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20 Jahre Kardiologie am UniversitätsSpital Zürich, 1996–2016

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Ventricular arrhythmias in congenital heart disease: how can the electrophysiologist help?

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Summary

Patients with congenital heart disease often have ventricular hypertrophy, dilatation and/or fibrosis as part of a direct consequence of their malformation. Moreover, they often have ventricular scars and/or patches and develop secondary haemodynamic overload or valvular abnormalities as a consequence of reparative surgery/interventions that worsen ventricular remodelling. This ventricular remodelling predisposes to polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF) and sudden cardiac death, as in other forms of heart disease. The presence of an extensive ventricular scar/patch leads to the occurrence of rapid and often poorly tolerated sustained monomorphic reentrant VT, resulting in haemodynamic collapse and even sudden cardiac death. Acute therapy of VT/VF is applicable in accordance with standard guidelines. Chronic management includes reparative therapy of the underlying congenital heart malformation and heart failure treatment, but specific arrhythmia management should ideally be provided by a qualified electrophysiologist who can precisely diagnose the arrhythmia and its mechanism, provide prognostic stratification, determine the substrate, administer specialised electrical therapies including antitachycardia pacing and automatic internal cardiac defibrillation from an implanted device, or perform catheter ablation of the VT substrate. Finally, electrophysiological evaluation can provide valuable information to guide the surgeon to incorporate arrhythmia-neutralising incisions into reparative surgery.

Key words: congenital heart disease; ventricular tachycardia; sudden death; catheter ablation; ICD

Arrhythmogenic milieu in CHD patients

Underlying CHD often results in pathological ventricular hypertrophy, dilatation and/or fibrosis of either or both ventricles, and heart failure. As a result, in much the same way as with other diseases leading to ventricular remodelling and heart failure, the majority of sustained ventricular arrhythmias are polymorphic VT or ventricular fibrillation. Monomorphic sustained VT, however, is uncommon in the absence of a ventricular scar: for example, after atrial switch for d-transposition of the great arteries (d-TGA), sustained monomorphic VT occurred with an incidence of 0.5% per year, whereas polymorphic VT/VF were the most frequently recorded arrhythmias in these patients when

As in the general population, the spectrum of ventricular arrhythmias in patients with congenital heart disease (CHD) ranges from ventricular ectopics to non-sustained ventricular tachycardia (VT), sustained monomorphic VT, polymorphic VT and ventricular fibrillation (VF). Accordingly, the clinical manifestations can be variable and include palpitations, syncope, heart failure secondary to tachycardiomyopathy, or sudden cardiac death (SCD) from malignant ventricular arrhythmias. The incidence of sudden cardiac death in the CHD population in general is estimated to be about 0.1% per year [2]. Sudden cardiac death (20%) and heart failure (30%) account for nearly half of all late deaths in mixed cohorts of children and adults with CHD [3]. Although nonsustained VT has not been linked to sudden death in a heterogeneous population of patients with CHD, it has been associated with inducible and clinical ventricular tachyarrhythmias in patients with tetralogy of Fallot (TOF) [4]. This article provides an overview of the electrophysiological treatments of ventricular arrhythmias in the setting of congenital heart disease.
implanted with an implantable cardioverter-defibrillator (ICD) [5].

In the preoperative state, the haemodynamic consequences of atrioventricular and great arterial valvular regurgitation or outflow obstruction result in ventricular dilatation, dysfunction, hypertrophy, ischaemia and fibrosis. The occurrence of coronary artery anomalies, atrioventricular nodal and conduction system abnormalities, the metabolic milieu (hypoxia, acidosis), and the haemodynamic-rheological burden of polycythaemia can all contribute to the proarrhythmic environment. After surgery, a patient may develop haemodynamic overload in other chambers or worsening of existing burdens, secondary valvular abnormalities, coronary injuries, injury to the atrioventricular node and conduction system or the haemodynamic and electrophysiological effects of the ventricular incision. Metabolic and electrolyte abnormalities, drug effects, systemic illnesses and inflammation can also play an important role at different times.

In patients with CHD, the burden of the original cardiac malformation is frequently combined with the sequelae of reparative surgery, and this combination increases these patients’ vulnerability to arrhythmias. After reparative surgery, the presence of surgical scars and prosthetic and patch material modifies mechanical and electrical properties of the ventricles by producing large inexcitable areas with adjoining, relatively delimited isthmuses of slowed conduction. This combination, as is well known at the atrial level, lends itself readily to monomorphic reentrant ventricular arrhythmias. Accordingly, in patients with repaired TOF and an ICD, more than 80% of all treated ventricular arrhythmias have been monomorphic VTs [5, 6]. Similarly, monomorphic VTs have also been reported in patients with d-TGA and ventricular septal defect (VSD) closure or repaired outflow tract obstruction. The presence of iatrogenic scars, however, does not exclude the occurrence of polymorphic VT/VF in these patients; since residual defects (VSD or outflow obstruction) or postsurgical sequelae (e.g., pulmonary regurgitation) still produce ventricular hypertrophy, fibrosis and dilatation and heart failure, which is thought to be the substrate for polymorphic VT/VF.

Because of the generally downhill course of the natural history of most severe congenital heart disease states, in particular uncorrected ones, there is a significant time-dependent increased risk of ventricular arrhythmia. Both the underlying disease and the type of surgical/interventional correction can significantly influence this risk. The lifetime estimated risk of ventricular tachycardia ranges from <2% for atrial septal defect to 10–15% for TOF with the caveat that these figures also reflect the average lifespan for patients with these conditions in addition to the disease itself [2]. In the absence of a surgical scar or patch, systemic ventricular dysfunction is the dominant underlying predictor for sudden cardiac death in CHD patients, typically due to polymorphic VT or VF. Compare, for instance, the 7–9% estimated lifetime incidence of VT in d-TGA after atrial switch (with a systemic right ventricle, prone to late failure) with an incidence of <2% for d-TGA after an arterial switch [2]. Recent data indicate that heart failure is on par with or gaining against sudden cardiac death as the chief cause of late death in a mixed CHD population [3], probably as a consequence of increasing life expectancy and perhaps also of improved management of malignant ventricular arrhythmias. As with other categories of malignant ventricular arrhythmias, the decision to implant an ICD in patients with CHD should factor in overall life expectancy, and the risk of heart failure and comorbidities.

**Therapies for ventricular arrhythmias**

Therapy for ventricular arrhythmias in the setting of CHD includes specific reparative treatment of the underlying heart disease, and of the residual lesions, control of heart failure and treatment of comorbidities, as well as direct treatment of the ventricular arrhythmias. A case-by-case consultative interaction between electrophysiologists, heart failure specialists and GUCH specialists, as in our institution, can provide the close coordination and specific adjustments required for managing these complex patients.

Direct treatment modalities for ventricular arrhythmias include, of course, antiarrhythmic drugs, cardiac implantable devices including ICDs, and catheter and surgical ablation directed at the arrhythmia mechanism. Cardiac resynchronisation by itself is considered a heart failure management therapy and will not be detailed further here.

**How can the electrophysiologist help?**

Electrophysiologists can play an important and often a key role in diagnosing various arrhythmias and analysing their mechanisms. They can help in providing a prognostic risk stratification of arrhythmic death, and allow knowledgeable decision-making in the choice of appropriate therapy, in providing and implementing catheter ablation, and in counselling the patient on appropriate lifestyle choices, including leisure and professional pursuits as well as personal choices such as parenthood. Additionally, the electrophysiologist can provide specialised electrical therapy (cardiac resyn-
chronisation) for the treatment of associated heart failure and can provide input to the cardiac surgeon in order to mitigate the arrhythmogenicity of surgical scars or guide the surgeon to modify the scars in therapeutically useful ways, such as extending a scar to a nonexcitable boundary such as the pulmonary valve annulus during a surgical revision for right ventricular outflow obstruction.

In the acute situation, when faced with a VT in a patient with CHD, standard guideline-based management applies. Sustained ventricular arrhythmias should certainly be terminated expeditiously, particularly in patients with complex CHD and/or precarious haemodynamics. In most instances, electrical cardioversion or defibrillation is the preferred treatment option. In patients with CHD, it is useful to remember to modify external defibrillation paddle or pad positioning according to the position of the heart (e.g., dextrocardia). And in patients with intracardiac devices, the paddles/pads need to be placed at a distance of at least 8 cm away from the generator. Drug treatment for cardioversion of sustained VT may be considered in the rare patient with stable haemodynamics and a well-tolerated arrhythmia without significant ventricular scar or remodelling. Long-term drug treatment of ventricular arrhythmias is often limited by the extent and severity of ventricular remodelling, the risk of pro-arrhythmia and heart failure, and drug-specific long-term side effects. There is not much of an evidence base to fall back upon in this patient cohort and our experience has centred around amiodarone and sotalol as specific agents and beta-blockers as adjuvant treatment when possible. Clearly, safe and effective antiarrhythmic drug therapy is an unmet need, possibly even more pronounced in this cohort of patients. A more detailed discussion of antiarrhythmic drug therapy can be found elsewhere [4].

Arrhythmia evaluation

Holter monitoring for the detection of nonsustained and sustained ventricular arrhythmias should be considered in those adult CHD patients at high risk, including TOF (over 35 years of age), TGA-atrial switch or Fontan palliation. Implantable loop recorders may also be useful for evaluating recurrent but fleeting symptoms in these high risk patients. The best studied subgroup of patients is those with repaired TOF in whom a number of features have been found to be associated with a high risk of malignant ventricular arrhythmias and/or SCD. They include older age at repair, transannular repair with or without right ventricular dysfunction-dilatation, significant pulmonary regurgitation, left ventricular dysfunction-dilatation, severe or increasing QRS prolongation, atrial arrhythmias, syncpe, nonsustained VT, or inducible malignant sustained ventricular arrhythmias [6–8]. Patients with multiple risk factors even without arrhythmias can be considered for an electrophysiological (EP) study in order to improve risk stratification and even to evaluate possible interventional treatment.

In patients with implanted devices, additional diagnostic and therapeutic options have become available, including device monitoring for arrhythmia detection, diagnosis and burden estimation, noninvasive EP studies to evaluate inducibility and risk stratification, as well as overdrive pacing for terminating VT. After surgical repair, patients frequently demonstrate a wide QRS even in sinus rhythm, thus rendering the distinction of supraventricular from ventricular arrhythmias even more difficult, and electrogram information from implanted devices can be very helpful in this respect.

**Electrophysiological studies**

An EP study including programmed stimulation that demonstrates inducible sustained ventricular arrhythmias may indicate an arrhythmogenic ventricular substrate and, in some subsets of patients, a higher risk of malignant ventricular arrhythmias including clinical VT and sudden death [2]. The EP study also allows evaluation of sinus node function, atrioventricular nodal and infranodal conduction, as well as supraventricular arrhythmia inducibility. In most centres today, an EP study is usually performed with a view to a subsequent therapeutic option, whether catheter-based or intraoperative. An EP study is indicated particularly in patients with unexplained syncpe, resuscitated sudden death or potentially life-threatening arrhythmias and a high risk CHD substrate. If haemodynamically significant sustained ventricular arrhythmias can be induced, ICD implantation may be considered. An EP study should be considered particularly when a therapeutic option (catheter ablation) could be performed during the same procedure. The therapeutic-diagnostic yield of an EP study may also depend upon the underlying specific CHD substrate. There is limited data derived from subgroup analysis suggesting that inducible VT does not predict clinical outcomes in patients with TGA and intra-atrial baffles. [9]; nevertheless, even in these patients EP studies may have a role in assessing atrial arrhythmia inducibility and tolerability, and in evaluating the atrioventricular conduction system. Atrial arrhythmias in this subgroup could, in fact, trigger ventricular tachycardias and sudden death, possibly...
owing to rapid atrioventricular conduction concurrent with exertion resulting in haemodynamic instability from the atrial tachyarrhythmia itself or by secondary degeneration into a malignant ventricular tachyarrhythmia [2]. In CHD patients with significant ventricular arrhythmias, syncope or resuscitated sudden death and who are scheduled for surgery, an EP study should be considered in order to evaluate possible integration of therapy directed at the specific arrhythmia substrate during the surgical repair — intraoperative ablation or incisional lesions (see later). In some CHD patients, particularly those with a surgical ventricular scar, an EP study may also be required to reliably distinguish supraventricular arrhythmias.

Catheter ablation for ventricular tachycardia

The current state of the art of catheter ablation for VT has evolved considerably, but its efficacy is still limited by the inability to delineate the complete electrophysiological activation sequence and the detailed reentrant circuit of the ventricular arrhythmia, either because it is intramural or more frequently, the “mapping” is precluded by haemodynamic compromise during sustained ventricular arrhythmia. Considerable progress has been made, however, in delineating potential “isthmuses” (“alley-ways” of pronounced slow conduction which play a key role in permitting the existence and stability of reentrant circuits) during sinus rhythm or a paced ventricular rhythm, particularly in patients with other forms of structural heart disease such as ischaemic and nonischaemic cardiomyopathies [10, 11]. These techniques can be applied to patients with operated CHD as well. The therapeutic aspect of catheter ablation relies upon the acute creation of electrically inactive myocardium (as a result of thermally mediated coagulative necrosis), but typically has a limited spatial extent (nontransmural and/or noncontiguous) and a nonnegligible component of reversible tissue injury. Therefore, ineffective ablation may be the result of inaccessible or unlocalisable isthmuses, noncontiguous/nontransmural coagulative necrosis, or tissue oedema instead of irreversible necrosis. Advances in catheter ablation technology, including irrigated radiofrequency ablation and, more recently, real-time contact force sensing [12] combined with 3D localisation, are thought to have resulted in significant improvements in ablation efficacy, although prospective long-term data are lacking.

Sustained monomorphic VT is most frequently related to a substrate composed of scar, anatomical obstacles and slow-conducting myocardium. This correlates well with the high incidence of sustained monomorphic VT in CHD patients with a surgical ventriculotomy, such as patients after corrective surgery for TOF. The majority of these VTs are fast and haemodynamically poorly tolerated (precluding detailed mapping during the arrhythmia) and therefore requiring a substrate-based ablation approach [7]. In repaired TOF patients, the surgical right free wall ventriculotomy, the ventricular septal defect (VSD) patch, the tricuspid valve and the pulmonary valve together result in multiple candidate isthmuses of which four are discrete and amenable to catheter ablation. In the typical case, an isthmus is formed between the right ventriculotomy or patch and the tricuspid annulus (no. 1). If the right ventriculotomy/patch does not traverse the pulmonary valve, the intervening tissue from the superior end of the scar to the pulmonary valve annulus forms another discrete isthmus (no. 2). A third lies between the superior border of the VSD patch and the pulmonary valve annulus (no. 3), whereas the fourth is formed between the VSD patch and the tricuspid annulus (no. 4) [13]. In post-mortem series of repaired TOF, isthmuses 3 and 1 were present in almost all specimens, whereas isthmuses 2 and 4 were observed in only 25 % and 13 %, respectively. In specimens from patients aged ≥5 years at the time of death, isthmus 3 was significantly narrower and thinner with more interstitial and replacement fibrosis than isthmus 1 [13, 14].

Macro-reentry using these isthmuses is the most frequent mechanism of sustained monomorphic VT in these patients and, depending upon the exit site (right ventricular free wall or septal) can produce different ECG morphologies (e.g., a characteristic QS or QR, respectively, in V1). Anatomical and surgical variations can result in interindividual differences in isthmus dimensions; for example, a transannular ventriculotomy abolishes the isthmus between the pulmonary valve and the superior limit of the ventriculotomy. Similarly, variations in VSD morphology and location can alter the dimensions of the surrounding isthmuses. Although slow conduction is well known to be a mandatory requirement for the establishment of sustained reentry, only recently have detailed electrophysiological mapping studies established objective and sensitive demarcations of arrhythmogenic isthmuses, chiefly by use of parameters of conduction velocity. Kapel et al. performed a detailed EP study including right ventricular endocardial voltage and activation mapping in these patients and were able to show that sustained monomorphic VT was either inducible, or occurred spontaneously and was inducible only when the involved
isthmus(es) exhibited a conduction velocity below 0.5 m/sec. The isthmuses in these patients with inducible or both spontaneous and inducible sustained monomorphic VT were significantly narrower and longer and produced fractionated electrogams during sinus rhythm (or right ventricular pacing) [15]. These isthmuses could be successfully targeted by radiofrequency catheter ablation, resulting in termination of sustained VT and VT noninducibility with complete conduction block in sinus rhythm. Kapel et al. further showed the prognostic importance of targeting these isthmuses, since none of the patients lacking or with successful ablation of the slow conducting isthmuses developed recurrent or spontaneous sustained monomorphic VT during 262 patient-years of follow-up. Although based on a limited number of patients from three centres, these results are very promising and suggest the possibility of relatively simple individualised risk stratification in these patients based on right ventricular endocardial mapping. Furthermore, catheter ablation could also be utilised as primary prevention by ablating potentially arrhythmogenic isthmuses, although the utility and safety of this approach remains to be shown. On the other hand, identification of a select group of low-risk patients in whom catheter ablation may be performed without ICD implantation is likely to be challenging.

With the introduction of a combined transatrial-transpulmonary approach and only limited patch augmentation for pulmonary valve stenosis, anatomical isthmuses 1 and 2 may be prevented in the majority of patients. However, isthmus 3 will remain. Evaluation of its potential arrhythmogenicity with electroanatomic mapping is appealing, and could allow personalised risk stratification and tailored treatment for contemporary patients with repaired TOF. Whether preventive transection of isthmus 3 during initial repair is feasible and safe needs careful, multidisciplinary consideration.

Patients with a repaired TOF and high risk features or suggestive symptoms may benefit from this approach of stratification and primary prevention by catheter ablation. In addition, EP evaluation of potential isthmuses may also help guide surgical incision making and/or adjunctive cryotherapy if revision surgery is necessary. In some patients, therefore, an EP study may help to decide if surgical treatment of arrhythmias is necessary or can be useful. During the EP study, mapping of the arrhythmia substrate can help the surgeon “design” an effective incisional or intraoperative ablation lesion. Intraoperative cryoablation of the infundibular septum between the VSD patch and pulmonary annulus during surgical repair of TOF has been proposed, but neither efficacy nor safety (from proarrhythmia) have been evaluated.

Radiofrequency catheter ablation of VT in these patients remains challenging owing to the variable anatomy with occasionally difficult or limited access (occluded femoral vessels, interrupted inferior vena cava, surgically created obstacles, prostheses and baffles), the sometimes hypertrophied myocardium and a complex and highly variable arrhythmogenic substrate that is dependent on the original malformation and the type of repair that has been performed. Pre-existing anatomical or surgical obstacles and associated or resultant fibrosis may render effective catheter ablation difficult, and alternative approaches, such as from the systemic arterial side of the circulation into the subaortic ventricle, may be effective [16].

Published results of ventricular tachycardia ablation in adults with CHD have obvious limitations, including small numbers as well as mixed substrate populations, thus restricting the value of estimates of arrhythmia-free survival [13].

Because the correlation between sustained monomorphic VT and sudden death remains imprecise, and because the risk of recurrence even after acutely successful ablation remains relatively high, VT ablation is only rarely seen as a substitute for ICD therapy, and most commonly as an adjunct to reduce multiple ICD shocks, for example for a VT storm. Catheter ablation of VT in adults with CHD can also be considered as an alternative to drug therapy in patients with an ICD and symptomatic VT, and may also be reasonable for nonsustained VT or relatively well tolerated VT when targeting anatomical isthmuses (see below) or for frequent ectopy with progressively worsening ventricular function. Much more rarely, ablation can be helpful for resolving the haemodynamic risk in patients with slow but incessant tachycardias.

Sudden cardiac death and implantable cardioverter defibrillators in congenital heart disease

The incidence of SCD in repaired CHD is 0.9 per 1000 patient years, which is 25- to 100-fold higher than for the general population [5].

ICD interrogation in patients with repaired TOF and TGA, implanted for both primary and secondary prevention, has shown that >80% of all ventricular arrhythmias that prompted ICD therapy in repaired TOF and around 50% in TGA patients are fast and monomorphic VT, often with heart rates >200 bpm [8, 9]. Identifying risk factors in these patients is complicated by time- and age-dependent changes, such that factors
identified in earlier series of patients may become less relevant to younger cohorts. Risk estimates also change as patients age and progress further along their disease course.

Factors most consistently associated with SCD in TGA with Mustard or Senning baffles include systemic ventricular dysfunction, severe tricuspid regurgitation, prolonged QRS duration, and atrial tachyarrhythmias [3, 18]. Interrogation of ICDs implanted for primary prevention in TGA has, however, reported rather low rates of subsequent ventricular arrhythmias. For example, in a multicentre cohort in which 35% of patients had a systemic right ventricular ejection fraction <35%, the appropriate ICD shock rate was 0.5% per year [9]. It may be that the 35% threshold value for primary prevention in case of a systemic left ventricle is not applicable to a systemic right ventricle, since normal values for a subpulmonary right ventricle are 20% lower than for a systemic left ventricle. To date, there are only limited data on patients with univentricular hearts who represent a minute fraction (<2%) of ICD recipients with CHD [19].

As with other pathologies, ICD implantation is indicated for secondary prevention of symptomatic, haemodynamically significant VT, and resuscitated sudden death due to malignant ventricular arrhythmias. It is also indicated for primary prevention in CHD with biventricular physiology, systemic left ventricular dysfunction (≥35%) and New York Heart Association grade II or III symptoms. ICD implantation may be reasonable in TOF patients at high risk of sudden death even in the absence of spontaneous sustained malignant ventricular arrhythmias. In a multicentre study of 252 patients with TOF who underwent programmed ventricular stimulation, inducible sustained ventricular tachycardia was independently associated with a nearly 5-fold higher rate of clinical ventricular tachycardia or sudden cardiac death on follow-up [20]. However, as indicated earlier, in the absence of a ventricular scar, for example in patients with transposition and atrial baffles, inducible VT does not appear to predict clinical events and thus the value of programmed stimulation in these patients is unclear.

Young adults with CHD today are quite likely to outlive their heart disease course. The following history may provide a useful example of many of the issues discussed above in the management of VT in the setting of complex CHD.

A 14-year-old boy with recurrent monomorphic VT was referred to our EP unit. He was born with a double-outlet right ventricle, d-TGA and a nonrestrictive VSD. He underwent an atrial septostomy and pulmonary artery banding in infancy, followed at 3 years of age by a Rastelli-type correction involving subaortic conal resection, patch closure of the VSD with creation of an in-

Implantable cardioverter-defibrillator programming options

Current implantable devices offer sophisticated programming options, and individualised programming can significantly reduce inappropriate and avoidable shocks. Inappropriate shocks are most commonly due to sinus tachycardia, supraventricular arrhythmias, T-wave oversensing, or lead failure, and can be reduced by adjuvant atrioventricular nodal blocking therapy or catheter ablation of supraventricular tachycardias (SVTs) (mostly intra-atrial reentrant tachycardias, often relatively slow with resulting frequent 1:1 atrioventricular conduction) [2].

Useful programming options to reduce avoidable shocks include antitachycardia pacing (ATP) and adjustment of detection time/intervals. ATP can be highly effective in terminating ventricular tachycardia without shocks in patients with CHD, and is therefore painless. It is safe, but sometimes causes VT acceleration, which is usually handled well by device safety algorithms and appropriate shocks if necessary. Longer detection delays for VF detection have also been found to be safe and effective in reducing the incidence of shocks. ATP can be programmed for slow and fast VT zones, as well as before or during charging.

Illustrative case

The following history may provide a useful example of many of the issues discussed above in the management of VT in the setting of complex CHD.
ternal hemi-tube establishing left ventricular outflow continuous with the aorta, and an external right ventricle to pulmonary artery conduit (mandated by an anomalous left anterior descending artery originating from the right coronary artery and crossing the anterior right ventricle). This conduit required percutaneous dilatation once and was surgically revised another time thereafter. Since the age of 7, monomorphic sustained VT recurred multiple times (fig. 1, left panel), despite antiarrhythmic drug treatment including sotalol and amiodarone, and required electrical cardioversions.

In our laboratory, an electroanatomic voltage map (fig. 2, right panel) and an activation map (fig. 1, right panel) of the right ventricle was created in sinus rhythm, confirming a low voltage zone with delayed activation in the septal outflow region, consistent with the VSD-left ventricular outflow patch, and another similar zone in the anterior outflow, consistent with the origin of the conduit to the pulmonary artery (fig. 1, middle panel: conduit indicated by white arrows on fluoroscopic views).

The clinical VT demonstrated a left bundle-branch block and leftward axis configuration with a precordial transition indicating a right ventricular free wall exit. A sequence of contiguous radiofrequency lesions was created on the anterior wall of the right ventricle extending from the inferior border of the anterior zone, and continuing to the anterior border of the tricuspid annulus (fig. 1, left and right panels). Additional lesions were made in the narrow zone of normal-voltage tissue interposed between the septal and anterior scar zones. Inducibility testing confirmed that the clinical VT could not be induced, but a different sustained monomorphic VT was induced (VT2), with an inferior axis, QR morphology in V1 and a transition in V3, suggesting a septal superior exit, probably nearer the septal left ventricular outflow tract patch (figs 1 and 2, right panels). Diastolic potentials were recorded on the right ventricular side of this region during on-going VT (fig. 2, centre panel), and because of proximity to the His bundle potential, radiofrequency lesions were prudently delivered to this region in sinus rhythm (fig. 3). Although a VT similar in morphology to the second VT...
remained inducible thereafter, no further attempts at ablation in this region or on its corresponding left side were made in view of the proximity to the atrioventricular conduction system and noninducibility of the clinical VT. A couple of weeks later, the conduit was surgically revised for haemodynamically significant stenosis and a single chamber ICD implanted without complications or arrhythmia recurrence. Over 5 years of follow-up, although he had an ICD intervention during early follow-up (unclear whether appropriate), he has been doing well for the last 3 years without antiarrhythmic therapy and without any further ICD intervention.

This patient illustrates many of the key issues relevant to ventricular arrhythmias in patients with complex CHD. The anatomical obstacles in this patient included the surgical scars of the implanted conduit, as well as the VSD-left ventricular outflow patch, with an intervening zone of low voltage tissue. The clinical VT compatible with a right ventricular free wall exit was prob-
ably related to a macro-reentrant circuit around the tricuspid annulus or around the conduit implantation site. The right free wall lesion, as shown in the images, was created to interrupt passage of electrical activation sustaining either or both of the above reentrant circuits and accordingly could not be re-induced. However, the second VT manifested mid-diastolic potentials at the septal VSD-left ventricular outflow patch region, with a surface ECG indicating a septal exit, but could not be eliminated despite ablation at this site. It is likely that the critical pathway maintaining this VT was deep within the fibrous tissue at the edge of the septal patch, close to the His bundle and not susceptible to prudent radiofrequency-induced tissue heating from the right side. The inducibility of the residual VT, despite being non-clinical, prompted ICD implantation. Follow-up revealed no ICD intervention or VT during the last 3 years without antiarrhythmic drug treatment.

Clinical implications

As in other patients, ventricular arrhythmias are a major cause of morbidity and mortality in patients with CHD. Appropriate diagnosis and specific treatment can provide effective management for most patients with VT. Current expertise in diagnostic electrophysiology can lead to individualised recognition of current and potential arrhythmogenic tissue isthmuses, allowing in most cases their neutralisation by catheter ablation with resulting improvements in arrhythmia control and symptoms, although prognostic benefits have not yet been demonstrated.

Disclosure statement

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Die Trigger für das Takotsubo-Syndrom sind vielfältiger als bisher angenommen

Das Happy-Heart-Syndrom: positive Emotionen und Takotsubo-Syndrom

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Summary

Takotsubo syndrome (TTS) is an underestimated acute heart failure syndrome masquerading as acute myocardial infarction at presentation and mostly affecting postmenopausal women. As TTS is often precipitated by emotional stress especially after negative life events (e.g. grief, anger, fear) the widespread term of the broken heart syndrome was coined. So far the role of positive emotional stress in TTS is less clear. Data from the International Takotsubo Registry (InterTAK Registry, www.takotsubo-registry.com) have demonstrated that happy life events such as becoming a grandmother, son's wedding, or winning several jackpots can ultimately lead to TTS. These new findings should lead to a paradigm shift in clinical practice as they show that the triggers for TTS can be more diverse than initially thought. These results have recently been published in the European Heart Journal.

Key words: Takotsubo syndrome; broken heart syndrome; happy heart syndrome; acute heart failure; positive emotions; brain-heart connection


Abbildung 1: Briefmarke mit Diogoras auf den Schultern seiner Söhne. Nachdruck aus Katsanos et al. [10], mit Genehmigung.

Ergebnisse des Internationalen Takotsubo-Registers (InterTAK Registry)

Europa und den USA beteiligen, wurden 485 Patienten mit eindeutigen emotionalen Stressfaktoren eingeschlossen, von denen 20 (4,1%) einen positiven Trigger aufwiesen [12]. Diese Fälle wurden in Analogie zum «broken heart syndrome» als «happy heart syndrome» klassifiziert. Die spezifischen Stressfaktoren der «happy hearts» sind in Tabelle 1 dargestellt. In einem Vergleich der beiden Gruppen waren Frauen gleichermaßen stark betroffen (95,0% vs. 94,6%, P = 1,0) [12]. Auch die klinische Präsentation, elektrokardiographische Befunde, Vitalparameter, kardiale Biomarker sowie das Kurz- und Langzeitoutcome waren zwischen beiden Gruppen vergleichbar [12]. Interessanterweise konnten wir mittels einer Post-hoc-Analyse eine erhöhte Prävalenz des midventrikulären Typen in der «Happy heart»-Gruppe im Vergleich zu der «Broken heart»-Gruppe (35,0% vs. 16,3%, P = 0,030) beobachten, während sich keine signifikanten Unterschiede bei der klassischen apikalen Ballonierung sowie bei dem fokalen und basalen Typen zeigte [12].


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<th>Happy heart events (n = 20)</th>
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<tr>
<td>Patient 1  Birthday party</td>
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<td>Patient 2  Son’s wedding</td>
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<td>Patient 3  Meeting after 50 years with friends from high school</td>
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<td>Patient 4  Preparing 50th wedding anniversary (pleasant anticipation)</td>
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<td>Patient 5  Positive job interview</td>
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<td>Patient 6  Wedding</td>
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<td>Patient 7  Favourite driver won race car competition</td>
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<td>Patient 8  Becoming grandmother</td>
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<td>Patient 9  Surprise farewell celebration</td>
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<td>Patient 10 Son’s company opening</td>
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<td>Patient 11 Favourite rugby team won game</td>
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<td>Patient 12 Emotional speaking during a friend’s birthday</td>
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<td>Patient 13 Celebrating 80th birthday</td>
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<td>Patient 14 Winning several jackpots at the casino</td>
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<td>Patient 15 Celebration of normal PET-CT scan</td>
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<td>Patient 16 Visiting opera with her family</td>
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<td>Patient 17 Family party</td>
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<td>Patient 18 Unexpected visit from favourite nephew</td>
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<td>Patient 19 Grandchildren visiting from London (abroad)</td>
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<td>Patient 20 Becoming great-grandmother</td>
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Das Happy-Heart-Syndrom – ein Paradigmenwechsel

Während weitgehend bekannt ist, dass negative Belastungssituationen zu einem TTS führen können [3, 6], wurden bisher erfreuliche Ereignisse noch nicht in einem solchen Zusammenhang gestellt. Die Ergebnisse unserer Studie haben eine neuartige klinische Präsentation des TTS enthüllt und sollten zu einem Paradigmenwechsel in der klinischen Praxis führen, der behandelnde Ärzte dazu veranlassen sollte, an das facettenreiche Auftreten eines TTS besonders auch nach erfreulichen Erlebnissen zu denken.

Ein noch unbekannter Pathomechanismus


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Literatur
Die vollständige Literaturliste finden Sie in der Online-Version dieses Artikels unter www.cardiovascmed.ch.
Exacerbations of COPD should not be underestimated and should be prevented when possible

COPD exacerbation and prevention

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Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Introduction and definition

Chronic obstructive pulmonary disease (COPD), a common, preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [1]. COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing [2].

Globally, as of 2010, it affected approximately 329 million people (4.8% of the population) [3]. Presently, COPD is the third leading cause of mortality in the world [4].

An exacerbation of COPD is characterised by a change in the patient's baseline dyspnoea, cough and/or sputum that is acute in onset, beyond usual day-to-day variation, and may warrant a change in regular medication, in a patient with underlying COPD [5].

Epidemiology

Based on data collected in the observational study Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) [6], exacerbations become more frequent as the severity of disease increases and can lead, through dynamic hyperinflation, to life-threatening respiratory failure. Diagnosis of acutely exacerbated COPD (AECOPD) is based on Anthonisen’s criteria. It is assessed through careful history-taking, observation of clinical signs and consideration of certain laboratory parameters. Differential diagnoses, especially a cardiac origin for the patient’s symptoms, should be excluded. Most COPD exacerbations are associated with viral and bacterial infections. Even though the exact role of the lung microbiome is still subject to debate, we do know that its composition changes during an exacerbation. Several biomarkers for AECOPD, such as percentage of blood eosinophils, are being investigated. Episodes of AECOPD carry an increased risk for cardiovascular events, possibly the consequence of an underlying systemic inflammation. Elevated levels of N-terminal prohormone of brain natriuretic peptide and troponin T predict increased mortality during exacerbations. Coronary angiography is a valuable diagnostic and therapeutic tool in this context. Smoking cessation, influenza and pneumococcal vaccines, optimising therapy (including inhaler technique and treatment with long-acting inhaled bronchodilators) reduce the number of exacerbations. Adding inhaled corticosteroids and phosphodiesterase-4 inhibitors may be of benefit. Pulmonary rehabilitation reduces the risk of rehospitalisation after a recent exacerbation. Long-term immunomodulation with azithromycin can be used in patients with frequent exacerbations who are nonsmokers. Acute exacerbations of COPD are an important event in the course of the disease, can irreversibly accelerate lung function decline and are associated with significant mortality. Their prevention and treatment is therefore of utmost importance. It has recently become clear that several different phenotypes of COPD patients exist, for stable disease and exacerbations, which could guide optimal therapy in the future.

Key words: acute; exacerbation; COPD
studies, the risk of developing an exacerbation correlates with advanced age, productive cough, duration of COPD, preceding courses of antibiotic therapy, hospitalisation due to an exacerbation in the previous year, a peripheral blood eosinophil count >0.3 × 10^9 cells/l and the presence of multiple associated comorbidities (eg, coronary artery disease, chronic heart failure, or diabetes) [7–13]. Other risk factors for COPD exacerbation are gastro-oesophageal reflux disease and pulmonary hypertension [14, 15].

Pathophysiology

In stable COPD patients, pulmonary function tests are used for diagnosis, characterisation and follow-up. However, spirometry or peak flow measures for the diagnosis of an acute exacerbation are not recommended. The main mechanism leading to respiratory failure during a severe exacerbation is expiratory flow limitation, causing lung hyperinflation with serious mechanical consequences [16].

During an exacerbation, worsening expiratory flow limitation results in dynamic hyperinflation with increased end-expiratory lung volume (EELV) and residual volume (RV). Corresponding reductions occur in inspiratory capacity (IC) and inspiratory reserve volume (IRV). Total lung capacity (TLC) is unchanged. Mechanically, increased pressures must be generated to maintain tidal volume (TV). At end-expiration during exacerbations, intrapulmonary pressures do not return to zero, representing the development of intrinsic positive end expiratory pressure (PEEPi) which imposes increased inspiratory threshold loading (ITL) on the inspiratory muscles; during the subsequent respiratory cycle, PEEPi must first be overcome in order to generate inspiratory flow.

In COPD patients, the available time for lung emptying during spontaneous breathing is often insufficient to allow EELV to reach its natural relaxation volume. This leads to lung hyperinflation. Dynamic hyperinflation is defined by an acute and variable increase in EELV above its baseline value. It occurs as a consequence of an abrupt increase in airway resistance during COPD exacerbation, secondary to sputum overproduction and plugs, bronchospasm and mucosal oedema. In stable COPD, respiratory muscles adapt to chronic thoracic hyperinflation at rest. But these adjustments may become inadequate in the event of a sudden increase of dynamic hyperinflation (DH). Acute DH shortens inspiratory muscles, flattening the diaphragm and causing respiratory muscle weakness. Exposure to oxidative stress and lactic acidosis may also contribute to muscular exhaustion in the setting of an exacerbation [17].

Arterial oxygen desaturation, carbon dioxide retention and acidosis lead to an increased central respiratory drive but also produce neuromechanical dissociation. In the presence of limited respiratory flow, this produces a worsening ventilation/perfusion (V/Q) mismatch and increases the shunt fraction finally resulting in respiratory failure [18].

**Diagnosis and assessment**

The diagnosis of an exacerbation relies exclusively on a patient’s clinical presentation: dyspnoea, cough, and/or sputum production that is beyond normal day-to-day variation. Based on Anthonisen’s criteria, type 1 exacerbation is defined as the occurrence of increased dyspnoea, sputum volume and sputum purulence. Type 2 exacerbation is characterised by the presence of two of these three symptoms, and type 3 refers to the presence of only one of these symptoms in addition to at least one of the following: upper respiratory tract infection (sore throat, nasal discharge) within the past 5 days; fever without any other identifiable cause; increased wheezing; increased cough; or an increase in respiratory rate or heart rate by 20% compared with baseline [19].

The assessment of a COPD exacerbation is based on the patient’s medical history and clinical signs of severity as well as some laboratory tests, if available [1] (table 1). Several tests should be considered to assess the severity of an exacerbation:

- Pulse oximetry is useful for monitoring and adjusting supplemental oxygen therapy.

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Figure 1: Association of disease severity with the frequency and severity of exacerbations during the first year of follow-up in patients with COPD. (Adapted from Hurst JR, Vestbo J, Anzueto A, et al. N Engl J Med. 2010;363:1128–38; reprinted with permission).
The measurement of arterial blood gases is vital if the coexistence of acute or acute-on-chronic respiratory failure is suspected: PaO₂ < 8.0 kPa (60 mm Hg) with or without PaCO₂ > 6.7 kPa (50 mm Hg) breathing ambient air.

Assessment of acid-base status is necessary before initiating mechanical ventilation.

Chest radiographs are useful for excluding alternative diagnoses.

An ECG may help for the diagnosis of coexisting cardiac problems.

The whole blood count may identify polycythaemia (haematocrit >55%), anaemia or leucocytosis. Moreover, eosinophilia has been associated with an increased risk of readmission in severe COPD exacerbations [63].

Spirometry is not recommended during an exacerbation because it can be difficult to perform, and measurements are considered not accurate enough.

The presence of purulent sputum can be a sufficient indication for starting empirical antibiotic treatment. A sputum culture with antibiotic sensitivity tests should be performed.

**Differential diagnosis**

COPD patients who present to the hospital with acute worsening of dyspnoea should be evaluated for potential alternative diagnoses, such as heart failure, cardiac arrhythmia, pulmonary thromboembolism, pneumonia, pleural effusion and pneumothorax [19].

One study reported a series of 43 consecutive patients who were admitted to hospital for an acute COPD exacerbation and died within 24 hours of hospitalisation [20]. Despite the small size of the study, there were several notable findings. First, the leading cause of death was, surprisingly, not respiratory failure but cardiac failure, accounting for 37% of all deaths, followed by pneumonia and thromboembolic events, each contributing 28% and 21%, respectively, to total mortality. Only 14% of deaths could be primarily attributed to respiratory failure secondary to COPD.

A recent systematic review including 880 patients with unexplained AECOPD found a pooled prevalence of 16.1% of pulmonary embolism on HRCT-angiography [64]. Two thirds of these emboli were found on occasions with a clear indication for anticoagulation, emphasising the clinical importance of these results.

**Aetiology, triggers and biomarkers**

COPD exacerbations are heterogeneous events that are now thought to be caused by complex interactions between the host, respiratory viruses, airway bacteria and environmental pollution, leading to an increase in the inflammatory burden [21].

Viral and bacterial infections are associated with the vast majority of severe COPD exacerbations requiring hospitalisation, and presence of infection is related to exacerbation severity [22] (table 2).

A study examined 64 patients with COPD when hospitalised for exacerbations as well as in stable convalescence, using sputum sample cultures and polymerase chain-reaction (PCR) analysis for respiratory virus, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Of the 64 samples analysed, respiratory viruses were detected in 31 (48%) sputum samples during exacerbations: 17 rhinovirus, seven influenza virus, four respiratory syncytial virus (RSV), two parainfluenza virus, two coronavirus and three human metapneumovirus (HMPV). On the other hand, respiratory viruses were detected in only four (6.25%) sputum samples during exacerbations: two rhinovirus and two RSV (significantly less than during exacerbations, p < 0.001). Positive bacterial cultures were obtained from 35 (54.7%) sputum samples during exacerbations: nine

### Table 1: Assessment of COPD exacerbations.

<table>
<thead>
<tr>
<th>Medical history</th>
<th>Severity of COPD based on degree of airflow limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of worsening or new symptoms</td>
<td>Number of previous episodes (total/hospitalisations)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Present treatment regimen</td>
</tr>
<tr>
<td>Previous use of mechanical ventilation</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs of severity</th>
<th>Use of accessory respiratory muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paradoxic chest wall movements</td>
<td>Worsening or new onset central cyanosis</td>
</tr>
<tr>
<td>Development of peripheral oedema</td>
<td>Haemodynamic instability</td>
</tr>
<tr>
<td>Deteriorated mental status</td>
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</tbody>
</table>

### Table 2: Most common bacterial and viral pathogens isolated from patients with COPD exacerbations.

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Haemophilus influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moraxella catarrhalis</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td></td>
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<tr>
<td>Pseudomonas aeruginosa</td>
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</table>

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Rhinovirus</th>
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<tbody>
<tr>
<td>Coronavirus</td>
<td></td>
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<tr>
<td>Influenza</td>
<td></td>
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<tr>
<td>Parainfluenza</td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td></td>
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<tr>
<td>Respiratory syncytial virus</td>
<td></td>
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</tbody>
</table>
Haemophilus influenzae, eight Streptococcus pneumoniae, seven Moraxella catarrhalis, four Staphylococcus aureus; four Pseudomonas aeruginosa, three Enterobacter spp. Only 24 (37.5%) positive bacterial cultures were obtained in convalescence: six H. influenzae, five S. pneumoniae, four M. catarrhalis, four S. aureus, three Enterobacter spp., two P. aeruginosa (p = 0.08 vs exacerbations). The bacterial load in positive samples was 106 cfu/ml or more. Samples yielding a bacterial growth of 107 cfu/ml or more were as follows: 27 at exacerbation (77% of the positive samples) and only 12 in stable conditions (50% of the positive samples; p <0.01).

Increasing evidence suggests that the lung microbiome plays an important role in COPD severity. However, its dynamics during COPD exacerbations and its potential role in disease aetiology remain poorly understood [23]. Bafadhel and colleagues conducted a study evaluating microbiome dynamics in samples collected from 87 subjects with COPD at four visits defined as stable state, exacerbation, 2 weeks post-therapy and 6 weeks recovery. Interestingly, distinct microbiome profiles at both phylum and genus levels were observed during exacerbations across different phenotypes (fig. 2). Compared with the other subgroups, differences were greatest for bacterial and eosinophilic exacerbations. Dynamic microbiome changes during COPD exacerbations are potentially implicated in mediating inflammatory host responses. This opens a field for new biomarkers and respiratory therapeutics.

The diagnosis of COPD exacerbations relies on the patient’s clinical presentation. The need for specific biomarkers supporting the diagnosis and facilitating tailored therapeutic decisions has prompted investigators to seek for clusters of molecules in this field. The most studied blood-based biomarkers are C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and eosinophils. Bafadhel and colleagues investigated serum and sputum biomarker expression in COPD exacerbations according to different phenotypes: bacteria-, virus-, and sputum eosinophil-associated. The biomarkers that best identified these clinical phenotypes were sputum IL-1β with an area under the receiver operating characteristic curve (ROC) of 0.89 (95% confidence interval [CI] 0.83–0.95); serum CX-C motif chemokine ligand 10 (CXCL10) (ROC 0.83, 95% CI 0.70–0.96); and percentage of peripheral eosinophils (ROC 0.85, 95% CI 0.78–0.93), respectively [24]. These results pave the way to the future use of phenotype-specific biomarkers to direct therapy.

Procalcitonin (PCT) and CRP have also been studied as biomarkers for guiding antibiotic therapy in patients with AECOPD requiring hospitalisation. In a randomised controlled trial, Stolz and colleagues found a reduction in antibiotic use for up to 6 months in a PCT-guided therapy group, but there was no difference regarding clinical outcomes or FEV1 at 14 days and at 6 months. The exacerbation rate, the readmission rate and the mean time to the next exacerbation were similar in both groups [65]. In another study, CRP and PCT performed similarly as predictors of clinical outcome and bacterial presence, but even patients with low PCT levels (<0.1 μg/l) seemed to benefit from antibiotic treatment. The authors therefore suggested that CRP might be a more valuable marker in these patients [66]. Other investigations have demonstrated that elevated levels of CRP, fibrinogen and leucocyte count in individuals with COPD were associated with an increased risk of exacerbations [25].

**Cardiovascular consequences**

Cardiovascular disease is an important comorbidity in patients with COPD. Patients suffering from COPD exacerbations are at increased risk of cardiovascular events, and about one third of COPD patients die of cardiovascular disease [26]. This might be a consequence of the systemic inflammation that is associated with acute exacerbations. Donaldson and colleagues found a 2.27-fold (95% CI 1.1–4.7; p = 0.03) increased risk of...
myocardial infarction 1 to 5 days after exacerbation [27, 28]. In a cohort of patients admitted to hospital for AECOPD, Chag et al. investigated the association between plasma levels of cardiac biomarkers (N-terminal prohormone of brain natriuretic peptide [NT pro-BNP] and troponin T) and mortality. Elevated NT-proBNP (≥220 pmol/l) was present in 65/244 patients (27.5%) and significantly predicted 30-day mortality (odds ratio [OR] 9.0, 95% CI 3.1–26.2, p <0.001). Elevated troponin T (>0.03 μg/l) was found in 40/241 patients (16.6%) and significantly predicted 30-day mortality [OR 9.0, 95% CI 3.1–26.2, p <0.001]. NT-proBNP and troponin T levels appeared to have additive associations with mortality: 30-day mortality among patients with abnormalities of both NT-proBNP and troponin T was 15-fold higher than among patients with normal values [29].

Pizarro and colleagues studied the diagnostic value of coronary angiography in patients with AECOPD and elevated cardiac troponin. Coronary angiography confirmed the presence of ischaemic heart disease in 59 patients (67.0%), 34 of whom (38.6% of the total study population) underwent percutaneous coronary intervention. Among these, the vast majority (n = 26, 76.5%) had no previously known ischaemic heart disease, whereas only 8 out of the 34 patients (23.5%) gave a history of ischaemic heart disease. Patients requiring coronary intervention had significantly reduced left ventricular ejection fraction (45.8 ± 13.1% vs 55.1 ± 13.3%, p = 0.01) and more often electrocardiographic ST-segment depression (20.6% vs 7.4%, p = 0.01). These results should raise awareness for ischaemic heart disease in acutely exacerbated COPD patients requiring hospitalisation and presenting with high troponin levels [30].

**Prevention**

COPD exacerbations can often be prevented. Smoking cessation, influenza and pneumococcal vaccines, optimal therapy including a check of inhaler technique and adherence, treatment with long-acting inhaled bronchodilators, combined or not with inhaled corticosteroids, and possibly phosphodiesterase-4 inhibitors, reduce the number of exacerbations and hospitalisations.

**Influenza and pneumococcal vaccination**

Influenza vaccination is currently recommended in COPD patients, mainly based on observational studies showing a decreased number of exacerbations and hospitalisations in vaccinated patients. A Cochrane systematic review by Poole, based on randomised control trials, found a significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo (weighted mean difference −0.37, 95% CI −0.64 to −0.11, p = 0.006) [31].

COPD patients have an increased risk of pneumococcal infection. To our knowledge, there is no trial evaluating the impact of pneumococcal vaccination on COPD exacerbations. Decisions about vaccination in COPD patients depend on local policies. Nevertheless, a randomised control trial carried out in 596 COPD patients showed that the 23-valent pneumococcal polysaccharide vaccine (PPV) is effective in preventing community-acquired pneumonia, mainly in patients aged less than 65 years and with severe obstruction [67]. A recent study evaluating the cost-effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) in COPD patients older than 50 years in Spain demonstrated higher health benefits than vaccination with the polysaccharide vaccine [32].

**Smoking cessation**

Smokers with mild COPD who cough and produce phlegm achieve substantial symptom reduction in the first year after smoking cessation, with less lung function decline and lesser symptoms upon sustained cessation. In general, effective smoking cessation programmes include behavioural, physiological and psychological components, comprising an acknowledgment of current smoking followed by advice to quit, pharmacological therapies (nicotine replacement therapy, antidepressants, nicotine receptor modifier therapy) and counselling. Although the effect of and evidence for smoking cessation in the prevention of acute exacerbations of COPD are low, this should be considered the most important intervention for all COPD patients regardless of the degree of disease severity.

**Pulmonary rehabilitation**

It has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance, and dyspnoea, reducing the risk of hospitalisations in patients with COPD who have had a recent exacerbation (i.e., <4 weeks post-hospitalisation). Pulmonary rehabilitation does not directly improve lung mechanics or gas exchange. Rather, it optimises the function of other organ systems and therefore minimizes the effect of lung dysfunction [33].

A systematic review and meta-analysis including 18 cohort studies and randomised controlled trials showed that the control groups had a higher overall rate of hospitalisation than did the pulmonary rehabilitation groups (control: 0.97 hospitalisations/patient-year, 95% CI 0.67–1.40; rehabilitation: 0.62 hospitalisations/patient-year, 95% CI 0.33–1.16) [34].
Pharmacological treatment

Long-acting bronchodilators

The use of long-acting β2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) alone or in combination is recommended for most COPD patients. Bronchodilation improves expiratory airflow and decreases air trapping. Both LABAs and LAMAs have proven their efficacy in reducing exacerbations compared with placebo when used alone or in combination [37–41]. Some studies comparing the effectiveness in reduction of exacerbation rates between LABAs and LAMAs suggest that the latter have a greater impact [42, 43]. Dual bronchodilation (LABA/LAMA) has shown superiority in AECOPD reduction when compared with other therapeutic options. The LANTERN study of moderate-to-severe COPD patients found a significant 31% reduction in moderate or severe exacerbations with indacaterol/glycopyrronium (IND/GLY) compared with salmeterol / fluticasone propionate (SFC), even though exacerbations were not a primary endpoint [44]. Recently, the FLAME study demonstrated that IND/GLY was more effective than SFC in preventing AECOPD in patients with a history of exacerbations during the previous year. The annual rate of moderate or severe exacerbations was lower in the IND/GLY group than in the SFC group (0.98 vs 1.19; rate ratio 0.83 95% CI 0.75–0.91; p <0.001), and the time to the first moderate or severe exacerbation was longer in the IND/GLY group than in the SFC group (hazard ratio 0.78, 95% CI 0.70–0.86; p <0.001), as was the time to the first severe exacerbation (hazard ratio 0.81, 95% CI 0.66–1.00; p = 0.046) [45].

Long-acting bronchodilators and inhaled corticosteroids

GOLD recommends inhaled treatment with a LABA plus inhaled corticosteroids (ICS) combination for COPD patients with ≥2 exacerbations (or one exacerbation requiring hospitalisation) [19]. Patients with asthma/COPD overlap syndrome (ACOS) probably benefit from ICS because of the predominant eosinophilic phenotype in ACOS patients. An association between the sputum eosinophil count and the response to ICS has been demonstrated in a randomised, double-blind, crossover trial of mometasone furoate versus placebo. Compared with placebo, the net improvement in post-bronchodilator FEV1 increased with mometasone progressively from the least to the most eosinophilic tertile [46]. In the study Towards a Revolution in COPD Health (TORCH), a randomised, double-blind trial compared salmeterol at a dose of 50 μg plus fluticasone propionate at a dose of 500 μg twice daily (combination regimen, SFC), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone for a period of 3 years. SFC was associated with a 25% reduction in exacerbation rate versus placebo (p <0.001), a 12% reduction versus salmeterol (p = 0.002) and a 9% reduction versus fluticasone propionate (p = 0.02) [47]. A study including GOLD class III–IV patients with ≥1 exacerbation in the previous year, a combination of budesonide/formoterol significantly reduced the risk of exacerbations by 28.5, 22.7 and 29.5% versus placebo, budesonide and formoterol, respectively (p <0.05 for all) [48].

Because of the increased risk of pneumonia, osteoporosis/fractures, diabetes and other potential side effects, the safety of long-term ICS treatment is still subject to debate. The WISDOM trial, a 12-month, double-blind, parallel-group study including 2485 severe and very severe COPD patients with a history of exacerbation, evaluated the time to the first moderate to severe exacerbation in patients on triple inhaled therapy (LAMA/LABA/ICS): those who withdrew from ICS therapy but remained on LABA/LAMA were compared with those who remained on ICS with LABA/LAMA. In patients with severe COPD receiving tiotropium and salmeterol, the risk of moderate or severe exacerbations was similar amongst those who stopped inhaled glucocorticoids and those who continued them. However, there was a greater decrease in lung function during the final step of glucocorticoid withdrawal [49].

Switching from LABA/ICS to LABA monotherapy seems to be safe in patients at low risk of exacerbation. In the INSTEAD trial (Indacaterol: Switching Non-exacerbating Patients with Moderate COPD From Salmeterol/Fluticasone to Indacaterol), the withdrawal of ICS occurred with no efficacy loss [50].

Triple inhaled therapy (LABA/LAMA/ICS)

The addition of LAMA to LABA/ICS combined therapy showed to be of benefit in COPD patients with post-bronchodilator FEV1 lower than 50%, one or more moderate-to-severe COPD exacerbations in the previous 12 months, and COPD Assessment Test total score of 10 or more. The TRILOGY study showed, over a mean follow-up of 4.65 years, that triple therapy with beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide (BDP/FF/GB) was associated with a 35% reduction in all-cause mortality (p <0.001), a 29% reduction in moderate exacerbations (p <0.001) and a 15% reduction in severe exacerbations (p = 0.04) compared with beclometasone dipropionate and formoterol fumarate (BDP/FF) treatment alone [51].
Phosphodiesterase-4 inhibitors

Phosphodiesterase-4 (PDE-4) inhibitors (roflumilast and cilomilast) have been demonstrated to be useful for COPD patients who are at high risk of exacerbations and have a chronic bronchitis phenotype [19]. In this particular group of patients, roflumilast is associated with a reduction of 13–17% in moderate/severe exacerbations when compared with placebo [52, 53].

A double-blind, placebo-controlled trial evaluated roflumilast in exacerbated severe or very severe COPD patients with two or more exacerbations/hospitalisations in the previous year. Roflumilast failed to statistically significantly reduce moderate and/or severe exacerbations in the overall population, but improved lung function and reduced exacerbations in participants with frequent exacerbations (more than three) and/or history of hospitalisation [54]. Tolerability of roflumilast may be a limitation for more extensive use in severe COPD. Its most common adverse effects are gastrointestinal, specifically diarrhea and weight loss. Psychiatric effects (insomnia, anxiety, depression / suicidal behaviour) also occurred more often with roflumilast than with placebo in clinical trials [55]. Nevertheless, roflumilast, as part of a combination regimen with long-acting bronchodilators with or without ICS, appears to be a reasonable treatment option for patients with severe to very severe COPD associated with chronic bronchitis and a history of exacerbations despite optimal inhaled therapy.

Macrolide antibiotics

COPD exacerbations are generally thought to arise as a result of a complex interplay between bacterial and/or viral infection associated with an aberrant immune response. A Cochrane systematic review of seven randomised controlled trials involving 3170 patients found that continuous use of macrolide antibiotics as prophylactic therapy resulted in a significant reduction of exacerbations (OR 0.55, 95% CI 0.30–0.77) [56]. There are, however, no data on macrolide efficacy and safety beyond 1 year.

Long-term use of antibiotics may induce bacterial resistance. Macrolide resistance has indeed been documented in COPD patients treated with this approach [57]. Continuous macrolide treatment is also associated with gastrointestinal events, whereas hearing loss or QT segment prolongation seem very rare and are probably dose dependent [68]. In addition, little evidence of a treatment benefit has been found among current smokers [58]. Thus, long-term treatment with azithromycin should be reserved for nonsmokers who suffer from frequent exacerbations despite optimal inhaled therapy.

N-acetylcysteine and other mucolytic agents

Oxidants have long been known to play an important role in the pathogenesis of COPD. Cigarette smoke generates a significant amount of oxidant radicals, which can modify the structure of the respiratory tract and sustain lung inflammation in COPD through several mechanisms. Therefore, exogenous supplementation of antioxidant compounds could at least partially counteract the oxidative stress. N-acetylcysteine (NAC) has great potential owing to its capacity to directly oppose oxidants with its free thiols, and to its ability to act as a donor of cysteine precursors aimed at glutathione restoration [59].

A recent systematic review evaluated the effect of mucolytic agents compared with placebo, including 34 randomised controlled trials recruiting a total of 9367 participants. Results showed that the chance of being exacerbation-free during the study period was greater among mucolytic groups (Peto OR 1.75, 95% CI 1.57–1.94). Compared with placebo, use of mucolytics was associated with a reduction of 0.03 exacerbations per participant per month (mean difference −0.03, 95% CI −0.04 to −0.03; 7164 participants; 28 studies; I² = 85%), that is, about 0.36 per year, or one exacerbation every 3 years [60]. However, these results should be interpreted with caution because there were considerable differences in the patient populations and definitions of exacerbation. Some of these studies included patients with chronic bronchitis, without the requirement for COPD criteria. Besides, there was also a wide range of mucolytic dosages prescribed. A meta-analysis including 13 studies and 4155 patients (NAC n = 1933, placebo or controls n = 2222) showed that patients treated with NAC had significantly and consistently fewer exacerbations (relative risk 0.75, 95% CI 0.66–0.84; p < 0.01), NAC was well tolerated and the risk of adverse reactions was not dose-dependent (low doses ≤600 mg per day: relative risk 0.93, 95% CI 0.89–0.97; p = 0.40; high doses >600 mg per day: relative risk 1.11, 95% CI 0.89–1.39; p = 0.58) [61].

Erdosteine, a mucolytic agent with anti-inflammatory, antioxidant and bacterial antiadhesive properties, has recently been reported to reduce the rate (17%) and duration (44%) of exacerbations compared with placebo in GOLD moderate to severe COPD patients and at least two exacerbations in the previous year [62].

The results on the therapeutic effect of NAC on AECOPD have been encouraging, even if much of the data come from the larger trials conducted in Chinese populations. High-dose oral NAC offers interesting perspectives as add-on therapy for COPD patients.
**Beta-blockers**

Cardiovascular disease is a primary cause of death in patients with COPD. Retrospective studies have suggested that beta-blocker use in patients with COPD is associated with a reduction in the frequency of acute exacerbations as well as with lower mortality. A meta-analysis based on observational studies revealed that beta-blocker treatment significantly decreased the risk of overall mortality and exacerbation of COPD [35]. In a prospective follow-up of the COPDGene cohort based on GOLD class 2 to 4 COPD patients, beta-blocker use was associated with a significantly lower rate of total (incidence risk ratio (IRR) 0.73, 95% CI 0.60–0.90; p = 0.003) and severe exacerbations (IRR 0.67, 95% CI 0.48–0.93; p = 0.016). In those with GOLD stage 3 and 4 and on home oxygen, use of beta-blockers was again associated with a reduction in the rate of total exacerbations (IRR 0.32, 95% CI 0.19–0.58; p <0.001) and severe exacerbations (IRR 0.35, 95% CI 0.16–0.76; p = 0.008). Exacerbation reduction was greatest in GOLD stage B. There was no difference in all-cause mortality with beta-blocker use [36].

**Conclusions**

Exacerbations of COPD are important events in the course of the disease. Given their detrimental impact, they should not be underestimated, and their prevention should be a key goal of COPD treatment. AECOPD negatively affect a patient’s quality of life and symptoms. Lung function may take several weeks to recover or its decline may be accelerated. Exacerbations are associated with significant mortality, particularly in those who require hospitalisation. In-hospital mortality of patients admitted for a hypercapnic exacerbation with acidosis is approximately 10%. Mortality reaches 40% at 1 year after discharge in those needing mechanical ventilation, and all-cause mortality 3 years after hospitalisation is as high as 49%. Exacerbations are associated with a high socioeconomic burden, accounting for most of COPD-related healthcare expenditure.

It can be helpful to consider exacerbations as heterogeneous events, as their nature seems to differ between different subgroups of patients, presenting as different phenotypes. Exacerbations can be triggered by many factors. The most common appear to be viral or bacterial respiratory tract infections. Peaks of air pollution or maintenance therapy discontinuation can also precipitate AECOPD. In one third of cases, the exact cause cannot be identified. Conditions that mimic and/or are associated with exacerbations, particularly those of cardiovascular origin, need to be considered and appropriately treated if present.

COPD exacerbation can often be prevented. Smoking cessation, and influenza and pneumococcal vaccination should be encouraged; current therapy and inhaler technique should be regularly checked. Pulmonary rehabilitation increases quality of life and reduces hospitalisation rates. Fixed LABA/LAMA combination therapy significantly decreases exacerbations. The significance of blood or sputum eosinophils is not yet completely understood, but they probably predict responsiveness to ICS. ACOS patients may be particularly likely to benefit from ICS/LABA therapy, having a predominantly eosinophilic phenotype. On the other hand, ICS therapy can probably be safely withdrawn in patients at low risk of exacerbations. Triple LABA/LAMA/ICS combination therapy is superior to LABA/ICS in preventing exacerbation. Azithromycin, roflumilast and N-acetylcysteine further reduce exacerbation rates in patients with frequent exacerbations/hospitalisations, but their tolerability can be problematic. Here we present our proposition of inhaled treatment for symptomatic COPD patients (fig. 3).

**Disclosure statement**

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**References**

The full list of references can be found in the online version of this article on www.cardiovascmed.ch.
A patient with atrioventricular block and a family history of dilated cardiomyopathy

Lamin A/C cardiomyopathy: case report and review of the literature

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Summary

A 45-year-old man known for bradycardia underwent cardiac evaluation because of complete atrioventricular block. His mother underwent heart transplantation at the age of 60 for dilated cardiomyopathy. Echocardiography revealed mild left ventricular dilatation, and a subnormal left ventricular ejection fraction (LVEF) of 50% due to septal hypokinesia. Cardiac magnetic resonance imaging showed linear mid-myocardial late gadolinium enhancement of the basal septum, indicating myocardial fibrosis. We decided to implant a dual chamber pacemaker programmed in DDD modality. On the basis of the clinical history we suspected a lamin A/C (LMNA) mutation cardiomyopathy. A known pathogenic heterozygote mutation c.1129C>T (p.Arg377His) in the LMNA gene was identified, confirming the diagnosis of LMNA cardiopathy. At this time we suggested an upgrade to an implantable cardioverter-defibrillator in order to prevent sudden cardiac death, but the patient refused. Eighteen months after the pacemaker implantation the patient is alive and well.

Key words: dilatative cardiomyopathy; lamin A/C

Case report

A 45-year-old man known for bradycardia for at least 5 years underwent a cardiac evaluation in our department. He had no symptoms and took no medication. His family history revealed that his mother underwent heart transplantation at the age of 60 for dilated cardiomyopathy (DCM). On physical examination he appeared in excellent condition, with weight 90 kg for a height of 185 cm. The pulse was regular and bradycardic at 39 bpm, blood pressure was 130/80 mm Hg. Cardiac and chest auscultation were unremarkable. Chest x-ray showed a slightly dilated cardiac silhouette. The ECG revealed sinus rhythm with 2:1 atrioventricular block (AVB) (fig. 1) alternating with complete AVB (fig. 2). During Holter monitoring there was normal sinus rhythm with persistent high-degree AVB (Mobitz type 2; advanced second degree – 2:1 and 3:1 – and complete AVB) with mean ventricular rate 41 bpm and maximum R-R interval of 4 s. An echocardiogram revealed mild left...
ventricular dilatation (left ventricular end-diastolic diameter 62 mm), and a subnormal left ventricular ejection fraction (LVEF) of 50% due to septal hypokinesia. Cardiac magnetic resonance imaging (CMR) confirmed the mild left ventricular dilatation and showed linear mid-myocardial late gadolinium enhancement of the basal septum, indicating myocardial fibrosis (fig. 3). On the basis of the family history of DCM, the complete AVB, the mild left ventricular dilatation with sub-normal LVEF and linear mid-myocardial septal fibrosis, we suspected cardiomyopathy due to a lamin A/C (LMNA) gene mutation.

We decided to implant a dual chamber pacemaker programmed in DDD modality (fig. 4) and performed genetic testing using the TruSight Cardio Panel (Illumina, San Diego, USA), which includes 176 genes. All associated mutations/variants were confirmed by direct Sanger sequencing. A known disease-causing heterozygote missense mutation c.1129C>T (p.Arg377His) in the LMNA gene was identified, confirming the diagnosis of LMNA cardiopathy. Six months after pacemaker implantation the patient remained asymptomatic. Left ventricular dimension and function were unchanged. The pacemaker memory showed an episode of atrial arrhythmia (atrial flutter and atrial fibrillation) lasting 15 days, and several short episodes of relatively slow
(150–180 bpm) nonsustained ventricular tachycardia (fig. 5). Beta-blocker therapy was initiated but after a few weeks was stopped because of side effects.

At this time the question was: "What to do? Upgrade to a defibrillator (ICD)? To a resynchronisation system (CRT)? Close clinical follow-up?"

After extensive discussion with the patient, and considering that he had several risk factors for malignant ventricular arrhythmia, we suggested an upgrade to an ICD in order to prevent sudden cardiac death (SCD). Nevertheless, the patient refused our proposal. Eighteen months after the pacemaker implantation, the patient is alive and well. He has two sisters, who are asymptomatic with a normal ECG and echocardiogram. A genetic analysis has been planned.

**Discussion**

DCM is characterised by a dilated left ventricle with systolic dysfunction that is not caused by ischaemic or valvular heart disease [1]. The prevalence is about 1 DCM case in 2500 individuals [2]. DCM is currently responsible for approximately 10 000 deaths and 46 000 hospitalisations each year in the United States [3]. Despite a comprehensive evaluation, about 50% of cases lack an underlying diagnosis and are classified as idiopathic DCM [4]. Familial DCM accounts for up to 50% of all cases of idiopathic DCM [5]. LMNA gene mutations are one of the most frequent genetic abnormalities involved in DCM and it has been estimated that LMNA mutations cause up to 10% of familial DCM [6]. Lamin A and C are both encoded by the LMNA gene, which is localised to chromosome 1q21.2-q21.3 [7]. Lamins are type V intermediate filament proteins that are able to polymerise and form the nuclear lamina, an organised meshwork that lies between the inner nuclear membrane and the chromatin [8]. Mutations in LMNA are highly penetrant and may cause severe and progressive cardiopathy in a relevant proportion of patients. Furthermore, patients carrying a mutation in the LMNA gene may have one of several forms of muscular dystrophy such as Emery-Dreifuss muscular dystrophy [9], autosomal dominant limb girdle muscular dystrophy [10], or sensory and motor axonal neuropathy Charcot-Marie-Tooth type 2 [11].

LMNA mutations are associated with cardiac abnormalities characterised by arrhythmias (sinus node dysfunction, AVB, atrial and ventricular arrhythmias) and DCM leading to heart failure [12, 13]. Fatkin et al. [14] evaluated the clinical features of LMNA mutations in 39 affected patients with cardiac involvement. The study showed that the onset of disease occurred in middle age (mean age 38 years, range 19–53 years). Eighty-seven percent had sinus-node dysfunction or atrioventricular disturbances (sinus bradycardia, or first-, second- or third-degree heart block). Atrial fibrillation or atrial flutter were present in 59% of affected people and 64% had DCM. Pacemakers were implanted, owing to high-grade AVB or brady-arrhythmias, in 54% of affected patients. Oftentimes LMNA cardiopathy, conduction disturbances or arrhythmia anticipate left ventricular dysfunction [12–15]. It was the case in our

**Figure 4:** After DDD pacemaker implantation: sinus rhythm 65 bpm with sequential atrio-ventricular pacing.
patient with AVB, atrial arrhythmia and nonsustained ventricular tachycardia, but preserved LVEF. In addition to history, ECG and echocardiography, CMR plays an important role in determining cardiac involvement in LMNA cardiomyopathy. Holmström et al. [16] showed that 88% of patients with LMNA cardiomyopathy had left ventricular myocardial fibrosis. The pattern of enhancement was typically linear and less than 50% of the area of the segment. In all the patients, late gadolinium enhancement occurred in the basal or mid-ventricular septum, which strongly correlated with segmental wall motion abnormalities. Our patient had exactly this typical pattern.

Patient with LMNA cardiopathy have a significantly worse prognosis than other patients with idiopathic DCM [12], with a high incidence of phenotypic progression and adverse arrhythmic and nonarrhythmic events during long-term follow-up. Besides heart failure due to left ventricular dysfunction, arrhythmias are a major threat, and cardiac arrest due to bradyarrhythmia or ventricular arrhythmia has been reported in up to 50% of patients [12–15, 17–19]. Life expectancy is around 50 to 60 years [15, 19].

There is consensus regarding the efficacy of ICD in the primary and secondary prevention of SCD in patients with cardiovascular diseases [20]. In LMNA cardiomyopathy, the risk factors of SCD are incompletely elucidated and have been correlated to several clinical and genetic factors. In a study including 94 patients, New York Heart Association (NYHA) functional class, competitive sporting activity and type of mutation predicted the incidence of heart failure and ventricular arrhythmia [17]. In a multicentre European registry of 269 patients, four independent risk factors for malignant ventricular arrhythmia were identified: nonsustained ventricular tachycardia, LVEF <45%, male sex and non-missense mutations of the LMNA gene [19]. In this study, malignant ventricular arrhythmias occurred only in subjects with at least two of these risk factors and there was a cumulative risk per additional risk factor. Male sex, non-missense mutations and LVEF ≤50% were also associated with malignant ventricular arrhythmias in a recently published multicentre study of 122 patients [15]. In two studies of 47 and 41 patients, malignant ventricular arrhythmias were correlated with atrioventricular conduction disorders even when LVEF

Figure 5: Electrograms from the pacemaker memory. A: Nonsustained ventricular tachycardia (6 complexes, 160–180 bpm). B: Beginning of the episode of atrial arrhythmia. A = atrial electrogram; V = ventricular electrogram; MC = marker channel.
was preserved [21, 22]. It was suggested that implanta-
tion of an ICD in patients requiring a pacemaker should
be considered [21]. The presence of myocardial fibrosis
in the interventricular septum may be the mechanism
of the relationship between atrioventricular conduc-
tion disease and ventricular arrhythmias [21, 22]. No
study so far has evaluated the role of electrophysiological
testing with programmed electrical stimulation or
other testing (e.g., stress testing, etc.) in the risk stratifi-
cation of patients with lamin A/C cardiopathy. Accord-
ing to the 2015 European Society of Cardiology Guide-
lines for the prevention of SCD [20], the implantation of
an ICD is a class IIa recommendation in patients with
DCM due to LMNA mutations and clinical risk factors
(male sex, LVEF <45%, nonsustained ventricular tachy-
cardia, non-missense mutations), and a class IIb recom-
mendation in patients requiring a pacemaker. Our pa-
tient had several risk factors for malignant ventricular
arrhythmias: male gender, advanced AVB and nonsus-
tained ventricular tachycardia. Therefore, we proposed
an up-grade to an ICD.

In patients with LMNA cardiomyopathy needing a pace-
maker, implanting a CRT should be considered, even
with preserved LVEF, because the progressive nature of
the disease leads in a substantial number of patients to
left ventricular dysfunction and heart failure. How-
ever, no study has addressed the preventive role of CRT
in these patients so far.

We have described a patient with LMNA cardiomyop-
athy discovered through a high grade AVB. This case
highlights several important elements. First, in a
young patient with advanced AVB accompanied by left
ventricular dysfunction or family history of DCM, one
should think of LMNA cardiopathy; genetic analysis
can confirm the disease. Second, LMNA cardiopathy
has a poor prognosis, and risk stratification should be
individualised on the basis of several clinical, instru-
mental and genetic factors. In patients deemed at risk
of SCD, an ICD should be considered. Finally, genetic
screening of family members should be offered. Mut-
ation-positive, phenotype-negative patients should
have close electrical and functional follow-up, given
the highly penetrant nature of the disease.

Disclosure statement
No financial support and no other potential conflict of interest
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References
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article at www.cardiovascmed.ch.
Eine Erfolgsgeschichte

20 Jahre Kardiologie am UniversitätsSpital Zürich, 1996–2016

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Die Zeit vor 1996


In den 60-er Jahren des letzten Jahrhunderts kehrte Paul Robert Lichtlen nach einem USA-Aufenthalt an der Johns Hopkins University und einem Besuch bei Mason Soanes an der Cleveland Clinic als Oberarzt an die Medizinische Klinik nach Zürich zurück und führte die Koronarangiographie am damaligen Kantons- spital ein.


komplikationsreichen Methode, so dass sie heute ohne chirurgischen Back-up durchgeführt werden kann. Supraventrikuläre Rhythmusstörungen wurden durch Lukas Kappenberger, später Ordinarius in Lausanne, zunächst intraoperativ mit Marko Turina und danach mit Ablationskathetern im Katheterlabor kurativ behandelt.

Eine Abteilung für Kardiologie


Der Aufbau

Zunächst wurde eine Forschungsabteilung im Institut für Physiologie im Campus Irchel gegründet, die über die Jahre an Bedeutung und Grösse gewann und heute im Campus Schlieren als Center for Molecular Cardiology (www.cmc.ch) 9 Forschungsgruppen mit rund 35 Mitarbeitern umfasst (Abb. 3). Das Center for Molecular Cardiology und seine Vorgängerinstitutionen in Bern und Basel gehören zu den meist zitierten Zentren weltweit. Es hat über die Jahre zahlreiche Mitarbeiter aus über 15 Ländern ausgebildet, die heute bedeutende Position weltweit einnehmen (Abb. 4).


Das Universitäre Herzzentrum


Mit dem Ausbau der Herzkatheterlabors auf nun vier Einheiten (davon ein Hybridsaal) sowie der Einrichtung der ersten zertifizierten «Chest Pain Unit» in der Schweiz konnte die Notfallbetreuung von Patienten in


Abbildung 5: Alumni der Klinik für Kardiologie und ihrer Vorgängerinstitutionen in Basel und Bern, die international leitende Positionen erlangt haben.
stationäre Patienten sowie 600 teilstationäre Patienten und verbuchte in den verschiedenen Sprechstunden rund 10.000 Visiten für ambulante Patienten.

Forschung


Lehre

Ebenso erfolgreich war die Lehre mit Fortbildungsveranstaltungen des «Zurich Heart House» (www.zhh.ch) für Niedergelassene und Spitalärzte am UniversitätsSpital und am «Cardiology Update» in Davos. Weiter bietet die Klinik an der Universität Zürich mit dem «Zurich Heart House» und der «ESC Heart Failure Association» den ersten «Postgraduate Course» für Mediziner an, den «Postgraduate Course in Heart Failure Management», der mit einem «Certificate of Advanced Studies» verbunden ist. An diesem Kurs nehmen 60 Ärzte aus über 30 Ländern teil, was die internationale Ausstrahlung unterstreicht.


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Literatur

Die vollständige Literaturliste finden Sie in der Online-Version dieses Artikels unter www.cardiovascmed.ch.