulmonary hypertension
   - Myocardial injury by chronic hypoxia (VSD with pulmonary stenosis)
   - Pressure overload (Eisenmenger syndrome)

6. Acquired ischaemic heart disease and ventricular dysfunction
   - Cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, smoking)
   - Congenital coronary artery abnormalities (anomalous origin and/or course, extrinsic compression by a dilated pulmonary artery, coronary kinking after re-implantation of coronary arteries)

7. Systolic dysfunction of the systemic ventricle due to tachyarrhythmias

Table 1: Trigger factors of heart failure with impaired systolic function
### Systolic Heart Failure

<table>
<thead>
<tr>
<th>Condition</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
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</thead>
<tbody>
<tr>
<td><strong>Systemic ventricle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphological left ventricle (EF 40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic or Symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAAS blocker</td>
<td>Beta-Blocker</td>
<td>Mineralocorticoid receptor antagonist</td>
</tr>
<tr>
<td><strong>Morphological right ventricle (EF 40%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>No medical treatment</td>
<td></td>
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<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAAS blocker</td>
<td>Beta-blocker</td>
<td>Mineralocorticoid receptor antagonist</td>
</tr>
<tr>
<td><strong>Sub-pulmonary ventricle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphological left or right ventricle (EF 40%)</td>
<td>Asymptomatic</td>
<td>No medical treatment</td>
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<tr>
<td>Symptomatic</td>
<td></td>
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<tr>
<td>Diuretics (loop and thiazide)</td>
<td>Mineralocorticoid receptor antagonist</td>
<td>Pulmonary vasodilator (pulmonary arterial hypertension)</td>
</tr>
<tr>
<td><strong>Single ventricle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fontan circulation (EF 40%)</td>
<td>Morphological left ventricle</td>
<td>Asymptomatic</td>
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<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAAS blocker</td>
<td>Beta-Blocker</td>
<td>Mineralocorticoid receptor antagonist</td>
</tr>
<tr>
<td>Morphological right ventricle</td>
<td>Morphological left and right ventricle</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
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</tr>
<tr>
<td>RAAS blocker</td>
<td>Beta-Blocker</td>
<td>Mineralocorticoid receptor antagonist</td>
</tr>
<tr>
<td>Persistent right-to-left shunt</td>
<td>Asymptomatic</td>
<td>No medical treatment</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics (loop and thiazide)</td>
<td>Agents reducing afterload</td>
<td></td>
</tr>
</tbody>
</table>

### Heart Failure with preserved EF

<table>
<thead>
<tr>
<th>Condition</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No medical treatment</td>
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Table 2: Medical treatment for heart failure in Congenital Heart Disease (modified after: Budts W et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2016 Jan 18. doi:10.1093/eurheartj/ehv741 Eur Heart J.)

### References


Heart failure is a leading cause of death in adult congenital heart disease (ACHD) patients. Therefore, the identification of possible prognostic predictors is of interest. Hyponatremia is an important prognostic predictor of mortality in heart failure of non-congenital origin. Recent studies indicate a role for hyponatremia as a predictor of morbidity and mortality in ACHD patients. While treatment aimed solely on correcting sodium levels probably does not improve the clinical outcome, a closer clinical surveillance of ACHD patients with hyponatremia is warranted.

Heart failure has important prognostic implications for adult congenital heart disease (ACHD) patients, and is a leading cause of death (1). Therefore, the identification of possible prognostic predictors is of interest. Hyponatremia (HN) is one promising candidate.

**Hyponatremia in heart failure of non-congenital origin**

Despite increased plasma and extracellular fluid volumes in heart failure of non-congenital origin, reduced cardiac output and systemic blood pressure lead to neurohumoral activation and increased release of antidiuretic hormone, also known as vasopressin, resulting in reduced excretion of water and sodium, increased water and sodium reabsorption in the glomeruli, and increased thirst (2). The consequence is HN, which is encountered in 20–25% of patients with heart failure (3). In several studies, HN has been established as an important prognostic predictor of mortality in a variety of heart failure patients, ranging from hospitalized to ambulatory patients (3).

**Hyponatremia in ACHD**

In a study of 1004 ACHD patients with a variety of underlying CHD, HN was present in 15.5% (4). The prevalence was
higher in patients with more complex CHD. Furthermore, HN was a strong predictor of mortality (Figure 1A), independent of functional class, ventricular function, creatinine levels, or the use of diuretics (4). The hazard of death decreased with increasing sodium levels up to a value of 136 mmol/L and appeared to be constant thereafter (Figure 1B) (4).

In a study of 91 adult patients after the Fontan operation, HN was present in 28.6% (5). Plasma sodium level was the only independent predictor for unscheduled rehospitalizations in this study (5). Interestingly, levels of plasma norepinephrine, vasopressin, and plasma renin activity were higher in the hyponatremic group compared to the normonatremic group, indicating neurohumoral activation (5).

Treatment of hyponatremia in heart failure

There is currently no evidence that correction of HN improves the clinical outcome of patients with heart failure. Restricting fluid intake is still an important measure. Furthermore, based on pathophysiological rationale, it is best to avoid thiazide-type diuretic agents and mineralocorticoid receptor antagonists, as these interfere directly with the kidneys’ capacity to produce hypotonic urine, and instead prefer loop diuretics (2). However, clinical evidence for this approach is lacking. Vasopressin receptor blockers like Tolvaptan increase free water clearance (6). Tolvaptan was studied in patients hospitalized with heart failure (7). While it increased serum sodium levels in patients with HN significantly, it had no effect on long-term mortality or heart failure-related morbidity. Studies in ACHD patients addressing these questions are lacking.

Conclusion

Hyponatremia is an independent predictor of mortality in ACHD patients. While treatment aimed solely on correcting sodium levels does probably not improve the clinical outcome, a closer clinical surveillance of patients with HN is warranted.

References


Figure 1A: Cumulative mortality curves according to the presence of hyponatremia. Patients with hyponatremia (sodium concentration < 136 mmol/L) had a three-fold increased mortality risk in this study.

Figure 1B: Functional form of the unadjusted relationship between sodium concentration and the hazard of death (on a logarithmic scale) using smoothing splines with 4 degrees of freedom. The fitted spline function is plotted with pointwise standard errors. From Dimopoulos et al (4), European Heart Journal – an official Journal of the European Society of Cardiology, by permission of Oxford University Press
Can we prevent the development of heart failure in ACHD?

Helmut Baumgartner  
Division of Adult Congenital and Valvular Heart Disease  
Department of Cardiovascular Medicine  
University Hospital Muenster  
Muenster, Germany

KEY POINTS

Prevention of the development of heart failure in ACHD remains challenging. No evidence is available for medical treatment of asymptomatic ventricle dysfunction. Early intervention with optimization of hemodynamics remains key but requires careful weighing of risks and benefits of intervention.

Late development of heart failure remains one of the main long-term problems in ACHD and one of the most frequent causes of late death.

As soon as the heart failure syndrome becomes obvious in a patient, the search for hemodynamic disorders that can eventually be repaired, surgically or interventionally, and in this way at best resolve heart failure symptoms is key. However, treatable hemodynamic disorders may not be present or heart failure not resolve despite successful improvement of hemodynamics due to irreversible damage of ventricular myocardium or the vascular system.

The challenges of treating heart failure in adult patients with congenital lesions gives little evidence and frequent conditions that may not allow the application of the treatment standards established for acquired – mainly left heart – disease, will be covered by other presentations. The present contribution is supposed to deal with the patient who is still asymptomatic but at the risk of developing heart failure. The ultimate goal in the management of congenital heart disease is obviously to prevent the development of heart failure in the first place. In this context two issues need to be addressed:

- How early is surgical or catheter intervention required to avoid irreversible damage and optimize long-term outcome?
- Can early medical treatment of still asymptomatic ventricular dysfunction prevent or at least delay development of overt heart failure when repairable hemodynamics is not present?

To start with the latter: For acquired heart disease, large randomized trials are available that could demonstrate the benefit of treating asymptomatic left ventricular (LV) dysfunction with β-blockers and ACE inhibitors. Although ACHD patients were rarely included in such studies it may still be justified to apply such results to asymptomatic LV dysfunction. However, in the ACHD population we are more commonly faced with failing right ventricles.
in settings such as transposition of the great arteries with atrial switch operation or repaired tetralogy and univentricular hearts, nowadays typically with Fontan circulation. Application of the data gathered in LV dysfunction can hardly be applied to such conditions differing markedly in pathophysiology. Thus, medical treatment of asymptomatic ventricular function remains controversial and based on mostly non-conclusive small studies. Early intervention with the goal to relieve the ventricles from the burden of pressure and/or volume overload with eventual development of ventricular failure is a very logical concept. However, no intervention is without risk and careful weighing of this risk against the possible benefits is requested. While recommendations are relatively easy when patients suffer from symptoms and interventions are available that are likely to improve them, current guidelines frequently struggle with the recommendations for asymptomatic patients in whom solid data to support the treatment benefit are commonly lacking.

**In this context the question arises – what means asymptomatic?**

Studies using cardiopulmonary exercise testing (CPET) demonstrated that exercise limitations and quite abnormal test parameters are relatively common in ACHD patients even when they report themselves to be asymptomatic. In addition, elevated plasma levels of brain natriuretic peptides (BNP, NT-proBNP) – accepted markers of heart failure - have been reported in a significant number of asymptomatic ACHD patients.

Both, CPET and BNP have been reported to be important predictors of outcome and it has therefore been suggested to include them in the decision making to improve timing of early intervention.

High interest exists in the early detection of interstitial fibrosis by MRT in this context but more data are required to define its role in asymptomatic patients.

The threshold for intervening in asymptomatic patients with significant lesions will obviously be highly dependent on acute and long-term risks of the intervention.

While recommendations can be more liberal for interventions where these risks are very low, such as interventional atrial septal defect closure, balloon dilation of pulmonary stenosis or very low risk surgical procedures, the weighing of risk and benefits becomes more difficult when operative risk rises – particularly multiple re-operations – or if an intervention already implies a future re-intervention as in the case of implantation of biological valve substitutes.
KEY POINTS

With the expected continuous increase in the number of adults with congenital heart disease (ACHD), the problem of the choice of the appropriate therapy will also increase. It is also to be expected that rising numbers will make randomized multicentric studies possible, which it is hoped will provide clear evidence validating the different therapy algorithms for the ACHD population. This is certainly an urgent need, to underpin the treatment of our patients with the necessary knowledge and guidelines.

In the past 50 years enormous progress has been made in the treatment of congenital heart disease (CHD), so that nowadays not only do children born alive with CHD have an almost 90% chance of surviving to adulthood but also the majority of them will have good quality of life and good physical capacity. Nevertheless, many of the procedures performed today are still more palliative than curative. This means complications, especially for the group of patients with highly complex heart defects, during the long-term course, and often the development of chronic heart failure.

A unified treatment concept for these heart defects is unfortunately not available (1). On the contrary, the wide variety of defects, the differing etiology of the patients’ heart failure, inadequate predictive data concerning the progression of the disease and the lack of validation of the different treatment possibilities make it necessary, in most cases, to develop an individually tailored treatment concept (2).

It is not so much acute heart failure with sudden emergency situations but chronic, progressive heart failure, which develops inexorably but with great age differences, that requires a highly complex treatment strategy.

Nowadays it is clear that structural cardiac causes of heart failure, such as valve degeneration and volume or pressure overload, should be specifically addressed by interventional or surgical procedures to ensure a balanced load on the myocardium (3). Despite this, the development of heart failure in adults with congenital heart disease (ACHD) is multifactorial and results in systolic and/or diastolic heart failure, which is often exacerbated by acute or chronic arrhythmia. The aim of all treatment must be to avoid adverse remodeling and
the formation of fibrosis, which both cause irreversible changes in the myocardium that can no longer be influenced (1, 2, 4, 5).

Currently it is common practice to assume that the basic mechanisms of heart failure in most patients with CHD are the same as those in adults with acquired heart disease, and to extrapolate and apply to them heart failure data and guidelines relating to adults with acquired disease. However, this does not really work in cases of specific anatomical preconditions such as systemic right ventricle, right-heart-based heart failure or univentricular defects.

Further, the interaction between the two ventricles is of key importance in the development of additional left ventricular heart failure following right ventricular failure. Nevertheless at present there are no better guides than extrapolating the effects of the different pharmacological treatment strategies for chronic heart failure from the existing therapy algorithms.

In addition to pharmacological treatment options, electrophysiological diagnostic procedures and ablation therapy and antiarrhythmic treatment with implantable defibrillators (ICD) are gaining increasing importance, especially since acute arrhythmia is one of the most frequent causes of death in patients with CHD, although as yet we have no data on the survival advantage provided by ablation and ICD treatment in this patient group (6–9).

Often pharmacological treatment remains unsuccessful and heart transplantation has to be considered as the ultimate ratio option. Closely related is also the question of mechanical circulatory support (MCS) as destination therapy, when transplantation is not possible or not likely to succeed or when no donor organ becomes available in time. Although the use of MCS in the treatment of terminal heart failure on the whole is growing, this is not the case in ACHD patients. This is no doubt due to the complexity of the underlying diseases and the patients’ comorbidity, where MCS no longer represents a real therapy option.

Since not only the therapy algorithm for chronic heart failure in ACHD is based on little data, but also the indication for heart transplantation has no individually applicable basis in data, and especially in view of the multiple comorbidity of chronically ill ACHD patients, the decision to list a patient for organ transplantation is mainly based on the specific experience of the individual transplant center (10–15). In any case it is clear that ACHD with terminal heart failure will remain on the transplantation waiting list for longer than patients without structural heart disease and have less chance of being allocated an organ, which in turn means a comparable increase in the incidence of death on the waiting list.

References

**KEY POINTS**

Major subgroups of patients with congenital heart disease include those with Marfan syndrome and related Heritable Thoracic Aortic Disorders and patients with Bicuspid Aortic Valves. Phenotypic differences and differences in outcome should be recognized and may help us to guide management.

Molecular genetic testing plays an important role in correct diagnosis and may be used in the future for personalized management.

At present, β-blockers should be considered as first-line therapy to slow down progressive aortic growth in these disorders.

**Aortic root dilatation in Congenital Heart Disease**

Aortic root dilatation (ARD) is defined as enlargement of the proximal ascending part of the aorta. Depending on the underlying cause, maximal dilatation may be located at the sinuses of Valsalva or at the tubular ascending part of the aorta. Care should be taken when assessing the diameters of the aorta and comparison with the correct reference values is crucial (1–3).

In patients with structural congenital heart disease (CHD), ARD is not infrequent. Primary aortic dilatation is mainly associated with bicuspid aortic valve, coarctation of the aorta, and conotruncal abnormalities such as tetralogy of Fallot, pulmonary atresia with ventricular septal defect, or truncus arteriosus. The evolution of the aortic diameter results from a combination of intrinsic pathology, associated malformations, surgical or catheter interventions, and control of risk factors later in life.

Secondary aortic dilatation may occur after arterial switch operation or systemic outflow tract reconstruction in patients with a single ventricle (4).

An important proportion of ARD encountered in CHD patients is in the setting of underlying heritable thoracic aortic disorders (H-TAD), with Marfan syndrome (MFS) being
the paradigm disorder. Many aspects related to management and treatment of patients with ARD is based on the insights obtained in MFS and this brief overview will therefore have an important focus on this disorder.

**Marfan syndrome**

Marfan syndrome is caused by mutations in the *fibrillin1* gene (*FBN1*).

ARD at the level of the sinuses of Valsalva, leading to aneurysm and dissection is the main determinant of morbidity and mortality in MFS. It is estimated that aortic root dilatation is present in >80% of adult MFS patients (5). Aortic root growth rate in untreated MFS patients is estimated at 0.2 mm/y – the rate in treated patients varies between 0.3 and 0.9 mm/y across different studies with a higher rate in men than in women in some studies (6, 7). This growth rate is significantly increased when compared to the average of 1 mm/10 y in the general population (3). Despite the availability of prophylactic replacement of the aortic root, even current surgical series document that up to one third of MFS patients present with aortic dissection, mainly Stanford type A dissection (8). Such high numbers of acute aortic emergencies indicate the persisting deficiency of timely diagnosis and adequate risk estimation (9).

Both structural and local hemodynamic factors interact in the process of ARD in MFS – a complex process known as mechanobiology (10, 11). Structural abnormalities in the ascending aorta arise from the complex and not fully unravelled interplay between embryologic factors, abnormalities in the elastic fibre formation and homeostasis and altered signalling pathways, including the TGFβ pathway. Hemodynamic factors in the aortic root are characterized by its exposure to the repetitive stress of left ventricular ejection, eventually contributing to progressive dilatation.

**Other Heritable-Thoracic Aortic Disorders**

Clinical recognition of both distinct syndromic entities as of patients and families presenting nonsyndromic thoracic aortic disease is established for many decades. The recent advances in molecular genetic diagnostics have already unraveled part of the genetic background of these disorders.

An example of a distinct syndromic TAD entity is the *Loeys-Dietz syndrome (LDS)* caused by mutations in the *TGFBR1* or *2* gene and characterized by dysmorphic features including hypertelorism and cleft bifid uvula (12).
More widespread vascular disease and a tendency for a more aggressive course of ARD in LDS may indicate perspectives for genotype-based treatment and management with extended vascular imaging and a lower threshold for prophylactic aortic root surgery. More recent studies have however revealed that at least some patients with TGFBR1/2 mutations show a less aggressive course with an aortic phenotype indistinguishable from classic MFS with an estimated growth rate of 0.67 mm/y (13–15).

Not labeling all TGFBR1/2 mutation carriers as “LDS”, distinguishing a subcategory of nonsyndromic TAD may be a solution. Multicenter registries analyzing the clinical evolution in these patients are underway and will definitely help defining improved guidelines.

Very similar observations are also true for genes identified later, including the SMAD3 gene, the TGFβ2 gene and the TGFβ3 gene with some patients presenting a severe phenotype reminiscent of LDS and others presenting much milder phenotypes with “Isolated Thoracic Aortic Disease”. A useful common denominator for these conditions is “Heritable-Thoracic Aortic Disease or H-TAD”, covering all genetic entities, both syndromic and nonsyndromic and offering the possibility to include those patients/entities in whom the underlying genetic defect has not been identified yet(16).

Currently established genes in H-TAD (17), grouped according to their main function and with their corresponding phenotype are listed in table 1.

### Bicuspid aortic valve

BAV is the most common congenital cardiac disease with an estimated prevalence of 0.5–2 % (18).

BAV associates with different forms of syndromic H-TAD, such as MFS and LDS (19), as well as with Turner syndrome and aortic coarctation, but in the majority of cases, it presents as an isolated feature.

Thoracic aneurysm formation is a well-known association with BAV and the ascending aorta is usually the most affected segment. The prevalence of aneurysms in BAV ranges from 20 to 84 % in different reports (20).

Both hemodynamic factors and abnormal intrinsic wall properties, similar to those found in MFS, are the underlying pathophysiological mechanism of BAV-associated aneurysms (21). Although the incidence of dissection in patients with BAV is lower than in MFS (4 %), the higher prevalence of BAV makes it a more common problem (18).

A recent prospective study comparing mortality and dissection rates in MFS, nonsyndromic TAD and BAV indicates that clinical outcome in nonsyndromic TAD and MFS is similar but worse than in BAV(22).

### Medical treatment

The ultimate goal of medical treatment in ARD would be to arrest aortic root growth but, realistically, postponing the need for aortic root surgery and avoiding dissection are the outcomes that have conventionally been aimed at.

So far, unfortunately no study proving this goal has emerged, partly due to the low prevalence of these disorders and the inherently low occurrence of events.

Decreasing aortic growth has been used a surrogate outcome parameter in most studies. Slowing down aortic root growth may be achieved through reducing hemodynamic stress on the proximal aorta.

The first report on the use of β-blockers in MFS dates from 1971 indicating that reduction in the rate of increase in aortic pressure over time (dP/dt) was more effective than could be explained by reduction of blood pressure alone (23).

Since then, no less than 2022 MFS patients have been included in at least 20 different trials with β-blockers. The only placebo-controlled randomized trial showed a significant reduction in aortic root growth with propranolol (24).

The beneficial effect of β-blockers has not been consistent in all studies (25, 26). Differences in the populations studied, in the drug types and dosage and in the study design render the interpretation and comparison of these trials particularly challenging.
Alternatives for β-blockers including Calcium channel blockers and ACE-inhibitors have been suggested and studied in small series (27, 28).

A seemingly major breakthrough in the search for improved medical treatment in MFS patients was achieved with the documentation of involvement of the TGFβ pathway in the process of aneurysm formation. This led to the insight that interference with TGFβ signaling using Losartan, an angiotensin receptor blocker with known TGF β inhibiting potential may have a beneficial impact on aortic growth. Aortic growth and architecture were restored in MFS mice treated Losartan (29). An initial small cohort study in severely affected children with MFS treated with losartan on top of β-blocker treatment showed hopeful results (30). At least 10 randomized trials ensued, recruiting >2000 patients in total, spanning all age ranges. Four large trials have been reported so far, and overall, these studies fail to confirm the initial positive results. Neither head-to-head comparison of β-blockers versus losartan nor the combined treatment of both drugs shows a significant benefit of losartan (31–34). More research is needed to explore whether specific subgroups can be identified for whom medical treatment can be personalized. A large meta-analysis addressing these issues is underway (35).

With regards to medical treatment in the other H-TAD entities and BAV, very little – if any - data are available. Management is often adopted from the evidence obtained in MFS. The ESC guidelines on Aortic Disease on medical treatment in BAV is to consider β-blockers in in patients with BAV and a dilated aortic root >40 mm (ClassIIb indication – level C) (36).

### H-TAD related to genes encoding components of the extracellular matrix

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease Features</th>
<th>H-TAD Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBN1</td>
<td>Neonatal MFS</td>
<td>Isolated/Nonsyndromic TAD (37, 38)</td>
</tr>
<tr>
<td>COL3A1</td>
<td>vEDS</td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
<tr>
<td>MFAP5</td>
<td>MFS features</td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
</tbody>
</table>

### H-TAD related to genes encoding components of the TGFβ pathway

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease Features</th>
<th>H-TAD Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGFBR1</td>
<td>LDS; vEDS</td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
<tr>
<td>TGFBR2</td>
<td>LDS; vEDS</td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
<tr>
<td>SMAD3</td>
<td>LDS</td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
<tr>
<td>TGFβ2</td>
<td>LDS</td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
<tr>
<td>TGFβ3</td>
<td>LDS, syndrome presenting at birth with distal arthrogryposis, hypotonia, bifid uvula, a failure of normal post-natal muscle development</td>
<td>MFS features</td>
</tr>
</tbody>
</table>

### H-TAD related to genes encoding proteins involved in the contractile apparatus of vascular smooth muscle cells

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease Features</th>
<th>H-TAD Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTA2</td>
<td>TAD with multisystemic SMC dysfunction</td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
<tr>
<td>MYLK</td>
<td></td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
<tr>
<td>PRKG1</td>
<td></td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
<tr>
<td>MYH11</td>
<td></td>
<td>Isolated/Nonsyndromic TAD</td>
</tr>
</tbody>
</table>

Table 1: Schematic overview of Heritable Thoracic Aortic Disease (H-TAD) entities, according to the underlying gene defects and according to degree of manifestations outside the aorta (Syndromic Gradient, from left to right). Two major groups of gene mutations associated with H-TAD can be distinguished, namely those affecting structure (i.e. the ECM) and those that affect the ability to modify structure in response to changes in mechanical load imposed on the aortic wall (i.e. cell-signalling pathways and the contractile apparatus).


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**Alternatives for β-blockers** including Calcium channel blockers and ACE-inhibitors have been suggested and studied in small series (27, 28).

A seemingly major breakthrough in the search for improved medical treatment in MFS patients was achieved with the documentation of involvement of the TGFβ pathway in the process of aneurysm formation. This led to the insight that interference with TGFβ signaling using Losartan, an angiotensin receptor blocker with known TGFβ inhibiting potential may have a beneficial impact on aortic growth. Aortic growth and architecture were restored in MFS mice treated Losartan (29). An initial small cohort study in severely affected children with MFS treated with losartan on top of β-blocker treatment showed hopeful results (30). At least 10 randomized trials ensued, recruiting >2000 patients in total, spanning all age ranges. Four large trials have been reported so far, and overall, these studies fail to confirm the initial positive results. Neither head-to-head comparison of β-blockers versus losartan nor the combined treatment of both drugs shows a significant benefit of losartan (31–34). More research is needed to explore whether specific subgroups can be identified for whom medical treatment can be personalized. A large meta-analysis addressing these issues is underway (35).

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References


KEY POINTS

Thromboembolic disease in ACHD is currently managed similar to other heart disease. Until recently, direct oral anticoagulants (DOACs) have not been specifically studied in ACHD.

For the first time the current data on the use of DOAC in ACHD, show that DOACs are increasingly used and well tolerated in this very heterogeneous population.

As the experience with DOACs in ACHD is still limited, the potential for as yet unrecognized adverse events exists. Therefore, further studies are necessary in these vulnerable and unique patients to evaluate and improve treatment efficacy and safety.

Thromboembolic events (TEE) are common in adults with congenital heart disease (ACHD) and morbidity and mortality from these complications are high. Therefore, adequate oral anticoagulation (OAC) for prophylaxis or treatment of TEE is of outstanding importance.

A recent study, including more than 800 adults with a broad spectrum of CHD, has proven that 22% of the included patients were on oral anticoagulation, nearly always with vitamin K antagonists (VKA) (1).

Main indications for OAC in ACHD is prevention of TEE caused by supraventricular arrhythmias, venous thrombosis, replaced mechanical or biological heart valves and also specific situations like Fontan-Circulation, Eisenmenger Syndrome, or after implantation of conduits, stents, or closure devices.

VKA, however, come along with considerable disadvantages, including interactions with food and drugs, a narrow therapeutic window, inter- and intra-individual variability in dose response, a delayed onset of action, a long half-life and the need for regular blood tests. All these factors may increase the risk of under- or over-anticoagulation (2).

Meanwhile, however, also Direct Oral Anticoagulants (DOAC) have been introduced for prevention and/or treatment of venous and arterial TEE (Figure 1):

- Direct thrombin-inhibitor dabigatran (Pradaxa®, Boehringer Ingelheim)
- Factor Xa-inhibitors (Rivaroxaban, Xarelto®, Bayer HealthCare; Apixaban Eliquis®, Bristol-Myers Squibb; Edoxaban Lixiana®, Daiichi Sankyo).
There is an increasing interest in these substances as DOACs have major pharmacologic advantages compared with VKA, including fast begin and offset of action, fewer drug and food interactions, and a more predictable pharmacokinetic, removing the requirement for routine coagulation monitoring. This is counterbalanced by concerns, particularly regarding dosing in some populations (e.g. renal dysfunction) and superior drug costs compared with VKA. Although so many ACHD need OAC, scientific data regarding the adequate choice and use of DOACs for preventing TEE are lacking. Neither guidelines nor evidence based treatment algorithms exist for this heterogeneous and unique population with own pathophysiology, pathobiocchemistry and hemodynamic. Therefore, the existing treatment recommendations cannot be transferred directly to ACHD. In any case, neither ACHD nor not-ACHD patients with mechanical heart valve prosthesis can be treated with DOAC’s (3).

First real-world experiences regarding the coagulation management of ACHD using DOACs have been published from our institution recently (4). These data, from a very heterogeneous cohort of ACHD, indicate for the first time that DOACs are an alternative to VKA for primary and secondary prophylaxis in ACHD. In a cohort of 75 ACHD there were during a follow-up up to 61 months (Median: 12 ± 11 months) neither clinically relevant thrombotic or major bleeding events nor major side effects. Nevertheless, as the experience with DOACs in ACHD is still limited, the potential for as yet unrecognized adverse events exists, and therefore, further studies are necessary in these vulnerable and unique patients to evaluate and improve treatment efficacy and safety.

References for figure

Bibliography
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KEY POINTS

Fabry disease is an inborn error of metabolism with X-linked inheritance pattern characterized by a deficiency in the activity of the lysosomal enzyme α-galactosidase A leading to progressive lysosomal accumulation of glycosphingolipids, mainly globotriaosylceramide. Due to random X-chromosome inactivation in females, both genders may be affected. Cardiac manifestation is common with left ventricular hypertrophy being the major cardiac manifestation. Fabry disease related cardiomyopathy represents a non-sarcomeric form of hypertrophic cardiomyopathy and shall be included in the differential diagnosis of unexplained left ventricular hypertrophy in adults. The effect of enzyme replacement therapy is related to the extent of left ventricular wall thickening as well as replacement myocardial fibrosis.

Fabry disease is an X-linked genetic disorder of glycosphingolipid metabolism caused by deficient activity of lysosomal enzyme α-galactosidase A. The disease is characterized by progressive intracellular accumulation of neutral glycosphingolipids, mainly globotriaosylceramide, within lysosomes of different tissues throughout the body. The intracellular deposition of the substrate starts already before birth and most likely represents an initial trigger that causes a cascade of pathophysiological cellular processes leading to structural cellular change, followed by tissue defects and finally – over some time – to organ failure. Reported estimates of the incidence of Fabry disease range from 1 in 40,000 males to 1 in 117,000 in the general population (1).

As an exception among lysosomal storage disorders, most patients are clinically asymptomatic during the very first years of life.
The first symptoms appear typically between the ages of 3 and 10 years in boys, and few later in girls. Typical symptoms in childhood and adolescence are acroparesthesia, pain crises, hypohidrosis, angiokeratomas and several gastrointestinal symptoms. Cardiac as well as renal and cerebrovascular manifestations appear in adulthood. Life-threatening cardiovascular complications and end-stage renal disease limit life-expectancy of untreated patients (2).

For a long time, Fabry disease was considered as a disease of affected males who developed severe “classic” phenotype consisting of numerous multiorgan manifestations, some of them mentioned above. With increasing knowledge about natural course of the disease, so called cardiac as well as renal variants were introduced for individuals with predominant or exclusive cardiac or renal involvement due to residual α-galactosidase A activity. Furthermore, female heterozygotes were originally incorrectly labeled as asymptomatic carriers. However, virtually all disease manifestations including vital organ involvement may also develop in females as a consequence of random X-chromosome inactivation (a process called lyonization), about a decade later than in males.

Fabry disease is thus associated with a wide spectrum of clinical phenotypes, ranging from asymptomatic disease course occasionally seen in some females to severe multi-systemic involvement in males (3).

The diagnosis of Fabry disease in males is based on analysis of α-galactosidase A activity in leukocytes and plasma (absent or low activity in positive cases). Molecular analysis of the GLA gene is necessary to diagnose female heterozygotes because of the significant levels of enzyme activity that may be present in blood samples due to random X-inactivation (4).

Cardiac involvement is associated with pathologic substrate accumulation in all cellular components of the heart, including cardiomyocytes, conduction system cells, valvular fibroblasts, endothelial cells and vascular smooth muscle cells.

Left ventricular hypertrophy is the hallmark of cardiac manifestations in Fabry disease, present in more than 50% of adult patients. The pathogenesis of this hypertrophy is not clearly understood as globotriaosylceramide accumulation represents only 1-2% of the total cardiac mass. The disturbance in myocardial energy metabolism together with activation of other signaling pathways, including increase of trophic factors like globotriaosylsphingosine and sphingo-
sine-1-phosphate, lead to evolution of “true” myocardial hypertrophy with subsequent interstitial remodeling (5). In most Fabry disease patients, a concentric left ventricular hypertrophy with prominent papillary muscles is present (Figure 1); however, asymmetric septal hypertrophy as well as dynamic left ventricular obstruction may also be detected, though rarely. Of note, Fabry disease related left ventricular hypertrophy is regarded as a non-sarcomeric phenocopy of hypertrophic cardiomyopathy and shall always be included in differential diagnosis of unexplained hypertrophic cardiomyopathy in adults. Indeed, several studies have shown that Fabry disease may be found in 1–5 % of males with unexplained left ventricular hypertrophy/hypertrophic cardiomyopathy (6).

Global left ventricular systolic function as assessed by ejection fraction is preserved for a long time in Fabry disease related cardiomyopathy; however, strain imaging confirms subclinical abnormalities of myocardial deformation properties even in mild forms of cardiac disease. Left ventricular diastolic function is logically impaired; however, restrictive filling pattern is present only in advanced stages of this cardiomyopathy. With age, progressive myocardial replacement fibrosis develops. Based on magnetic resonance studies, this replacement fibrosis almost invariably starts in midmyocardial region of the basal posterolateral left ventricular wall. With progression to transmural fibrosis in end-stage patients, regional and then global left ventricular systolic function worsens (Figure 2). Progressive congestive heart failure and malignant arrhythmias represent important causes of death in patients affected with Fabry disease (5, 6).

Enzyme replacement therapy, which is available since 2001, allows a causal treatment of Fabry disease and is based on lifelong administration of intravenous infusions with recombinant α-galactosidase A. The success of enzyme replacement therapy on Fabry disease related cardiomyopathy is heavily determined by the extent of left ventricular hypertrophy and replacement myocardial fibrosis. The highest effect of this treatment is seen in individuals with no or only mild ventricular hypertrophy and no fibrosis. Nevertheless, even in patients with advanced cardiomyopathy enzyme replacement therapy has a potential to prevent or slow down further progression of the disease. Early diagnosis of Fabry disease is thus the most important prerequisite for successful treatment (7).

References

Hypertrophic Cardiomyopathy (HCM) occurs in 0.02% of adults with much lower rates of diagnosis in patients <25 years of age. HCM is defined by the presence of increased left ventricular (LV) wall thickness – ≥15 mm in one or more LV myocardial segments – that is not solely explained by abnormal loading conditions. In up to 60% of patients with HCM, the disease is an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes.

Two-thirds of patients with HCM have dynamic intracavitary obstructions at rest or during exercise – mainly of the left ventricular outflow tract (LVOTO) caused by contact between the mitral valve and the interventricular septum during systole. Bedside physiological provocation with Valsalva manoeuvre and standing should be routinely performed during echocardiography to determine if LV outflow obstruction can be provoked. Diagnostic cascade of HCM considers clinical and non-invasive evaluation and search of diagnostic red flags of systemic disease. Careful individual risk stratification of each individual patient includes history (age, unexplained syncope, premature familial HCM-related cardiac death), echo measurements (maximal gradient, LA diameter, maximal LV wall thickness), and 24–48 hours holter (nsVT ≥3 VB’s ≥120 bpm) and resulted in development of a new risk calculator (HCMRiskSCD) (http://doc2do.com/hcm/webHCM.html) for prediction of 5 years risk of SCD. The calculated risk should guide the use of implantable cardioverter defibrillators (ICD).

Treatment of symptomatic patients with left ventricular obstruction consists of medical treatment, septal ablation, and surgical myectomy.

Two decades after introduction of ablation it turned out to be the preferred method in most clinical situations. Total heart block with need of pacemaker implantation is the most observed complication. Long-term observational studies showed excellent clinical follow-up without increased morbidity and mortality.

Nevertheless, sufficient clinical and hemodynamic results can not be achieved in 5–10% of the patients mainly due to anatomic reasons. Therefore, surgical myectomy is necessary for symptom relief.

Both, surgical myectomy and interventional septal ablation are complementary treatment options and require special expertise in the diagnosis, genetics, risk stratification and management of myocardial disease.

References

Eisenmenger syndrome (ES) is a multisystem disorder placing a high burden on those affected by entailing a multitude of complications and poor exercise capacity. In two recent studies, we found an immortal time bias to be present in almost all ES studies contradicting the reported relatively beneficial survival outcome in these patients. Furthermore, we could confirm the benefits of disease targeted treatment in ES patients and a positive effect of these patients’ receiving care at larger specialized centers. These results point to the need of appropriate treatment in ES patients which seems to be best delivered by a specialized tertiary center.

Since its discovery in the late 19th century, Eisenmenger syndrome (ES) has been recognized as a detrimental condition with a high symptom burden and generally increased morbidity in those affected. Although it was identified as a multisystem disorder entailing a multitude of complications, several studies have suggested a relatively benign survival outcome in these patients, which has been the general assumption until recently. A single center study by Dimopoulos et al. (1) to investigate the effects of recently available disease targeting treatment (DTT) in ES patients was among the first to question the idea of benign survival in these patients. A poor outcome was identified especially for treatment naïve patients, for whom a mortality rate of approximately 25% at five years’ follow-up was calculated. Besides pointing to the importance of appropriate treatment, the study results suggested that the survival prospects of ES patients had been overestimated previously. Based on the results of mentioned study, we hypothesized an immortal time bias to be present in previous studies, that is, a bias resulting from only patients being included who survived up to the point of the first clinical follow-up. In a systematic review of available literature, combined with own data from a cohort of 219 untreated ES patients, we could confirm this hypothesis (2). The review revealed all but one of the surveyed studies to be prone to immortal
time bias. Furthermore, 10 year mortality rates between 30% and 40% were found in this meta-analytic study. In addition, the results of this study once more emphasized the importance of effective DTT.

We could further confirm these findings recently by means of an analysis of nationwide data, which were derived from the Germany-wide and representative National Register for Congenital Heart Defects (3). The analysis identified alarmingly poor survival rates among all surveyed ES patients and especially among those not receiving any DTT. Regarding the latter, mortality rates as high as 60% to 70% at 10 years’ follow-up were calculated. Interestingly, the study results also support the notion that patients receiving care in a larger center fare much better compared with the remaining patients.

In summary, one can conclude that a worse outcome than previously suggested has to be anticipated for ES patients and that, in fact, survival does not seem to have improved after the 1960s (in treatment naïve patients). Furthermore, the available results point to the benefits of DTT and healthcare being delivered by larger specialized centers. Accordingly, to ensure the best possible outcome for ES patients, referring patients to specialized tertiary centers where a proactive approach of treatment with DTT is possible should be considered.

References

Pulmonary vasoactive medication in adults with Fontan circulation

Jamil Aboulhosn, M.D.
Director, Ahmanson/UCLA Adult Congenital Heart Disease Center
David Geffen School of Medicine at UCLA, Los Angeles

KEY POINTS

Immediate and short-term improvement in functional capacity has been reported in Fontan patients receiving pulmonary vasodilator therapies. The existing data suggests greater benefit of the phosphodiesterase-5 inhibition over endothelin blockade. There are as yet no long-term studies that have assessed the impact of pulmonary vasomodulation on survival, arrhythmias, Fontan failure, hepatic dysfunction, or arrhythmias. Hence, there is a need for further studies, that are sufficiently powered and of sufficient duration to evaluate the long-term benefits and side-effects of pulmonary vasodilators in the Fontan population.

The prevalence of single ventricle patients palliated with the Fontan operation continues to grow worldwide (1–4). Fontan patients’ long-term survival and exercise capacity is largely dependent upon their pulmonary vascular resistance (PVR). Normal or low pulmonary arterial resistance is integral to the adequate function of the cavo-pulmonary circulation (5). With age, the pulmonary arterial resistance is known to gradually increase in Fontan patients and that elevated pulmonary resistance is associated with worse clinical outcomes. Pulmonary vascular constriction has been linked to the surface endothelin-1 receptors on the pulmonary vascular bed (6). It stands to reason that therapies that decrease pulmonary arterial resistance may improve pulmonary blood flow and functional capacity in patients with Fontan physiology. With the understanding that the pulmonary vascular bed is reactive to nitric oxide, safety and at least limited efficacy of sildenafil in non-failing Fontan patients has been demonstrated, including ~30% improvement in resting and exercise pulmonary blood flow, myocardial performance indices and estimates of cardiac output, and respiratory rate and minute ventilation at peak exercise as well as decreased ventilatory equivalents of carbon dioxide at the anaerobic threshold, though not peak
oxygen consumption (12–15). Furthermore, elevated endothelin-1 levels in Fontan patients suggest that endothelin blockade may be efficacious.

While endothelin receptor antagonists have been shown to increase exercise capacity, improve functional class, and hemodynamics in patients with pulmonary arterial hypertension, their efficacy has yet to be fully proven in patients with Fontan physiology.

In a small prospective but non-randomized study of bosentan in patients with failing Fontan physiology there were non-significant improvements in resting and ambulatory oxygen saturation but no improvements in maximum oxygen consumption, 6 minute walk distance, or quality of life measures (7). Another prospective randomized control trial also failed to demonstrate improvements in exercise, quality of life, or pro-BNP (10). A larger prospective randomized trial (TEMPO) out of Denmark did demonstrate an improvement in maximal oxygen consumption in patients randomized to Bosentan (11). Given the mixed results of these early studies, endothelin receptor blockers are still not widely used in this population.

References


KEY POINTS

- Indication of phlebotomy is moderate to severe hyperviscosity symptoms due to secondary erythrocytosis, or preoperative in patients with HT > 65%.
- Iron supplementation if clinical symptoms of ID are present.
- Prophylactic administration of iron in the absence of evident ID is controversial.
- Asymptomatic hyperuricemia in cyanotic ACHD is not routinely treated.
- From mechanism of hyperuricemia in cyanotic ACHD, uricosuric agents (URAT1 inhibitor) may be effective for prevention and treatment of hyperuricemia and gout.
- Hyperuricemia may be the trigger of various cardiovascular diseases and metabolic syndromes, therefore, possibly better to treat hyperuricemia in cyanotic CHD. But no positive data exist.

Causes of iron deficiency anemia (ID) in cyanotic CHD (CCHD) include excessive erythropoiesis, chronic kidney disease, pregnancy, menorrhagia, gastrointestinal bleeding especially in patients with chronic use of aspirin and/or anticoagulants, etc. Consumption of iron stores from recurrent phlebotomies can induce iron deficiency anemia that results in iron-depleted RBC, which are less deformable. Induced microcytosis increases blood viscosity, impairs oxygen delivery, increases anaerobic metabolism and lactate production in skeletal muscle worsening hyperviscosity symptoms.

Therefore, indications for phlebotomy are either moderate to severe hyperviscosity symptoms due to secondary erythrocytosis or preoperative phlebotomy for autologous blood donation if the hematocrit level is above 65%. Secondary hyperuricemia exerts little effect on renal function. Urate deposits seldom cause overt renal disease. Acute gouty arthritis is less common than would be expected from the relatively high prevalence of elevated UA levels. Asymptomatic hyperuricemia in CCHD is not routinely treated. Cause of hyperuricemia is muscular, renal, hepatic, and overproduction (erythrocytosis). Hyperuricemia possibly results from increased production and decreased renal clearance of uric acid. Uricosuric agents (URAT1 inhibitor, benz bromarone, probenecid) and UA synthesis inhibitors (allopurinol, febuxostat) are effective.
“Treat-and-repair” strategies might be a viable approach if individualized risk-benefit stratification is performed.

Significant cardiac shunts associated with pulmonary hypertension might be positioned on the systemic/pulmonary vein, atrial and ventricular level as well as between the great arteries.

The shunt direction of a non-restrictive atrial septal defect without any other cardiac lesions is defined by the relationship of the compliance of both, the right (RV) and left (LV) ventricle.

Considering serial circulation with a normal wall thickness of the RV to LV, a non-restrictive ASD leads usually to a Qp:Qs ratio of 3:1, if any higher shunt ratio is detected an additional reason has to be evaluated or excluded, in particular an increased LVEDP. The same is true if the shunt amount correlates not really with defect diameter.

The combination of an increased LVEDP with non-restrictive ASD is mostly associated with a precapillary pulmonary hypertension (PAH).

An isolated, non-restrictive ASD leads to a PAH only in context of genetic disposition for a pulmonary vascular disease in context of high flow shear stress of the pulmonary vascular bed.

A non-restrictive ventricular septal defect (VSD) causes after postnatal adaption an intracardiac left to right shunt, which leads to increased pulmonary vascular resistance (PVR) and pulmonary hypertension because of a high shear stress combined with an increased hydrostatic pressure.

Therefore, children with an un-restrictive VSD develop in almost 90% a nearly fixed PAH already after an age of 2 years. The question rises, why such a pathophysiology does not induce a 100% irreversibility of PAH. A protective genetic disposition has to be postulated, which is not discovered yet.

In the past, unrestricted VSD’s were the main reason for an Eisenmenger syndrome with a generalized full body cyanosis caused by an intracardiac right-to-left shunt with all the well-known long-term consequences.

The prognosis of such patients is limited, but better than an idiopathic PAH without any atrial, ventricular or even arterial communication.
Entirely different seems to be the situation of an adult patient with PAH with systemic or even supra-systemic pulmonary artery pressure, if primarily a restrictive, left-right shunting VSD was persistent. The question raises, repair or no repair, and if repair by which technique and perioperative strategy and if a so-called targeted drug therapy – as “treat and repair” strategy -- should be initialized.

Strategies

• At first, an exact diagnosis has to be performed by history, clinical examination, imaging and hemodynamic assessment.
• The most important hemodynamic assessments have to be focused on the pulmonary to systemic diastolic artery pressures (PAd/SApd) ratio and the oxygen transport parameters.
• Second, the best pre-conditioning strategy has to be analyzed and applied before and after repair surgery by utilizing the mentioned “targeted therapy” with the goal to influence the pulmonary vasculature or even the left ventricular compliance, if restrictive.
• Third, it has to be carefully considered that not any whole, in particular on the atrial level, has to be closed; patient’s survival might depend on persistence or re-opening of such an atrial communication.
• Fourth, in case of PH with severe right-to-left ventricular shunt and generalized cyanosis including coronary and cerebral vessels, a surgical or percutaneous modification of a VSD-type Eisenmenger-circulation to a PDA-type might be postulated as beneficial for the patients.

References

The future of PAH treatment on the horizon

Prof. Dr. med. Stephan Rosenkranz
Dept. of Cardiology, Pulmonology, and Intensive Care Medicine
Center for Molecular Medicine Cologne (CMMC)
Cologne Cardiovascular Research Center (CCRC)
Heart Center at the University of Cologne
Cologne, Germany

Key points

Despite recent improvements, the treatment options for pulmonary arterial hypertension (PAH) remain limited. Recent advancements were mainly achieved by optimizing and combining the currently established drug classes, i.e. endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostanoids. Current research aims at identifying novel targets particularly attempting to reverse pulmonary vascular remodeling, which include FoxO transcription factors and PI-3 kinase subunits such as p110.

Although the establishment of current therapies for pulmonary arterial hypertension (PAH) such as prostanoids, endothelin receptor antagonists (ERA), and phosphodiesterase type 5 inhibitors (PDE5i) has substantially improved morbidity and mortality in affected patients, PAH remains a devastating disease with reduced life expectancy, for which there is no cure. At present, the main achievable treatment goals include proper disease control, which involves stabilization at a reasonable hemodynamic and performance level, ideally without or with only mild symptoms, and with no signs of right heart failure or disease progression (1, 2). Nevertheless, the majority of the patients remain symptomatic, disease progression is only delayed, and mortality remains unacceptably high, so that there is a high need to further improve the treatment modalities in PAH. Recent progress was mainly achieved by improving the current treatment strategies which are based on targeting the prostacyclin, endothelin, and nitric oxide pathways,
respectively. To this end, novel compounds have been introduced such as the ERA macitentan (SERAPHIN study [3]), the soluble guanylate cyclase (sGC) stimulator riociguat (PATENT study [4]), and the prostacyclin receptor agonist selexipag (GRIphon study [5]), the latter awaiting regulatory approval. Collectively, the above studies have also demonstrated additive effects, when drugs targeting the three pathways were applied in combination. In parallel with the development of the above drugs, an evolution in trial design enabled investigators to capture the efficacy of PAH therapies on composite morbidity and mortality endpoints, demonstrating a substantial reduction of such events (3,5) (Figure 1). The AMBITION study particularly provided evidence that upfront combination therapy with an ERA (ambrisentan) and a PDE5i (tadalafil) in patients with newly diagnosed PAH was superior to either treatment alone in preventing morbidity and mortality events (6).

Accordingly, current guidelines recommend the use of early or even upfront combination therapy in patients with PAH (1,2), but proper diagnosis and distinction of PAH from other forms of PH, particularly PH due to heart failure with preserved ejection fraction (HFpEF), are important (8). A recent meta-analysis that included data from 4,095 patients enrolled in 17 trials provided reassurance that disease control can be achieved in an increasing number of patients and over longer periods of time, when combination therapies are utilized in PAH (7). Further studies are needed to evaluate whether even more aggressive approaches, i.e. triple combination, may be more efficient than dual combination therapy, as suggested e.g. by a subgroup analysis from the GRIphon study (5). In this context, the TRITON study (clinicaltrials.gov identifier NCT02558231), investigating the impact of selexipag versus placebo on pulmonary vascular resistance in patients on dual combination therapy with macitentan and tadalafil, is currently under way.
In addition to optimize the utilization of existing treatment concepts either by developing novel compounds belonging to the current three drug classes or by combining these approaches, current research aims at identifying novel targets particularly attempting to reverse pulmonary vascular remodeling. Currently, the efficacy and safety of an apoptosis-regulating kinase-1 (ASK-1) inhibitor are investigated in a phase II study (ARROW; clinicaltrials.gov identifier NCT02234141), which has already completed enrolment. Pre-clinical studies have identified peptide growth factors such as platelet-derived growth factor (PDGF) as important contributors to pulmonary vascular remodeling in PH, and PDGF inhibition by either pharmacological or genetic approaches was highly effective in reversing pulmonary vascular remodeling and PH (9,10). Consistently, the tyrosine kinase inhibitor imatinib has proven effective at least in a subset of patients with PAH in the phase III IMPRES study (11), but will not be approved for this indication due to safety concerns. Innovative new concepts focus on targets acting downstream of multiple growth factors, including Forkhead box O transcription factor-1 (FoxO1) and PI-3 kinase isoforms such as p110 (Figure 2) (12,13). However, these concepts await further evaluation and transition to human disease.
References

Electrophysiologic considerations in ACHD with heart failure

Prof. Dr. Dr. Karl-Heinz Kuck
Dept. of cardiology
Asklepios-Klinik St. Georg
Hamburg, Germany

Key points

• Ventricular tachycardia (VT) is the dominant cause for morbidity and mortality in patients with congenital heart disease (CHD) and repaired CHD.
• Treatment of these VTs by catheter ablation is highly effective.
• Whether effective ablation of VTs in patients with CHD and preserved right- and left-ventricular function can be considered as an alternative to ICD-implantation needs further evaluation.

Impact of ablation of ventricular tachycardia in patients with congenital heart disease

In Europe as well as in the United States sudden cardiac death is responsible for about 15% of the total mortality and 6% of the annual mortality. Similar to patients with an underlying ischemic or non-ischemic cardiomyopathy, sudden cardiac death is also the dominant cause of mortality in patients with congenital heart disease (CHD) with an incidence of 19–26%. (1, 2) The life expectancy of patients with CHD continuously increased over the last decades due to improved surgical as well as interventional strategies and techniques. Therefore, the majority of patients with CHD reaches higher ages and consequently the prevalence of SCD continuously increases. Ventricular tachycardia (VT) is one of the major causes for morbidity and mortality in patients with repaired and non-repaired CHD. The underlying substrate is mostly formed by anatomical or iatrogenic
post-surgical isthmuses. Ablation of those isthmuses using three-dimensional mapping systems in conjunction with radio-frequency catheters allows for effective treatment and significant reduction of the VT-incidence or even complete long-term suppression of the clinical VT. In a recently published study focusing on patients with VT after surgically repaired CHD VT non-inducibility was achieved in 74% of patients after ablation and block of the identified isthmus. (3) In addition, these patients were also free of recurrence of the clinical VT during long-term follow-up. These encouraging results raise the question, if successful ablation of VTs in patients with CHD and preserved right and left ventricular function might be considered as an alternative to ICD implantation. However, in the future this question needs to be answered by prospective, randomized studies.

References

KEY POINTS

Antiarrhythmic medications represent an essential tool in the acute and long-term treatment of tachyarrhythmias in adults with CHD, even in times of catheter interventions and antitachycardia devices. Application of antiarrhythmic agents requires careful adaption to pronounced limitations in hemodynamic tolerance and cardiac function, which are frequently found in patients with CHD. Antiarrhythmic drugs may be inserted as an exclusive antiarrhythmic strategy or as an adjunct to lower the arrhythmia burden in patients with ICD- or incomplete ablative treatment.

Arrhythmias represent the most frequent cause for emergency unit admissions in adults with congenital heart disease (CHD) (11, 12). Their prevalence increases with aging and dominates morbidity and mortality of this population next to heart failure (19, 23, 27).

An extraordinary and burdensome variety of potential substrates are apparent.: they range from congenitally given malformations of the sinus node or parts of the specific conduction system, accessory atrioventricular connections, to primary myocardial disease and injuries on myocardial or cellular level as a result of hypoxaemia, dilatation, hypertrophy, as well as any type of postoperative sequelae and genetics.

In the long-term course different subtypes of brady- and tachyarrhythmias may coexist in patients with congenital heart disease and mutually support arrhythmogenesis. Approximately 50% of the patients with CHD older than 20 years will develop atrial tachycardia, essentially based on alterations in intra-myocardial conduction, the most common type of arrhythmia in adults with CHD (4). But the initiation of such re-entry type tachycardia will be triggered i.e. by focal atrial automaticity, as a result of inadequate sinus bradycardia. By aging of the population, atrial fibrillation already represents an increasingly demanding focus for antiarrhythmic treatment. Furthermore in the future the prevalence of atrial fibrillation will grow as expected (17).
Despite of relatively rare absolute numbers, ventricular arrhythmias provide another demanding objective for treatment, as hemodynamic consequences are known to be high and are likewise recognized for being the leading cause of sudden death in diverse types of CHD (39).

Antiarrhythmic treatment in general is needed for most patients with CHD, mainly due to a lower hemodynamic compensation, but selecting of a proper strategy is often challenging as it needs to be individualized since conflictive arrhythmia problems may coexist.

Amongst all available strategies, antiarrhythmic medications still represent the primary treatment for most tachyarrhythmias, however, the acute and especially the long term use of such drugs may lead to severe and intolerable adverse effects due to both inherent abnormalities of the conduction system and an impaired systemic ventricular function.

Despite such limitations, antiarrhythmic drugs still represent an essential role for the termination of tachycardias or for rate control in the acute setting. Not any less frequent they are also applied as an adjunct therapy for interventional electrophysiology or device treatment, to corporately minimize the risk for arrhythmia recurrences. While in recent years catheter ablation is superior in eliminating circumscribed substrates and ICDs sufficiently terminate devastating ventricular tachycardia, antiarrhythmic agents carry
The potential of a global stabilizing impact on the myocardium and hence potentially lowering the arrhythmia burden.

For systematic reasons, the use of antiarrhythmic medications must be assorted according to its timing, i.e. acute setting, mid-, long-term administration and according to the targeted substrate, mechanism and arrhythmia type, i.e. atrial or ventricular level, AV-nodal or atrioventricular tachycardia, focal automaticity, re-entry or fibrillation.

Last but not least, distinction between symptoms related to treatment or targeting prognostic relevant arrhythmias is pathbreaking for the selection of a proper antiarrhythmic strategy.

The role of pharmacologic treatment of tachyarrhythmias in conjunction with other treatment options has recently been summarized in the “PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adults Congenital Heart Disease” (14).

Supraventricular/Atrial tachyarrhythmia

Acute termination
AV-node-dependent supraventricular tachycardia, if a vagal manoeuver fails, can be terminated by i.v. administration of adenosine or nondihidropyridine calcium channel antagonists (verapamil, diltiazem) (3). For pharmacologic conversion of atrial reentrytachycardias or fibrillation data and recommendations from literature are rare. General concerns are about risks for pro-arrhythmia, such as torsades de pointes with the use of Class III agents and ventricular tachycardia with the use of Class IA and IC drugs. For adults predisposed to sinus node dysfunction, the risk for significant sinus bradycardia following drug-mediated conversion is unpredictably high, especially when treating a long lasting or permanent tachycardia. There is few data about the use of ibutilide in children and adults with CHD for the conversion of atrial tachycardia and atrial fibrillation, showing a high success rate of 71 % and a low rate of complication but of severe quality. One patient of a series with 74 patients developed torsades de pointes tachycardias while another patient developed non-sustained ventricular tachycardias (10).

Sotalol had a 84 % conversion rate of IART and focal atrial tachycardia in another series, but with some patients requiring acute pacing for severe sinus bradycardia (22). In comparison to ibutilide, sotalol causes more hypotension and bradycardia, but the risk for torsade des pointes was seen as high as 4.3 % in a series investigating the efficacy of ibutilide in patients without CHD (17). Data in patients with CHD are missing about the efficacy and safety for the use of Class IA, IC or other Class III agents like i.e. amiodarone in the acute setting aiming to convert IART or atrial fibrillation.

Long-term medication
It is well recognized, that for patients with CHD, pharmacologic antiarrhythmic treatment is discouraging on the long-term perspective, regarding declining efficacy by time and the increasing risk of side effects. Nevertheless, its long-term use is inevitable for arrhythmias/substrates, which are not amenable for catheter ablation or just at the price of an unpredictable but high risk.

Targets of such antiarrhythmics can be divided into controlling the ventricular rate (“rate control”) or stabilizing sinus rhythm and preventing arrhythmia recurrences (“rhythm control”).
Rate control
Whenever conversion into or stabilization of sinus rhythm fails, the control of the ventricular heart rate aims to prevent aggravation of pre-existing heart failure or even sudden cardiac death as a potential consequence of fast conducted atrial tachycardia/fibrillation. In less complex forms of CHD, tachycardia related symptoms can be attenuated, exercise capacity might be improved and cardiac function can be preserved.

Management guidelines from normal heart patient cohorts suggest a maximum heart rate at rest of 100 bpm, but data from patients with CHD, especially from complex CHD, like i.e. univentricular hearts, are missing (24).

Recommended drugs in general for rate control are ß-blockers as well as nondihydropyridine calcium channel antagonists (verapamil, diltiazem). Digoxin is controversial for its potential for lethal complications. In patients with atrial redirection surgery of the Mustard or Senning-type for d-transposition of the great arteries, the use of ß-blockers is recommended, as additionally a decrease of ventricular arrhythmias could be shown (15).

In case of preexcitation, administration of digoxin or verapamil/diltiazem needs to be avoided, as it increases the risk for fatal ventricular arrhythmia due to accelerated atrioventricular conduction in case of fast atrial arrhythmias, like atrial fibrillation.

Rhythm control
Maintenance of sinus rhythm represents the preferred management target in contrast to rate control, but prospective data about the outcome of both strategies in patients with CHD are missing.

For long-term prevention of arrhythmia recurrences flecaïnide, propafenone and sotalol are considered to be favourable, but increased mortality has been shown in normal heart patients with heart failure or with ventricular scarring following infarction (6, 25). Analogue to this an increased all cause mortality has been observed while treating atrial fibrillation with the use of Class IA drugs (quinidine, disopyramide), which led to the recommendation to avoid Class I drugs in patients with coronary artery disease and heart failure (1, 18). Despite the lack of data from adults with CHD, such experiences need to be transcribed with all appropriate caution to this patients cohort, as adults with CHD frequently have a long lasting hemodynamic disturbance as well as myocardial scarring and fibrosis resulting from cyanosis or surgery, thereby presumably increasing the risk for potentially fatal proarrhythmia with the use of Class I agents.

One of the few existing studies regarding this purpose in adult CHD patients showed a nearly two-fold increased risk for ventricular arrhythmias in patients with tetralogy of Fallot under Class I antiarrhythmic drug therapy (16). There is conflictive data about the use of sotalol in children and adults with CHD and atrial tachycardia. The range goes from reasonable efficacy and safety in some series towards low efficacy and high rates of proarrhythmia in others, presumed involvement of generally accepted exclusion criteria for the use of Class III agents, like a prolonged QT-interval (2, 21).

Amongst all antiarrhythmic agents, amiodarone has the highest potential for rhythm control in patients with many types of tachyarrhythmias like focal atrial automaticity, atrial reentrytachycardia, atrial fibrillation and various arrhythmias on the ventricular level. But well-known time-
and dose-related side effects, especially in young adults are limiting its broad use. Young women with cyanotic heart disease or univentricular hearts with Fontan palliation are prone to amiodarone-induced thyreotoxicosis (26). Despite these limitations, amiodarone still may be considered as a first line therapy in adults with CHD in the presence of impaired ventricular function, ventricular hypertrophy or coronary artery disease as alternative drugs with reliable efficacy are missing.

More modern Class III agents like dronedarone, an amiodarone analog without iodine elements or dofetilide, a selective inhibitor of the delayed rectifier potassium current, are less effective i.e. in the suppression of atrial fibrillation recurrences and carry an increased risk for stroke and cardiovascular mortality, especially in patients with heart failure or after myocardial infarction (5). Further limitations are related to the need of unrestrained functions of liver (dronedarone) and kidneys, to minimize the drug induced risk for torsades de pointes tachycardia (dofetilide) (20).

Recent data suggest a relatively safe and effective use of dofetilide in adults with CHD for the treatment of atrial tachycardias, when initiation of therapy is controlled by close monitoring of the QTc-interval and an according adapted dosage (5).

Ventricular tachyarrhythmia (prognostic relevant)

Acute termination
In case of a hemodynamic stable ventricular tachycardia and if the primary use of an electrical cardioversion might not be favoured, i.v. application of amiodarone, lidocaine and procainamide is recommended. Significant hypotension can be a severe side effect with the use of amiodarone and procainamide. Lidocaine is known to be more effective in ventricular arrhythmias originating from ischaemic myocardium, whereas procainamide is superior in monomorphic macro-reentry tachycardias as seen in repaired tetralogy of Fallot.

In case of augmented automaticity or triggered activity adenosine or calcium antagonists might be of help, especially as electrical cardioversion is expected to be ineffective in terminating such autonomous mechanism.

Long-term management
For ventricular arrhythmias, classified as prognostic irrelevant, indication for antiarrhythmic drug treatment with all its inert limitations should be carefully outweighed against the potential benefits. If treatment is targeting disturbing symptoms or is aiming to reduce the risk for an arrhythmia-
induced impairment of the systemic ventricular function, the use of \textit{β}-blockers is widely accepted due to its universal effects on myocardial function and electrical stability.

For \textit{prognostic relevant ventricular arrhythmias} or for the \textit{secondary prevention of sudden cardiac death} in adults with CHD, the \textit{ICD} represents the first-line therapy, analogous to normal heart patients. In such case antiarrhythmic drugs are used aiming to reduce the risk of arrhythmia recurrences and subsequent ICD discharges.

There are only a few small series existing with this regard in patients with CHD showing favourable outcomes with \textit{mexiletine} and \textit{phenytoin} \cite{15}, \textit{sotalol} and \textit{amiodarone} \cite{16}. In patients with drug-refractory ventricular tachycardia mexiletine might be added to amiodarone according a retrospective study for the reduction of ICD shocks \cite{17}. The \textit{prognostic beneficial impact} of \textit{β}-blocking agents and amiodarone, as a general therapeutic aspect, was not shown in prospective data in adults with CHD so far, but is conjectural analogous to adults with ischemic cardiomyopathy or those with severely reduced cardiac function resulting from primarily dilated cardiomyopathy.

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Sudden death in ACHD: Risk stratification

Johan Holm MD, PhD
Associate professor
Skane University Hospital
Department of Heart failure and valvular heart disease
Lund University
Lund, Sweden

KEY POINTS

• Survival into adulthood after surgery for congenital heart disease is increasing over the years, and today 90% of the patients reach adult age. As the ACHD population age increase, we have to deal with late complications such as heart failure, arrhythmia and sudden death.
• Sudden death (SD) is a very small part of total mortality (7–19%), but still higher than in the ordinary population. Several mortality studies have been published, but also studies trying to identify risk markers for SD.
• In 2014 an expert consensus document was published by PACES/HRS (4) with recommendations for management of arrhythmias in congenital heart disease.
• Correct selection of high-risk patients for ICD is crucial, as ICD in young ACHD patients is problematic with more inappropriate shocks.

Introduction to the population

Median age of adults with congenital heart disease (ACHD) in a tertiary centre in the Swedish SWEDCON registry is 37.5 years with a majority between 20 and 30 years. The number of adult patients increases with roughly 10% per year. The incidence of arrhythmia increases in the third decade of life.

Factors leading to arrhythmia in ACHD

Surgery for congenital heart disease is often palliative with residual lesions. This provides an arrhythmia substrate with decreased myocardial function from volume or pressure overload, early cyanosis before correction, and not the least myocardial scarring from surgery that may provide re-entry circuits.

A combination of ventricular dysfunction, arrhythmia substrate and residual lesions contribute to the risk of sudden death (SD). The complexity of lesions makes it hard to pinpoint single risk markers. The earliest studies have been made on tetralogy of Fallot where QRS duration is associated with risk of SD. Coronary problems may be part of a congenital heart defect, but also superimposed by ischemic heart disease over time.
Mortality and survival in ACHD

Overall mortality in ACHD is 0.75% yearly and in a Swedish material median age at death 61 years. In a recent single centre retrospective study (1) 6969 ACHD patients had increased mortality (524 deaths) compared to controls, with chronic heart failure as a leading cause of death (40%). SD comprised 7%, which is lower than in previous studies with a yearly incidence of 0.1%. Highest mortality was among patients with complex ACHD, Fontan physiology and Eisenmenger syndrome. In an earlier multicentre study (2), 19% of the patients died suddenly.

Risk factors for SD in ACHD

Not surprisingly, the risk of SD is highest in patients with systemic right ventricle after Senning- or Mustard-type operation for transposition of the great arteries; left ventricular outflow obstruction (aortic stenosis or coarctation); and tetralogy of Fallot. It should however be kept in mind that any heart defect with residual lesions or poor myocardial function may have high risk of SD. Symptoms, hemodynamic evaluation, and cardiac function by echo or MRI are key parameters in every patient.

Tetralogy of Fallot

Risk factors for SD are listed below (5). It is important to remember that individual risk factors are indeed common, e.g. non-sustained VT, and do not alone predict SD, and they should rather be used in combination.

TGA – after Mustard- /Senning-type operation

The patients with atrial correction suffer from a right ventricle in systemic position with increasing risk of ventricular dysfunction, AV valve regurgitation and heart failure with age. There is also a risk of atrial arrhythmias from extensive scarring that may trigger ventricular arrhythmia. Finally, sick sinus bradycardia is common and should not be overlooked.

Left sided outflow obstruction

Many of these patients have reduced LV function after multiple surgeries for aortic stenosis during childhood or residual stenosis. There is often diastolic dysfunction with elevated pulmonary pressures from myocardial fibrosis. Systemic hypertension is common in patients with operated coarctation and may rise to dangerous levels during exercise.

Conclusion

The risk of SD increases with age in ACHD patients. Risk stratification involves thorough investigation of haemodynamic and myocardial function. Several risk factors have been identified in large trials, but must be used in combination and individualized. Ventricular function stands out as a major risk factor, but surgical history and presence of any arrhythmia is important.

References

KEY POINTS

Secondary prevention of sudden cardiac death and ICD implantation in ACHD focuses on patients after aborted cardiac arrest or symptomatic ventricular tachycardia. In primary prevention of sudden cardiac death major criteria for ICD placement are a reduced ejection fraction of the systemic ventricle or the presence of multiple, specific risk factors in patients with tetralogy of Fallot. Conventional, transvenous ICD therapy is burdened by an increased risk for lead complications and inappropriate therapies in ACHD. Whether new technologies such as the entirely subcutaneous ICD or leadless pacemakers reduce device associated morbidity in ACHD still needs to be assessed.

Sudden cardiac death is prevalent in adults with congenital heart disease (ACHD) (1). Risk stratification, however, is complex and hampered by limited numbers of patients available for clinical trials and a variety of sometimes rare entities required to be covered. Available data are usually derived from prospective registries or retrospective analyses lacking randomization. Therefore, ICD implantation in ACHD for many years has been limited to indications related to secondary prevention of sudden cardiac death. These patients have early been perceived as high risk patients and the effectiveness of ICD has been shown (2-4). The current guidelines recommend the placement of an ICD in survivors of aborted cardiac arrest in the absence of a reversible cause or in patients having experienced symptomatic sustained VT if hemodynamic and electrophysiological evaluation and optimization has been performed (5). ICD placement for primary prevention of sudden cardiac death in ACHD previously has been directed in many instances by individual considerations and beliefs. Recently published data, however, provide evidence for the usefulness of ICD in ACHD presenting with a systemic ejection fraction <35%, biventricular physiology and symptomatic heart failure (NYHA II or III) despite optimal medical therapy notably
In patients with transposition complexes (5,6).
In patients with tetralogy of Fallot an ICD should be considered for primary prevention of sudden cardiac death if multiple risk factors such as left ventricular dysfunction, non-sustained VT, QRS duration >180 ms or inducible ventricular tachycardias are present (2,5,7).
Despite of the potential benefits of ICD downsides of the therapy need to be considered when recommendations are made to the patient. Children and young adults are at an increased risk for lead failure and insulation breaks, vascular problems and infections (5,8) and inappropriate therapies due to sinus tachycardia, supraventricular arrhythmias and oversensing are not uncommon (8,9).
New technologies such as the entirely subcutaneous defibrillator are expected to alleviate problems associated with intravascular leads and for the first time offer a minimal invasive approach to the protection of patients with Eisenmenger syndrome.
The recently introduced leadless pacemakers offer new options in antibradycardia pacing and may be combined with the subcutaneous ICD in the future.
It remains to be determined, however, which of the available pacing and defibrillator systems is the most suitable for each of the individual patients.

References
Anregungen richten Sie bitte an:
Kaemmerer@dhm.mhn.de