Cardiovascular Medicine

249 Baris Gencer
Should we measure PCSK9 levels in patients with acute coronary syndromes?

256 Lars C. Huber, Mattia Arrigo
Betablocker und Asthma bronchiale: Ja oder Nein?

261 Aristotelis Panos, Patrick O. Myers
Robotic coronary revascularisation

272 Giuseppe Cocco, Philipp Amiet
Recurring tachycardia and syncope in a young person
Review article

Baris Gencer

Should we measure PCSK9 levels in patients with acute coronary syndromes?

The measurement of PCSK9 is currently poorly implemented in clinical practice. The findings presented here suggest that PCSK9 might be useful for clinicians to identify patients who might need more intensive lipid-lowering therapy (e.g., PCSK9 inhibitors) to lower LDL-C.

Lara C. Huber, Mattia Arrigo

Betablocker und Asthma bronchiale: Ja oder Nein?

Bei entsprechender Indikation sollte auch Patienten mit Asthma bronchiale eine Betablocker-Therapie nicht vorenthalten werden.

Original article

Aristotelis Panos, Patrick O. Myers

Robotic coronary revascularisation

Robotic LITA takedown and minimally invasive off-pump LAD revascularisation results in excellent perioperative outcomes, high graft patency and freedom from angina during follow-up.
Case report

Andreas Y. Andreou, Panayiotis C. Avraamides, Tereza Andoniade, Stasinos Theodorou, Chrisostomos Mavroudis, Theodoros Kyriakou

Iatrogenic left main coronary artery dissection: mind the catheter tip

Management of a potentially life-threatening complication of invasive coronary procedures.

Giuseppe Cocco, Philipp Amiet

Recurring tachycardia and syncope in a young person

A 23-year-old male patient was referred because of syncope during jogging. His first symptoms of cardiac arrhythmia began at the age of 12 years, during physical effort.

Varia

278 Ruth Amstein
Cardiology Update (11–15 February 2017)

Die Lachtherapie für Ihr Wartezimmer!

Christophe Badoux
KRANK GESCHRIEBEN
ISBN 978-3-03731-153-0
48 Seiten, farbig
15 × 19 cm, Hardcover
sFr. 16.–
Bestellnr. E 200
Weitere Informationen finden Sie unter www.emh.ch in der Rubrik „Bücher“.


Third photo on page 247:
© 2016 Intuitive Surgical, Inc.
By the winner of the Swiss Amgen Research Award – based on the award lecture held at the SSC Congress 2016

Should we measure PCSK9 levels in patients with acute coronary syndromes?

Baris Gencer
Cardiology Division, Geneva University Hospitals, Switzerland

Summary

**Background:** Several studies have shown that inhibitors of proprotein convertase kexin 9 (PCSK9) efficiently lowered levels of low-density lipoprotein cholesterol (LDL-C), especially in patients with familial hypercholesterolemia, intolerant of statins or with poorly controlled LDL-C on maximally tolerated statin treatment. However, circulating PCSK9 levels have been little studied in the acute phase of acute coronary syndromes (ACS), especially their evolution over time and association with clinical outcomes.

**Methods and results:** We observed that higher PCSK9 levels at initial presentation of 2030 patients with ACS were associated with the presence of familial hypercholesterolemia, the use of lipid-lowering therapy, the duration of chest pain and inflammation (C-reactive protein). To confirm this hypothesis, we found that PCSK9 levels increased 12–24 hours after ACS, probably with the inflammatory process during ACS. Then we assessed the increment value of adding PCSK9 to recommended risk stratification scores, such as the GRACE score, and found that PCSK9 did not predict mortality at 30 days and at 1 year. However, patients with high initial PCSK9 levels less frequently reached target LDL-cholesterol levels (<1.8 mmol/l) at 1 year.

**Conclusions:** The measurement of PCSK9 is currently poorly implemented in clinical practice. Our findings suggest that PCSK9 might be useful for clinicians to identify patients who might need more intensive lipid-lowering therapy (e.g. PCSK9 inhibitors) to lower LDL-C.

Key words: cardiovascular prevention; lipids; risk factors; pharmacological therapies

The 2016 Swiss Society of Cardiology meeting was a very exciting event in my career. With the publication of the article entitled “Prognostic values of PCSK9 in acute coronary syndrome” in the *European Heart Journal*, I was honoured to receive the 2016 Swiss Amgen Research Award from the Scientific Committee of the Swiss Society of Cardiology [1]. I had the opportunity to present this work during my lecture entitled “Should we measure PCSK9 levels in patients with acute coronary syndromes?”. This award provides not only strong support for young clinicians involved in clinical research, but also a recognition of the scientific activities in Swiss Universities. The project was the fruit of an extensive collaboration between universities and various experts in different fields (preventive medicine specialist, interventional cardiologist, statistician, fundamental and clinical researcher, study nurses). I would like to thank all my valuable colleagues and mentors, in particular Professor François Mach for his support in this project and the Swiss National Science Foundation (SPUM 33CM30-124112 and SPUM 33CM30-140 336). The current article refers to the lecture given during the annual meeting, following a longstanding tradition, of the Swiss Society of Cardiology. In addition to main findings reported in the *European Heart Journal*, this article extends and deepens the discussion and perspectives of a potential new biomarker.

**Dyslipidaemia and atherosclerosis**

Cardiovascular congresses and meetings have shown increasing interest in presenting scientific activities in the field of cardiovascular prevention and dyslipidaemia. Cardiovascular prevention remains the most cost effective intervention to minimise the morbidity related to cardiovascular disease [2]. The recent guidelines for cardiovascular prevention from the European Society of Cardiology (ESC) underlined both population-based and individualised approaches [2]. Lifestyle measures are recommended for everyone to keep a low global level of risk, while more intensive treatments are needed for subjects at high risk. Dyslipidaemias, especially of low-density lipoprotein cholesterol (LDL-C), are well-documented and established risk factors for atherosclerosis and cardiovascular disease (CVD). Treatments lowering LDL-C, such as statins, are associated with a reduction in CVD risk, and guidelines recommend specific targets according to the global
CVD risk [2]. Non-statin agents, such as proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors and ezetimibe, are now considered to be additional options for reaching recommended LDL-C targets.

Summary about discovery and clinical importance of PCSK9

PCSK9 became, in a few years, a major target for the management of hypercholesterolaemia and also a biomarker studied in various association analyses (table I) [3]. Development from the discovery of the loss-of-function mutations to the approval of therapeutic agents (PCSK9 inhibitors) was especially fast and impressive, taking place within a timeframe of 10–15 years [4]. There were several reasons for this success:

1. LDL-C is a well-established causal risk factor for CVD. PCSK9 plays a key role in the regulation of LDL-C levels and is a potential target to control LDL-C [5].

2. The concept of lower is better for LDL-C is supported by several studies, mainly with statin therapy. The reduction of CVD events by statin therapy depends on the absolute risk of the subjects and the reduction of the LDL-C levels by the treatment [6]. A huge decrease in LDL-C levels is associated with a lower risk of CVD events. PCSK9 inhibitors effectively reduce LDL-C by 50% compared with placebo, in combination with a statin [7]. Post-hoc analysis of the impact on CVD events is also very promising [7].

3. Familial hypercholesterolaemia (FH) gained a major focus in term of definition, diagnosis and risk stratification [8,9]. FH is the most prevalent genetic disease and the Dutch clinical classification is a practical tool for identifying those patients. We have reported that 20% of patients at very high risk, such as those hospitalised with acute coronary syndrome (ACS), had diagnostic criteria for FH [10]. The prevalence of FH was even higher (up to 50%) in subjects with a premature ACS event [10]. Recognising FH patients at an early stage is a major step for the use of PCSK9 inhibitors, especially in the presence of high-risk factors [11]. The following question remains open: Will the diagnosis of FH increase, given the availability of additional effective treatments?

4. Real-life data suggest that the achievement of recommended LDL-C targets is suboptimal. About 40% of contemporary ACS patients reached LDL-C targets of less than 1.8 mmol/l or had a decrease in LDL-C levels by 50% [12]. Although LDL-C control can be improved by the prescription of high-intensity statins or the recommended addition of ezetimibe, there is a room for improvement in the control of LDL-C levels and a need for alternate therapy on in addition to statins.

5. The residual risk of CVD events despite statin therapy with excessively high LDL-C levels is an argument for the development of additional therapy [5]. Ongoing large clinical trials with PCSK9 inhibitors are assessing their impact on clinical outcomes. In addition to LDL-C levels, PCSK9 inhibitors can decrease lipoprotein(a) (Lp(a)) by 30%. Several reports suggest that Lp(a) is a causal risk factor for CVD and will become an additional factor in the selection of intensive lipid-lowering therapy (e.g. Lp(a) ≥50 mg/dl) [13]. In contrast, the impact of statin therapy on Lp(a) levels remained controversial.

6. Intolerance to statin therapy is currently a strong argument for the use of a non-statin agent. Recently, the ESC published a consensus paper on the definition of statin-associated muscular symptoms (SAMS) and their management [14]. At least a switch between three different statin is needed before considering the use of an alternate non-statin agent. Further data are needed to evaluate the possible increase in diagnosis of statin intolerance following increased awareness of this and the approval of non-statin agents as alternative.

7. Statins are among the most prescribed drugs and remain a large market for pharmaceutical companies. The benefit of statins in secondary prevention is strong and growing evidence suggests a benefit in primary prevention also for selected patients (e.g. HOPE-3) [15]. Statins have been a target of negative reports in terms of safety. This negative image (or “conviction”) of statins by patients and also by physicians, and partially re-enforced by the media, is an issue for optimal adherence to the therapy in practice [16]. Administration of a PCSK9 inhibitor every 2 or 4 weeks subcutaneously might be a good alternative to optimise adherence to treatment. The role of clinician scientist in assessing the available evidence and informing the patient ac-

Table 1: Factors associated with high PCSK9 levels.

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolaemia (e.g. PCSK9 gene mutations)</td>
</tr>
<tr>
<td>High levels of low-density and small dense lipoprotein cholesterol</td>
</tr>
<tr>
<td>High triglycerides</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Inflammation (e.g. C-Reactive Protein)</td>
</tr>
<tr>
<td>Acute phase of acute coronary syndromes</td>
</tr>
<tr>
<td>Long chest pain duration</td>
</tr>
<tr>
<td>Use of statins or fibrates</td>
</tr>
<tr>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Women and postmenopause</td>
</tr>
<tr>
<td>HIV-infected patients</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus; PCSK9 = proprotein convertase subtilisin kexin 9.
cordingly concerning preferences and values is becoming more and more important [17].

(8.) PCSK9 inhibitors were among of the first monoclonal antibodies in cardiology; the others are abciximab and an antibody against digoxin [18]. Other fields of medicine, such as oncology, rheumatology, immunology, gastroenterology have widely used biological therapies. In this sense, it is rather a positive development for cardiology, but also a source of additional concerns about the costs. More data will be needed to assess the cost-effectiveness of a preventive treatment. For instance, it is estimated the number needed to treat to save one CVD event over 5 years would be 28, with an average treatment cost expected between 7000–8000 €/year [19]. As with some expensive emergent agents in the field of oncology, physicians would not only need to justify the use of PCSK9 inhibitors according to LDL-C levels of their high-risk patients, but also document either well-conducted statin therapy of high-intensity (e.g., rosuvastatin 20–40 mg or atorvastatin 40–80 mg), or the impossibility of prescribing recommended statin therapy due to side effects, especially for SAMS [20].

The effect of PCSK9 inhibitors in patients with coronary artery disease and ACS

The prognosis of ACS has considerably improved with the implementation of recommended therapies, but the risk of recurrent adverse events is persist [21]. The evidence for the efficacy of statins in the reduction of LDL-C levels and subsequently in the incidence of CVD events is strong and based on several randomised controlled trials and meta-analyses [22, 23]. The European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines make strong recommendations for the use of statins, especially high-intensity statin therapy after ACS (table 2) [21, 24]. According to the ESC guidelines, the recommended target LDL-C level is less than 1.8 mmol/l (70 mg/dl) in patients with very high CVD risk, such as those with ACS [21]. However, data from real life suggest that only one third of ACS patients and only 10% of patients who fulfilled the criteria of FH can reach such stringent targets [10, 12]. Several reasons could lead to such poor outcomes, such as (1) poor adherence to therapy and life-style recommendations, (2) side effects of statin treatment (e.g. SAMS), (3) inertia in statin therapy intensification by physicians, and (4) severe lipid disorders as observed in patients with FH [12, 16, 25].

The last 2015 ESC guidelines for the management of ACS recommended for the first time the use of non-statin agent in patients who need additional lipid-lowering (table 2) [21]. Currently, the evidence is available for ezetimibe. An additional relative decrease of 20% in LDL-C levels was associated with a significant reduction in the occurrence of major adverse cardiovascular events in the IMPROVE-IT trial [26]. However, the clinical significance of these results is still controversial, given the modest absolute effect, expressed as a high number needed to treat for 5 years. There is a need for the development of new lipid-lowering strategies in very high-risk patients [3, 8]. Several studies have shown that monoclonal antibodies inhibiting PCSK9 decrease LDL-C levels by 50% in comparison with placebo [5]. These promising results were also reported for combination therapy with a statin in patients with poorly controlled LDL-C or with statin intolerance [7].

Two ongoing trials are investigating the impact of PCSK9 inhibitors on clinical outcomes after ACS; observational studies have reported controversial results on the association with CVD events.

Higher PCSK9 levels were associated with more severe anatomical vascular disease as measured with angiography. Mechanistic studies reported that PCSK9 levels were associated with inflammation, an increased necrotic component of the plaque and an enhanced thrombotic substrate (fig. 1) [27]. Animal and human data suggest that the plasma PCSK9 concentration is increased in the acute phase of ACS, as is the expression of PCSK9 messenger RNA, reaching a peak at 48 hours. The administration of PCSK9 inhibitors subcutaneously is followed by a maximal effect on PSK9 within 3 days and might represent a very interesting therapeutic option for early plaque stabilisation of culprit and non-culprit lesions in ACS patients [27]. Several studies suggest that the inhibition of PCSK9 has specific effects beyond LDL-C reduction on the atheroscle-


<table>
<thead>
<tr>
<th>1. Proof of concept – do novel marker levels differ between subjects with and without outcome?</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Prospective validation – does the novel marker predict development of future outcomes in a prospective cohort or nested case-cohort study?</td>
<td>Possible, still controversial</td>
</tr>
<tr>
<td>3. Incremental value – does the novel marker add predictive information to established, standard risk markers?</td>
<td>Improbable</td>
</tr>
<tr>
<td>4. Clinical utility – does the novel risk marker change predicted risk sufficiently to change recommended therapy?</td>
<td>No data</td>
</tr>
<tr>
<td>5. Clinical outcomes – does use of the novel risk marker improve clinical outcomes, especially when tested in a randomized clinical trial?</td>
<td>No data</td>
</tr>
<tr>
<td>6. Cost-effectiveness – does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?</td>
<td>No data</td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease; PCSK9 = proprotein convertase subtilisin kexin
Why do this research?

In 2009, thanks to the Swiss National Science Foundation, we established in Switzerland a cohort of patients hospitalised for ACS (SPUM-ACS, www.spum-acs.ch) in order to identify new strategies for diagnosis and treatment of ACS. Recruitment is currently ongoing and has eached more than 4000 patients. The assessment of new biomarkers was one of the major aims of the SPUM-ACS project. PCSK9 has gained a lot of attention in the last decade as an emergent target for the treatment of hypercholesterolaemia, with the recent approval of PCSK9 inhibitors [3]. Several studies have shown that PCSK9 inhibitors efficiently lowered LDL-C levels, especially in patients with FH, intolerant to statins or with poorly controlled LDL-C on maximally tolerated statin treatment [7]. Large ongoing clinical trials are assessing the impact of PCSK9 inhibitors on clinical prognosis after ACS. However, PCSK9 has been little studied in the acute phase of ACS, especially its evolution over time and the association with clinical outcomes. In Geneva, we are working on clinical projects measuring PCSK9. Recently, one of them showed that an increase in physical activity might lower PCSK9 levels in healthy adults [30]. Therefore, we decided to measure PCSK9 in the SPUM-SCS during angiography for ACS, 12–24 hours and 1 year after the index ACS event.

What are the most significant findings?

We observed that higher PCSK9 levels at the initial presentation of ACS were associated with the presence of FH, the use of lipid-lowering therapy, the duration of chest pain and inflammation (C-reactive protein) [1]. To confirm this, we found that PCSK9 levels increased 12–24 hours after ACS, probably with the inflammatory process during ACS, in accordance with previous in vivo models suggesting that PCSK9 expression was enhanced in the context of ACS and inflammation [31, 32]. Then we assessed the incremental value of adding PCSK9 to recommended risk stratification scores, such as the GRACE score, and found that PCSK9 did not predict mortality at 30 days and at 1 year. However, we cannot exclude the possibility that blood sampling in the acute clinical setting could have biased the prognostic value of PCSK9. Patients who had usual statin therapy prior to the ACS index event had significantly higher PCSK9 levels than patients untreated with a statin. In addition, 1 year after ACS, PCSK9 levels were higher than at baseline, probably associated with a greater use of statins (94% vs 30%). This was in line with experimental studies in humans showing the increase of PCSK9 levels with the use of statins [33–35]. Similarly, patients with higher PCSK9 levels tend to be less likely to reach the recommended LDL-C level <1.8 mmol/l 1 year after ACS, suggesting that PCSK9 is involved in the phenomena of statin resistance.

Key messages from our research published in the European Heart Journal

- Lipid C
- Proteolysis / apoptosis
- Endothelial cell activation
- Inflammation
- Platelet aggregation/thrombosis
- Increased Risk of Vulnerable Plaque
- Platelet aggregation/thrombosis
- Inflammation
- Endothelial cell activation
- Proteolysis / apoptosis
- Lipid Core and fibrous cap

Figure 1: Potential role of PCSK9 in recurrent ischaemia in ACS. Mechanistic studies suggest that PCSK9 has adverse effects on coronary plaque through several pathways, including pro-inflammatory low-density lipoprotein oxidation and modification of plaque composition [27]. Levels of PCSK9 are increased during ACS, suggesting that PCSK9 inhibitors could be a beneficial treatment in the acute phase of ACS patients through effects on plaque stabilisation. This hypothesis needs to be explored in further trials.

ACS = acute coronary syndrome; FH = familial hypercholesterolaemia; CSK9 = proprotein convertase kexin 9
What are the implications for future research and for patient care?

The measurement of PCSK9 is currently poorly implemented in clinical practice. Our findings suggest that PCSK9 might be useful to clinicians for identifying patients who might need more intensive lipid-lowering therapy (e.g. PCSK9 inhibitors) to lower LDL-C. In addition, our findings suggest that PCSK9 is up-regulated in the acute phase of ACS (fig. 1) [27]. However, the clinical utility of measuring PCSK9 for risk prediction in ACS patients is poor and no recommendations can be formulated for this purpose.

The following steps summarize the evaluation of the clinical implications of PCSK9 (table 3) [36]:

1. **Proof of concept – do novel marker levels differ between subjects with and without outcome?**

   Yes, PCSK9 is a key target for hypercholesterolaemia and also higher in patients at high risk of cardiovascular disease (table 1) [3]. Mechanistic studies suggest that PCSK9 is involved in the acute phase of inflammation in ACS [27]. We have shown that PCSK9 was higher with inflammation, indicated by increased C-reactive protein, and FH according to the Dutch clinical classification.

2. **Prospective validation – does the novel marker predict development of future outcome in a prospective cohort?**

   PCSK9 levels at time of angiography for ACS are not associated with the occurrence of major adverse cardiovascular events at 1 year [1]. Conflicting results have been reported in primary prevention, with one positive study suggesting an association with the occurrence of CVD events, and another study not [37, 38]. However, in ACS patients who had higher PCSK9 values less frequently reached the recommended target for LDL-C [1].

3. **Incremental value – does the novel marker add predictive information to established, standard risk markers?**

   The addition of PCSK9 to the recommended GRACE score in ACS patients did not add significant incremental values (C-index, reclassification, integrated discrimination index) [1]. In primary prevention, the addition of PCSK9 did not improve the risk prediction and reclassification of the Framingham score [37, 38].

4. **Clinical utility – does the novel risk marker change predicted risk sufficiently to change recommended therapy?**

   No data are available to support the clinical utility of PCSK9 for risk stratification. However, ACS patients who had higher PCSK9 values less frequently reached the recommended target for LDL-C [1]. In addition, PCSK9 levels were significantly higher in subjects with FH and might be used to identify subjects who could benefit most from PCSK9 inhibitors [11].

5. **Clinical outcomes – does use of the novel risk marker improve clinical outcomes, especially when tested in a randomised clinical trial?**

   No randomised controlled trial has analysed PCSK9 as a marker for medical decision making and for identifying patients at high risk. Meta-analysis from post-hoc analysis of randomised controlled trials suggests that the use of PCSK9 inhibitors is associated with a reduction of CVD events [7]. The estimated risk reduction is about 50%. Large ongoing clinical trials will clarify the impact of PCSK9 inhibitors in combination with the maximum tolerated doses of a statin.

6. **Cost-effectiveness – does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?**

   Currently, measurement of PCSK9 is considered expensive and is not implemented as routine. Concerns regarding the costs of PCSK9 inhibitors will be a source of controversy and debate among clinicians, decision-makers and key stakeholders in the healthcare system [19].

**Conclusion**

Guidelines do not make any recommendations regarding the clinical effectiveness of the measurement of PCSK9 in patients with ACS. The data in a large Swiss cohort of ACS patients did not support the clinical utility
of PKC9 for risk stratification, but PKC9 measurement could help to identify patients with FH. However, PKC9 is an emergent target for monoclonal antibodies in the treatment of primary hypercholesterolaemia and, potentially, for secondary prevention in ACS patient, depending on the results of ongoing large clinical trials.

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

References
34. Berthold HR, Seidah NG, Benjannet S, Gouni-Berthold I. Evidence from a randomized trial that simvastatin, but not ezetimibe, upregulates circulating PKC9 levels. PloS One 2013:e60095.
Betablocker und Asthma bronchiale: Ja oder Nein?

Lars C. Huber*, Mattia Arrigo

* Klinik für Pneumologie, UniversitätsSpital Zürich, Zürich; ‡ Klinik für Kardiologie, UniversitätsSpital Zürich, Zürich

Summary

The medical history of beta-blockers is interesting. Even in patients with heart failure, for whom beta-blockers are now standard of care, they were considered contraindicated for a long time. In patients with chronic obstructive pulmonary disease, beta-blockers, once also contraindicated, are associated with reduced mortality and exacerbation rates. The use of beta-blockers in patients with bronchial asthma, however, remains controversial and, owing to fear of adverse respiratory effects and resistance to rescue medication, many review articles and clinical guidelines list beta-blockers as contraindicated in asthmatics. While there is a lack of data on long-term safety and lung function cutoffs below which beta-blockers should be avoided, evidence to support the recommendation that beta-blockers should not be used in asthma patients is rare. In stable patients with well-controlled asthma, beta-blocker-induced respiratory effects appear to be rare, and significant changes in symptoms, lung function and use of rescue medications (including systemic steroids and inhaled anticholinergics) have not been observed. Based on these findings and the fact that beta-blockers have considerable benefits in patients with cardiac diseases, we think that these agents should not be withheld from patients with asthma. In such a setting, it is prudent to use cardioselective beta-blockers. However, when indicated and used carefully, nonselective beta-blockers can also be used in asthmatics. In these patients, asthma needs to be well controlled, without markedly reduced pulmonary function at baseline. In addition, the dose of beta-blocker has to be carefully titrated and, in selected cases, therapy with inhaled anticholinergics might be indicated during the wash-in phase. Experimental data have even suggested that beta-blockers might be used as a therapeutic approach in patients with asthma. Although interesting, these data need to be confirmed in a clinical setting.

Key words: beta-blocker; bronchial asthma; cardioselectivity; respiratory adverse events

---

Betablocker in der Kardiologie


Tabelle 1: Übersicht über Betablocker-Klassen und Beispiele.

<table>
<thead>
<tr>
<th>Kategorie</th>
<th>Ohne ISA</th>
<th>Mit ISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nichtselektive Betablocker</td>
<td>Nadolol, Propranolol, Timolol</td>
<td>Pindolol</td>
</tr>
<tr>
<td>β1-selektive Betablocker</td>
<td>Atenolol, Esmolol, Metoprolol, Bisoprolol, Nebivolol</td>
<td></td>
</tr>
<tr>
<td>Kombinierte Apha-/Betablocker</td>
<td>Labetalol, Carvediol</td>
<td></td>
</tr>
</tbody>
</table>


**Betablocker und Asthma: Geschichte und Pathophysiologie**


Die Mechanismen der Betablocker-induzierten Bronchokonstriktion sind kompliziert und nicht vollends geklärt. Normalerweise wird der Tonus der Bronchialmuskulatur über das Zusammenspiel von sympathomimetischen und parasympathomimetischen Faktoren reguliert, die entsprechenden Abläufe sind vereinfacht in Abbildung 1 dargestellt (detailliert in [15]). Der am stärksten bronchokonstruktiv wirkende Faktor ist die Ausschüttung von Acetylcholin am präsynaptischen Ende eines cholinergen Neurons. Dieses bindet auf der postsynaptischen Seite an den muskarinergen M3-Rezeptor, den Haupteffektor der bronchi-


Bei neu aufgetretenen respiratorischen Symptomen nach Beginn einer Betablocker-Therapie sollte man an ein bisher nicht diagnostiziertes Asthma bronchiale denken.


Epidemiologie


Unerwünschte Wirkungen und Sicherheit von Betablockern bei Asthma


Betablocker zur Asthma-Therapie?
Betablocker sind aber nicht nur hinsichtlich ihrer Sicherheit bei Asthma-Patienten untersucht worden: einige Autoren haben postuliert, dass Betablocker paradoxerweise sogar einen therapeutischen Ansatz in der Behandlung von Patienten mit Asthma bieten kön nen [15, 29].

Könnten Betablocker paradoxerweise sogar einen therapeutischen Ansatz in der Behandlung von Patienten mit Asthma bieten?
Zwei experimentelle Studien verdienen diesbezüglich besondere Erwähnung [30, 31]: In einem Asthma-Mausmodell konnte gezeigt werden, dass der Einsatz eines nichtselektiven Betablockers (Nadolol) bzw. eines kombinierten Alpha- und Betablockers (Carvedilol) nach ei nem Zeitraum von 28 Tagen den maximalen Atem wegswiderstand (Peak Raw, Peak Airway Resistance) um beinahe die Hälfte reduzieren konnte. Im Lungen gewebe dieser Mäuse wurde gleichzeitig eine 8–10fache Aufregulation der Betarezeptoren beobachtet [30]. Während eine akute Betablokade also mit einer Erhö hung der Atemwegswiderstände und der bronchialen Antwort auf bronchokonstruktive Trigger einhergeht, scheint eine chronische Applikation von Betablockern die bronchiale Hyperreagibilität – und damit potentiell die Asthmaaktivität – über eine Aufregulation von Betarezeptoren zu vermindern. Eine weitere Studie untersuchte am gleichen experimentellen Modell die Eosinophilenzahl in der bronchoalveolären Lavage und das Ausmass der endobronchialen Schleimakkumulation unter Therapie mit Steroiden und Nadolol [31]. Diese Endpunkte wurden durch beide Therapien reduziert: die Eosinophilenzahl stärker durch Steroide, das Schleimvolumen stärker durch den Betablocker. Die Kombination der Thera-
Die Mechanismen der Betablocker-induzierten Bronchokonstriktion sind nicht vollends klar.
- Der präventive Einsatz von inhalativen Anticholinergika (Typ Tiotropium) kann den bronchokonstriktiven Effekt von Betablockern reduzieren.
- Unerwünschte respiratorische Wirkungen von Betablockern sind bei Patienten mit gut kontrolliertem Asthma bronchiale selten.
- Bei entsprechender Indikation sollte auch Patienten mit Asthma bronchiale eine Betablocker-Therapie nicht vorenthalten werden.
- Wenn immer möglich sollten kardioselektive Betablocker eingesetzt werden. Wenn ein nichtselektiver Betablocker eingesetzt werden muss, sollte während der Titrationsphase zusätzlich eine Inhalation mit Anticholinergika erfolgen.

Funding / potential competing interests
No financial support and no other potential conflict of interest relevant to this article was reported.

Referenzen

Korrespondenz:
Lars C. Huber
Klinik für Pneumologie
Universitätsklinik Zürich
Rämistrasse 100
CH-8091 Zürich
lars.huber[at]usz.ch
References


5. Packer M. Effect of Carvedilol on the Morbidity of Patients With Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016. doi:10.1002/ejhf.592.


8. Packer M. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. Circulation. 2002;105:2149-60. doi:10.1161/01.CIR.0000023653.72855.BF.


Robotic coronary revascularisation

Aristotelis Panos\textsuperscript{a,b}, Patrick O. Myers\textsuperscript{b}

\textsuperscript{a} Cardiac and Vascular Surgery Hirslanden, Clinique La Colline, Geneva
\textsuperscript{b} Cardiovascular Surgery, Geneva University Hospitals, Geneva

Summary

Objectives: Robot-assisted coronary revascularisation is a relatively new strategy. By performing a minimally invasive left internal thoracic artery (LITA) to left anterior descending (LAD) artery bypass, we are taking advantage of the survival benefit of the LITA-to-LAD bypass while decreasing the morbidity of the procedure associated with sternal spreading. The objective was to assess clinical outcomes and graft patency at 3 years.

Methods: From March 2011 to July 2014, 17 consecutive patients were operated on, with robotic LITA harvesting and manual anastomosis to the LAD on the beating heart through a small anterior thoracotomy. Patients underwent coronary (n = 6) or computed tomographic angiography (n = 11) 1 year after the operation.

Results: All patients were successfully revascularised as planned. There were no early or late deaths. All patients were fast tracked, with extubation during the first 2 hours in the intensive care unit, or (for six of them) in the operating theatre. The mean hospital stay was 4 ± 1.1 days. No patient required reoperation or re-expansion for bleeding. Follow-up ranged from 18 to 48 months. At 1 year, all patients had a patent LITA-LAD anastomosis. All patients remain symptom-free with a negative stress test at latest follow-up.

Conclusions: Robotic LITA takedown and minimally invasive off-pump LAD revascularisation results in excellent perioperative outcomes, high graft patency and freedom from angina during follow-up.

Key words: coronary artery disease; cardiac surgery; coronary artery bypass graft; off-pump; robotic cardiac surgery

Introduction

Coronary artery bypass grafting (CABG) is an established method of treating patients with coronary artery disease [1, 2]. Despite advances in optimal medical treatment and in stents, no alternative has been able to rival the efficacy and durability of the left internal thoracic artery (LITA) to left anterior descending (LAD) coronary artery bypass graft [2]. Less invasive surgical options for performing this anastomosis have been proposed, one of which is robot-assisted coronary artery bypass (roboCAB), in which the LITA is taken down with robotic assistance, and anastomosed on the beating heart through a mini-thoracotomy [3]. Although more complicated for the surgeon, minimally invasive and robot-assisted cardiac surgery has been shown to be less traumatic for the patient and to provide faster recovery [4]. The aim of this study was to describe our initial experience with roboCAB for minimally invasive off-pump LITA to LAD CABG.

Methods

Study design

This study was a retrospective review of all patients who underwent minimally invasive roboCAB at our institution between 2011 and 2014. Patients with single LAD disease referred for CABG, who had evidence of distal ischaemia on nuclear functional testing or magnetic resonance imaging (MRI), were included. Patients with multivessel disease were excluded from this initial experience. The primary endpoint was angiographic graft patency at 1-year follow-up, and the secondary endpoint was freedom from angina at latest follow-up. Clinical or treatment variables were recorded to determine predictors of the endpoints. All patients were followed up to December 2015.

Surgical techniques

After induction of anaesthesia, a double-lumen endotracheal tube for single-lung ventilation was used. Patients were positioned in the supine position with the left elbow bent and outside the surgical table. The da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA, USA) was set up by a dedicated nurse while the surgical tables were set up. The time necessary for this procedure is 15 minutes. The camera port was introduced into the left fifth intercostal space on the anterior axillary line. This incision was extended medially after LITA takedown to create the incision for the LITA-LAD anastomosis. After CO\textsubscript{2} insufflation at a pressure of 7 to 10 mm Hg and deflation of the left lung, the instrument ports were inserted through the third and the sixth intercostal spaces on the midclavicular line under thoracoscopic vision. The LITA was exposed and harvested, pedicled, from its origin to the sixth intercostal space with use of electrocautery. The time for LITA harvesting was 57 minutes (range 45–68 minutes) for the first six patients and continuously decreased to 41 minutes for the last five patients (range 35–47 minutes). After LITA harvesting, heparin was administered at half of the usual on-pump dose.
and the graft was clipped and partially divided at its distal end [3, 5]. Before the pericardium was opened, an infusion of 150 mg xylocaine was given to avoid ventricular arrhythmias. A small anterior thoracotomy was made without spreading the ribs and the LAD exposed with a soft tissue retractor (Edwards Lifesciences, Irvine, CA, USA). The LITA was then completely divided and prepared. The LAD was identified and stabilised with the help of the Octopus-NUVO TE stabiliser (Medtronic, Minneapolis, MN, USA). A coronary shunt was always used. The LITA was anastomosed manually to the LAD on a beating heart using running 8/0 polypropylene suture. We aimed for a fast-track postoperative care protocol, with rapid extubation (within 6 hours) and rapid mobilisation on the day after surgery. The additional cost of each procedure due to roboCAB, taking into account the life span of the robotic instruments (“20 lives” with four different instruments), was 723.35 CHF. The cost of the Octopus-NUVO stabiliser is 2700 CHF, which made a total cost of 3423.35 CHF per procedure.

Results

Demographics and surgical technique

From March 2011 to July 2014, 17 selected, consecutive patients were included. Patient baseline demographics and characteristics are detailed in table 1. They underwent roboCAB for stable angina and LAD disease due to chronic occlusion or stenosis unsuitable for a percutaneous approach. The mean age at operation was 45 ± 15 years. The mean left ventricular ejection fraction (LVEF) was 50 ± 15%. No patient had previously undergone cardiac surgery.

Early outcomes

All procedures were uneventful, and no patient required conversion to sternotomy or cardiopulmonary bypass. There were no re-examinations for bleeding and all had a fast-track extubation. No transfusion was required and all patients were operated on without stopping aspirin. They were discharged from the hospital on the fourth or fifth post-operative day. The mean intensive care unit (ICU) stay was 0.9 ± 0.5 days, and the mean hospital stay was 4 ± 1.1 days. One patient presented a pleural effusion (5.8%).

Late outcomes

Follow-up ranged from 18 to 48 months, during which time none of the patients reported any angina symptoms. No patient required a reoperation during late follow-up. Graft patency was assessed in all patients, with coronary angiography and the rest with computed tomographic angiography (n = 11) at 1 year after the operation. All LITA to LAD anastomoses were patent and free from stenosis at 1 year. All patients had negative stress testing and were clinically free of angina at latest follow-up in December 2015.

Discussion

Reuthenbuch [6] reported as early as 2003 their experience with robotic LITA take-down, although the rest of the operation was continued through a median sternotomy. We introduced minimally invasive and robot-assisted surgery into our routine practice in 2008 [7] and have expanded from intracardiac repairs such as mitral [7, 8] and tricuspid [10] valve repair, to tumour resection [11] and now CABG. Standardisation of the procedures associated with minimally-invasive and robotic cardiac surgery have played a central role in achieving an easy, fast and reproducible set-up in the operating room, as we have described previously [8]. Although minimally invasive and robotic approaches in cardiac surgery have shown benefits to patients, this has been predominantly in the repair of septal defects or of the mitral and tricuspid valves [4, 12–14], and the
penetrance in CABG has been limited. The three most common minimally invasive CABG procedures use a sternal-sparing approach and include minimally invasive direct coronary artery bypass (MIDCAB), robot-assisted coronary artery bypass (roboCAB), and robot-assisted totally endoscopic coronary artery bypass (TECAB) [3, 5]. Each approach has unique advantages and disadvantages. One reason robotic CABG has been slow to catch on in routine practice could be the combined difficulty in conventional LITA harvesting and the difficulty of a LITA-LAD robotic anastomosis. In roboCAB, the LITA harvest, pericardiotomy, and LAD identification are accomplished with robotic assistance, but the anastomosis is performed manually under direct vision, through a non-rib-spreading 3- to 4-cm anterior thoracotomy without cardiopulmonary bypass. This approach leverages the advantages of a minimally-invasive approach, the relatively simple takedown of the LITA with robotic assistance, while avoiding the learning curve associated with a robotic LITA-LAD anastomosis by performing this anastomosis through validated manual, direct-vision techniques through a small thoracotomy. For the LITA harvest and pericardiotomy, robotic techniques provide high-definition intrathoracic exposure, ease of three-dimensional manipulation and a smaller incision giving exposure without rib spreading, when compared with the MIDCAB LITA harvesting. These advantages overcome the difficulties of the exposure for the LITA harvesting in the setting of the MIDCAB, while keeping the major advantage of the MIDCAB, which is the quality of the direct hand-sewn anastomosis of the LITA to the LAD.

Our patients had excellent results, with no conversions or operative complications, fast-track post-operative care, 100% graft patency at 1 year and freedom from symptoms at 2 years. Given these outcomes, and increasing evidence with similar reported results [3, 5], cardiologists may be more willing to refer patients for this approach, providing patients with the best available treatment option for the LAD – the LITA – through a less invasive approach. Furthermore, patients with multivessel coronary artery disease may be referred for hybrid management, with operative roboCAB leveraging the long-term survival benefit of the LITA-LAD anastomosis while minimising invasiveness and operative risk through the percutaneous approach to other vessels. The relatively limited additional cost of the robotic procedure may be counterbalanced by the precision of the LITA harvesting and the relatively painless, smaller and more aesthetic incisions. Finally, although the long-term results of CABG compare favourably with those of percutaneous coronary intervention [2], stroke remains one of the main limitations of CABG. This approach, off-pump and without aortic manipulation, has the potential to decrease this Achilles’ heel of CABG [14].

This study was limited by its design: a retrospective study designed to review our results after introducing a novel and standardised approach to robotically assisted minimally invasive CABG, with a relatively limited sample size at this point.

Conclusions
Robotic LITA takedown and minimally invasive off-pump revascularisation results in excellent perioperative outcomes, high graft patency and freedom from angina during follow-up.

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

References
The full list of references is included in the online article at www.cardiovascmed.ch
References


Management of a potentially life-threatening complication of invasive coronary procedures

Iatrogenic left main coronary artery dissection: mind the catheter tip

Andreas Y. Andreou, Panayiotis C. Avraamides, Tereza Andoniade, Stasinos Theodorou, Chrisostomos Mavroudis, Theodoros Kyriakou

Department of Cardiology, Limassol General Hospital, Limassol, Cyprus

Summary

Iatrogenic left main coronary artery dissection is a rare but potentially life-threatening complication of invasive coronary procedures, which requires prompt recognition and management. We present cases of two patients with type C guiding catheter-induced left main coronary artery dissections that were successfully tackled with bail-out stent angioplasty. The aetiology, recognition, management and prevention of this complication is discussed.

Key words: coronary angiography; percutaneous coronary intervention; left main coronary artery; coronary dissection

Iatrogenic left main coronary artery (LMCA) dissection is a rare but dreadful complication of invasive coronary procedures with a reported incidence of ≤0.1% [1–4]. It is the result of mechanical trauma to the arterial wall during coronary artery instrumentation or manipulation leading to separation of the media by haemorrhage that creates a false lumen, with or without an associated intimal tear. The clinical presentation of iatrogenic LMCA dissection ranges from an asymptomatic, localised dissection with preserved blood flow to an extensive dissection leading to abrupt vessel closure and circulatory collapse. Timely recognition of the dissection and construction of a proper treatment plan based on the type of the dissection and the clinical status of the patient is needed to overcome this potentially fatal complication. Treatment consists of conservative therapy, salvage percutaneous coronary intervention (PCI) or urgent coronary artery bypass graft (CABG) surgery. Currently, iatrogenic LMCA dissection is most frequently treated with PCI, which has high procedural success and favourable long-term outcome [1–4]. Herein, we report two cases of catheter- induced LMCA dissection of type C according to the National Heart, Lung and Blood Institute (NHLBI) criteria, which is considered a detrimental major type posing a high risk of adverse repercussions such as acute vessel closure [5–7]. Both patients were managed successfully with drug-eluting stent (DES)-facilitated PCI.

Case 1

A 71-year-old, male patient was referred for coronary angiography because of non-ST-segment elevation myocardial infarction. The echocardiogram performed at the referring hospital showed hypokinesia of the inferior, inferior-septal and lateral left ventricular walls with an ejection fraction of 40%. The patient had a history of hypertension, hyperlipidaemia, inferior myocardial infarction and bare metal stent facilitated PCI of a dominant right coronary artery (RCA) and the proximal and distal left circumflex (LCx) artery. In 2011, he underwent CABG with a left internal mammary artery graft to the left anterior descending (LAD) artery and a saphenous vein graft to a diagonal artery; preoperatively, no significant viability was documented with low dose dobutamine echocardiography over the dependent myocardium of the chronically occluded, yet collateralised RCA demonstrated during angiography. Transfemoral angiography during the current admission revealed patent grafts and obstructive in-stent disease of the proximal LCx artery culminating in a tight lesion just distal to the outflow of the stent (fig. 1a). Therefore, we proceeded with PCI to the LCx artery. The LMCA was engaged without difficulty with a 6 French Extra Back-up (EBU) 4.0 guiding catheter and, after predilation, a 3.5 × 33 mm DES was uneventfully deployed across the lesion (fig. 1b). Because of stent underexpansion at the site of the tight lesion we successfully performed postdilation with use of a 3.75 × 15 mm noncompliant balloon (fig. 1c).
ond postdilation was then performed at a more proximal location (fig. 1d), yet subsequent angiography revealed persistent contrast staining outside the coronary lumen at the site of the LMCA ostium, which was compatible with a type C coronary dissection (fig. 1e). The patient was pain free and haemodynamically stable without electrocardiographic evidence of ischaemia. The dissection was immediately tackled with a 4.5 × 18 mm DES (fig. 1f). Postdilation was carried out with a 5.0 × 15 mm noncompliant balloon and final angiography showed complete sealing of the dissection flap (fig. 1g). Postprocedural creatine kinase and creatine kinase-MB isoenzyme levels were normal. The patient had an uneventful 2-day hospital course and was discharged home on life-long dual antiplatelet therapy. He remained stable 3.5 years post stenting with Canadian angina class I and no evidence of a cardiovascular event.

**Case 2**

A 58-year-old male patient with a history of hyperlipidaemia and cigarette smoking underwent transfemoral coronary angiography because of stable angina and ischaemia over the LAD artery territory, demonstrated with dobutamine stress echocardiography. Angiography showed diffuse nonobstructive LMCA disease (fig. 2a, b), significant proximal LAD disease (fig. 2a) and chronic occlusion of a left posterior descending artery with faint filling through bridging collaterals. Therefore, we proceeded with PCI to the LAD artery lesion. The LMCA was engaged with a 6 French EBU 4.0 guiding catheter, and a 3.5 × 13 mm DES was directly implanted across the lesion (fig. 2c). Shortly thereafter the patient complained of acute, severe chest pain, and after multiple views focal and persistent extraluminal contrast staining that was

---

**Figure 1:** (a) 45° left anterior oblique (LAO) view of the left coronary artery displaying a tight left circumflex (LCx) artery lesion (dashed arrow) located just distal to a previously implanted bare metal stent. A 6 French Extra Back-up (EBU) 4 guiding catheter is seen engaged in the ostium of a minimally diseased left main coronary artery (LMCA). The left anterior descending (LAD) artery, which contains a mid segment occlusion, is also shown. (b) LAO angiogram showing the stent deployment position. Note the unfavourable position of the guiding catheter resulting in the tip abutting against the wall of the LMCA ostium (arrow). Compare with its position during the first postdilation (c), the tip of the guiding catheter was too deep-seated during the second postdilation (d). (e) 40° LAO and 40° caudal view depicting persistent extraluminal contrast staining at the site of the LMCA ostium (type C coronary dissection). (f) Stent deployment across the dissection. (g) 45° LAO view showing an optimal angiographic result with complete sealing of the dissection flap.
compatible with a type C ostial LMCA dissection (fig. 2d) was revealed. The dissection was directly stented with a 4.0 × 15 mm DES (fig. 2e). Stent postdilation was performed with a 4.5 × 15 mm noncompliant balloon with a good final angiographic result (fig. 2f). Post-procedural creatine kinase and creatine kinase-MB isoenzyme levels were normal, and the patient was discharged home after a 2-day uneventful hospital course. He was prescribed life-long dual antiplatelet therapy. He remained stable 3.0 years after stenting with Canadian angina class I and no evidence of a cardiovascular event.

Discussion

Iatrogenic coronary artery dissection constitutes a complication with a significant impact on morbidity and mortality of patients undergoing diagnostic coronary angiography or PCI [8, 9]. In a multicentre study of 211,645 diagnostic cardiac catheterisations in the 1990s, the incidence of coronary artery dissection was 0.034% (71 cases) with a mortality of 0.0028% (6 cases) [10]. As shown in a large prospective PCI registry of nearly 21,000 patients, the incidence of in-laboratory severe coronary artery dissection (NHLBI dissection type ≥C or abrupt closure) decreased over the years from 1.0% in the prestent era to 0.7% in the first-generation stent era to 0.3% in the contemporary stent era (2000–2003) [11]. However, in contemporary practice, severe coronary artery dissection accounted for 6.2% of all PCI failures and was the most common reason (80%) for referring patients for emergency CABG after failed PCI. Coronary artery dissections may be caused by several mechanisms. Mechanical dilation of a coronary artery by angioplasty balloon inflation or stent implantation is associated with mechanical trauma to the vessel wall, which is a function of the biomechanical properties of the plaque and is the basis of an inherent risk of these procedures – coronary artery dissection. Accordingly, calcified, eccentric and long lesions, “complicated” lesions (ulcerated, thrombus-laden) and lesions located in angulated coronary segments carry a higher risk for the development of dissection [5]. Technical factors increasing the risk of iatrogenic coronary artery dissection include the use of stiff-tipped or hydrophilic-tipped guidewires to cross tightly narrowed
or totally occluded arteries, angioplasty balloon over inflation or oversizing (balloon to artery ratio >1.2), not coaxially and/or deeply engaged catheters, large-bore catheters and Amplatz-shaped catheters [12, 13]. Reported risk factors for catheter-induced coronary artery dissection include atherosclerotic disease, catheterisation for acute myocardial infarction, and variant anatomy of the coronary ostia necessitating extensive catheter manipulations, vigorous contrast media injection, and vigorous, deep inspiration [12]. As far as the arterial access site for performing coronary catheterisation is concerned (transfemoral versus transradial approach), no difference with regards to non-access site complications, including coronary artery dissection [14], has been reported. Nonetheless, a “universal” catheter, that is, a catheter that can be used for left and right transradial diagnostic coronary angiography and/or PCI, such as the Kimny catheter, may be associated with an increased risk of coronary artery dissection because of a difficult coaxial engagement or deep engagement, especially in a RCA with an inferior takeoff or when the catheter is removed from the LMCA without initial downward pressure and torque [2, 15]. Despite the decrease in the incidence of iatrogenic coronary artery dissection observed over the years, the constantly increasing complexity of PCIs (use of large-bore catheters and stiff-tipped guidewires for recanalisation of chronically occluded arteries, retrograde PCI, PCI to the LMCA, PCI to calcified bifurcation lesions) render iatrogenic coronary artery dissection a meaningful risk mandating good comprehension of its mechanisms and predisposing factors, as well as its angiographic presentation and management.

The RCA is the most frequently dissected vessel (84–87% of the cases), followed by the LAD, left main coronary and LCx arteries [16, 17]. Iatrogenic dissection of both the RCA and LMCA is mostly observed after inadequate alignment of a diagnostic or guiding catheter (1,2,4), yet the LMCA and RCA arise from their respective aortic sinuses at different angles: acute (range 20°–35°) and almost perpendicular (range 60°–88°), respectively. This might render the LMCA less susceptible to catheter-induced dissection by providing a better approach for catheterisation [17]. Three retrospective case series have reported the incidence of iatrogenic LMCA dissection during a coronary catheterisation procedure (PCI or diagnostic coronary angiography). Lee et al. [4] reported an incidence of 0.03% (10 cases out of 34190 procedures), Cheng et al. [2] an incidence of 0.07% (13 cases out of 18400 procedures), and Eshtehardi et al. [4] an incidence of 0.07% (38 cases out of 51452 procedures) with a twofold greater incidence of iatrogenic LMCA dissection during PCI (0.1% of all PCIs) than during diagnostic coronary angiography (0.06% of all diagnostic coronary angiographies). Dissection of the LMCA is most frequently caused by inappropriate positioning of the diagnostic or guiding catheter, with an incidence of 61.5% in the study by Cheng et al. [2] where a 6 French catheter was used in 84.6% of the cases, the Kimny miniradial catheter in 61.5% of the cases and the left Judkins catheter in 30.8% of the cases. Balloon dilation near the LMCA bifurcation and stenting at the LAD artery ostium were the second and third most frequent causes of LMCA dissection in this study, with an incidences of 23.1% and 7.7%, respectively. In the study by Eshtehardi et al. [4], inappropriate positioning of a diagnostic catheter was implicated in 58% of the cases of LMCA dissection where the left Judkins catheter was used in 82% of the cases; inappropriate positioning of a guiding catheter was implicated in 16% of the cases of LMCA dissection where extra backup catheters (Amplatz left-, EBU- or Q-curve) were used in 56% of the cases. The second most frequent cause of LMCA dissection in this study was deep intubation of the guiding catheter during balloon retrieval, which was observed in 26% of the cases. In our first case, as shown in fig. 1b, the 6 French EBU 4.0 guiding catheter was non-coaxially positioned and its tip abutted against the wall of the LMCA ostium without, however, causing pressure damping or ventricularisation. However, such a catheter position suggested that the catheter might have been “too short” for the patient and that a more coaxial LMCA engagement could have been achieved with an EBU 4.5 guiding catheter. Dissection of the LMCA occurred secondary to deep seeding of the guiding catheter and scraping of the LMCA wall during retrieval of the postdilating balloon. If we had disengaged the guiding catheter from the LMCA and pulling, to keep the catheter out of the LMCA ostium, had been more vigorous to withstand the resistance met during retrieval of the postdilating balloon, we would have prevented deep seeding of the guiding catheter and the resultant LMCA dissection. In our second case, the LMCA contained substantial, but nonobstructive atheroma. As shown in fig. 1d, the 6 French EBU 4.0 guiding catheter was non-coaxially positioned with its tip pointing vertically against the roof of the LMCA. Accordingly, a hydraulic LMCA dissection might have been created during contrast injection. Keeping the catheter coaxially positioned during every minute of the procedure, avoiding contrast media injection in the presence of pressure damping or ventricularisation and gradual ramping of the injection are essential actions in order to minimise the risk of LMCA dissection.
latrogenic dissection of the ascending aorta during cardiac catheterisation procedures is a rare complication and mainly a sequela of coronary artery dissection extending in a retrograde fashion into the aortic root; it is significantly more likely to occur during PCI than during a diagnostic procedure, with incidences ranging from 0.07% to 0.6% and from 0.01% to 0.08%, respectively [18]. The right aortic sinus is involved in more than 50% of the cases, suggesting that it may be vulnerable to retrograde extension of an RCA dissection [17–19]. The periostial aortic wall of the RCA has less interstitial type I collagen than the periosteal aortic wall of the LMCA. Also, the sinotubular ridge in the right aortic sinus has a smaller amount of smooth muscle cells within an extracellular matrix basically composed of type III collagen, whereas the sinotubular ridge in the left aortic sinus has a larger amount of smooth muscle cells within a dense extracellular matrix of type I collagen [7]. Because the tensile strength of type I collagen is greater than that of type III collagen, the RCA might thereby have less resistance to traction and RCA dissection might more easily extend retrogradely to involve the aortic root. In a retrospective series of 18 patients with iatrogenic aortic dissection occurring during cardiac catheterisation procedures reported by Gómez-Moreno et al. [18], the dissection involved the RCA and its corresponding aortic sinus in 67% of the cases, and was most often related to deep coronary catheter engagement and the use of unconventional catheters (Amplatz, XB, multipurpose) (39%). Balloon dilation, crossing of chronic total occlusion with a guiding wire and stent implantation were identified as additional causes of the dissection. Núñez-Gil et al. [19], in their retrospective series of 74 patients with iatrogenic aortic dissection occurring during cardiac catheterisation procedures found that the dissection, in the vast majority of cases (97.2%), took place during coronary catheter engagement of the RCA (56.8%) or the LMCA (40.5%) and was caused by a catheter (91.8%) of 6 French size (90.5%). Unconventional catheters (Amplatz, XB, multipurpose) were used in 48.6% of the cases and guiding catheters were used in 70.3% of the cases. There are several precautionary measures that can be taken in order to minimise the risk of catheter-induced coronary artery dissection. The first is the optimal selection of the catheter with adequate coaxial engagement of this catheter into the coronary artery followed by careful catheter handling. For left coronary artery catheterisation from the transfemoral approach in patients with a normal-sized aortic root and a normal length of the LMCA, the Judkins left 4.0 and 4.0 extra back-up type guiding catheter are good choices, downsizing to 3.5 or upsizing to 4.5 as needed [20]. Catheter-induced dissection of the roof of the LMCA in patients with a large-sized aortic root is commonly observed when using a “too short” Judkins left 4.0 or 3.5 backup type guiding catheter. In patients with a large-sized aortic root the Judkins left 5.0 or extra backup type 4.0–4.5 guiding catheter are good choices. Compared with the transfemoral approach, left coronary artery catheterisation from the right transradial approach in patients with a normal-sized aortic root is usually performed with catheters having a 0.5 cm shorter curve (Judkins left 3.5 and extra backup type 3.5 guiding catheter). If possible, catheter engagement in a coronary ostium must be performed with the catheter connected to continuous pressure monitoring in order to ensure that there is no pressure damping or ventricularisation, thereby avoiding inadvertent dissection during contrast injection. Gradual ramping of the injection can also help to minimise the risk of this event. Given that the extra backup type guiding catheters have been implicated in iatrogenic LMCA dissection, such catheters should be selected only in cases of complex PCI requiring a strong backup support. Maintaining coaxial alignment of the guiding catheter with the coronary ostium during the passage of interventional devices (stents, conventional balloons, cutting balloons, rotational ablative or distal protection devices, etc.) is important because these devices are usually rigid and of large profile and their passage through a non-coaxially engaged guiding catheter may lead to ostial dissection. Deep seating of the guiding catheter in order to achieve a strong “active backup” must be performed with extreme care and when the catheter tip is soft, if the artery is large enough to accommodate the catheter and there is no ostial or proximal lesion. Also, the guiding catheter must be first disengaged from the ostium and be kept there by continuous pulling during retrieval of interventional devices, in order to avoid coronary dissection secondary to deep seating of the guiding catheter. Extreme care is also required when using Amplatz-shaped catheters, since a simple withdrawal from the vessel can cause the tip to advance further into the vessel and cause dissection. In order to disengage the Amplatz catheter, one must first advance it under fluoroscopy to prolapse the tip out of the ostium and then rotate it so that the tip is totally out of the ostium before withdrawing it. Angiographically, coronary dissection appears as a radiolucent area within the vessel or as an extravasation of contrast agent. Based on their angiographic appearance, coronary dissections are classified into six types (type A to F), according to the NHLBI classifica-
As shown in studies conducted in the angioplasty era, the angiographic morphology of the dissection is associated with the clinical outcome, and it can thus help in selection of the most appropriate treatment strategy [6]. Dissection types C to F (type C: contrast appears outside the coronary lumen as an “extraluminal cap” with persistent contrast staining; type D: spiral luminal filling defects, often with persistent contrast contrast staining; type E: new, persistent intraluminal filling defects; and type F: dissection without any of the morphological characteristics described in this classification that is associated with impaired flow or total coronary occlusion) are characterised as major dissections having a significant risk of in-hospital complications such as acute vessel closure (31%), need for emergency CABG (37%), myocardial infarction (13%) and repeat angioplasty (24%) [5, 6]. In contrast, dissection types A and B (type A: minor intraluminal radiolucent areas with minimal or no persistent contrast staining, and type B: radiolucent tracks representing the luminal flap and coursing parallel to the vessel or a double lumen appearance separated by the radiolucent luminal flap with minimal or no persistent contrast staining) have not been shown to increase morbidity and mortality compared with those of patients without dissection, and neither do they affect procedural outcome; the incidence of abrupt vessel closure, myocardial infarction and need for CABG in patients with type B dissections has been reported to be less than 3% [6]. Alternatively, LMCA dissection can be classified into three types according to a simplified classification scheme described by Eshtehardi et al. [4]. Type I dissections are localised and do not extend into the LAD or LCx arteries, type II dissections are characterised by extension into the LAD and LCx arteries, and type III dissections are those extending back to involve the aortic root. Angiographically, iatrogenic aortic dissection appears as dense and persistent contrast staining of the aortic wall. A classification scheme proposed by Dunning et al. [21] recognises three classes of iatrogenic aortic dissection based on the extent of aortic involvement in the dissection. Class I dissections are limited to the corresponding aortic sinus, Class II dissections involve the corresponding aortic sinus and extend less than 40 mm into the aorta and Class III dissections involve the corresponding aortic sinus and extend more than 40 mm into the aorta. Depending on whether anterograde flow has been impaired and to what degree, the clinical spectrum of LMCA dissection ranges from an asymptomatic status to refractory cardiogenic shock and/or cardiac arrest. In the series of 38 patients with iatrogenic LMCA dissection reported by Eshtehardi et al. [4], no patient with type I dissection (21 patients) manifested haemodynamic instability. In contrast, 7 (41%) of 17 patients with type II or III dissections presented haemodynamic instability and 5 of these patients (29%) required cardiopulmonary resuscitation. Both our patients were diagnosed with a type C dissection according to the NHLBI classification scheme. Also, in both our patients, the LMCA dissection was localised and did not extend to the LAD or LCx arteries or retrogradely into the aortic root, thereby qualifying as a type I dissection according to the simplified classification scheme of Eshtehardi et al. [4]. Anterograde blood flow and haemodynamic stability were maintained in both cases.

Iatrogenic LMCA dissection is an emergency because it threatens a large territory downstream of the injury, and its management depends on the patency of the distal vessel and the extent of propagation of the dissection. Percutaneous or surgical revascularisation is generally mandated in the presence of myocardial ischaemia or acute vessel closure, whereas conservative management has been advocated in asymptomatic and haemodynamically stable patients with localised dissections and normal distal coronary flow. The currently prevailing management strategy of iatrogenic LMCA dissection that produces ischaemia is PCI, which can be performed rapidly after the occurrence of dissection with a high technical success rate and acceptable short- and long-term outcomes. PCI circumvents the delays associated with CABG and can expediently restore of coronary patency, thereby avoiding prolonged ischaemia, which is linked to an increased rate of myocardial infarction and death, something that is particularly important for the haemodynamically unstable patient. A literature review of bail-out PCI for iatrogenic LMCA dissection that included 54 patients revealed a procedural success rate of 92.6%, whereas only four patients underwent emergent CABG as a result of unsuccessful PCI [3]. The overall survival rate was 92.6% and of the four deaths recorded only two were of cardiac origin. In the series by Eshtehardi et al. [4], there was a 37% (14/37) rate of bail-out PCI and a 45% (17/37) rate of emergency CABG without in-hospital mortality, whereas at 5 years no significant difference was observed between the two revascularisation strategies with regards to major adverse cardiac events (36% vs 41%, respectively; p = 0.8). Surgical revascularisation is reserved for patients in whom PCI failed to treat LMCA dissection or for haemodynamically stable patients who otherwise would have been deemed surgical candidates on the basis of extensive multivessel coronary disease. Since surgery does not treat the dissection itself, surgical revascularisation solely for LMCA dissection not produc-
ing significant lumen compromise is not an appropriate treatment strategy, because of the risk of graft closure. Eshtehardi et al. [4], also reported that 6 of their 37 patients (16%) had a localised and stable LMCA dissection and received conservative treatment with favourable short- and long-term outcomes. Furthermore, in 12 of their patients (32%), the LMCA dissection showed signs of expansion within 90 minutes of the initial observation period, something that highlights the dynamic nature of the dissection and its potential to rapidly transform into an extensive dissection leading to haemodynamic collapse due to abrupt flow compromise with disastrous sequelae. However, Eshtehardi et al. [4] did not provide any information about the type(s) of dissection that expanded. Accordingly, when confronted with a patient with an iatrogenic LMCA dissection, the decision to intervene with either PCI or CABG or to treat the patient medically must take into account whether the dissection is minor or major based on several angiographic signs, the clinical status of the patient, the operator’s expertise and availability of equipment (intravascular imaging systems) to perform PCI to the LMCA successfully, and the time required to transfer the patient for CABG. Whilst major LMCA dissections (the dissections extending more than 20 mm, causing at least 50% residual stenosis and impairing flow, as well as dissection types C to F according to NHLBI criteria) generally require prompt PCI, dissection types A and B can be treated conservatively and under close monitoring with optimal medical therapy including a β-blocker. Conservative therapy has been applied successfully in highly selected patients with minor and asymptomatic LMCA dissections, yet late progression of an initially localised LMCA dissection into an expanding false lumen leading to significant reduction in luminal diameter with associated exertional angina has been described [22, 23]. The decision to treat a patient with LMCA dissection medically must therefore be accompanied by a revascularisation plan.

Both our patients were haemodynamically stable and had a type C LMCA dissection, which is considered a major type with a 10% risk of acute vessel closure [6, 7]. Acute LMCA occlusion is usually associated with rapid haemodynamic deterioration and cardiac arrest, but in such an unwanted event, our first patient would have faced less risk of haemodynamic compromise than our second patient owing to the presence of patent grafts to the LAD and diagonal arteries; however, the resultant significant ischaemia in the LCx artery territory could still cause some haemodynamic compromise because of his moderately reduced ejection fraction (40%) associated with his previous acute inferior myocardial infarction. Therefore, both patients were treated with implantation of a stent with complete dissection coverage, and both had a favourable immediate and long-term outcome. During PCI of a dissected coronary artery, insertion of a soft-tipped guiding wire into the true lumen is a crucial step of the procedure, and in the case of LCMA dissection both the LAD and LCx arteries should be wired in order protect them from possible extension of the dissection. Intracoronary imaging with means of intravascular ultrasound or optical coherence tomography can be very helpful if the position of the guiding wire is doubtful and it can also help define the dissection entry point and extent, the existence and extent of intramural haematoma, and vessel size, thereby facilitating PCI [24]. Intracoronary imaging for PCI of a dissected coronary artery ensures adequate stent coverage of the whole dissection flap, thereby preventing dissection/haematoma propagation that could result from inadvertent premature sealing of the dissection flap. Alternatively, conservative treatment with stenting of the dissection entry site only may be sufficient to stabilise this complication, providing that the residual false lumen is not obstructive and normal anterograde flow is obtained. This approach has been applied in a case of LMCA dissection reported by Binder et al. [25]. During PCI to a calcified proximal LAD artery lesion, the predilating balloon ruptured and produced an ostial LAD artery dissection extending retrogradely into the LCMA. They delivered two overlapping stents in the proximal and ostial LAD artery followed by examination of the LMCA and the LAD artery by means of optical coherence tomography. They found that the dissection entry site was located in the ostial LAD artery and was adequately covered by the stent, whereas the false lumen did not cause obstruction to the LMCA. Therefore they refrained from stenting the LMCA and at 6-months angiographic follow-up, no evidence of residual LCMA dissection or stenosis was documented. Similarly, conservative treatment with stent implantation sealing the dissection entry site in the coronary artery has also been reported to be a successful approach in about 50% of the patients with retrograde extension of the dissection in the ascending aorta [18, 19].

Conclusion

Iatrogenic LMCA dissection is a rare and potentially life-threatening complication of invasive coronary procedures. The fact that iatrogenic LMCA dissection is mostly catheter-induced underlies the need for proper catheter selection on the basis of the patient’s anatomy and the complexity of the PCI, meticulous handling of
coronary catheters with adequate coaxial engagement during every minute of the procedure, and gradual ramping of contrast media injection in the absence of pressure damping or ventricularisation. In the case of an iatrogenic LMCA dissection, prompt diagnosis and construction of a treatment plan is needed in order to overcome this potentially detrimental complication. Dissection types C to F according to NHLBI criteria are considered major dissections posing significant risk of adverse clinical outcomes if left untreated. Currently, bail-out PCI for iatrogenic LMCA dissection appears to be safe and feasible with acceptable short- and long-term outcomes. CABG is a valid treatment strategy in patients without haemodynamic instability who otherwise would have been deemed surgical candidates on the basis of extensive multivessel coronary disease. Conservative therapy may be considered in haemodynamically stable and clinically asymptomatic patients with localised dissections (types A and B according to NHLBI criteria).

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

References
8. de Bonis D. Complications of diagnostic cardiac catheterisation: results from 34,041 patients in the United Kingdom confidential enquiry into cardiac catheter complications. The Joint Audit Committee of the British Cardiac Society and Royal College of Physicians of London. Br Heart J. 1993;70(3):297–300.
A young man with a strong family history of sudden cardiac death and channelopathy

Recurring tachycardia and syncope in a young person

Giuseppe Cocco, Philipp Amiet

Cardiology office, Rheinfelden, Switzerland
Medical office, Rheinfelden, Switzerland

Summary

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac arrhythmia in the absence of structural cardiopathy with a strong potential for sudden cardiac death (SCD). A patient with a worrisome family history of SCD and genetically proven CPVT in various family members was found to have CPVT with exaggerated catecholaminergic burden and stress-induced complex cardiac arrhythmias. The arrhythmias are mediated by delayed after-depolarisation. The antiarrhythmic effect of the β-blocker metoprolol was insufficient. The patient refused other antiarrhythmic drugs. He received an implantable cardioverter defibrillator (ICD), which was effective in treating the recurring arrhythmia. Vigorous physical activity and high emotional stress must be avoided by these patients. The case underlines the importance of ICD in patients with recurring synapses, a strong family history of SCD with a genetically proven CPVT in various family members.

Key Words: catecholaminergic polymorphic ventricular tachycardia; inherited cardiac arrhythmia

Introduction

Sudden cardiac death (SCD) is a devastating event. In a prospective study [1] the addition of genetic testing to autopsy investigation found an annual incidence of SCD of 1.3 cases per 100,000 persons 1 to 35 years of age, 72% of the cases were boys or young men. At present approximately 30% of patients are genotype negative. A clinically relevant cardiac mutation was detected in 27% of cases and identified an inherited cardiac disease in 13% of the families in which unexplained SCD occurred. The genetic defects that cause catecholaminergic polymorphic ventricular tachycardia (CPVT) may be linked to mutations in chromosome 1 (115,700,007,768,781, reverse strand GRCh38: CM000663.2) [2]. Thus far, two genetic variants have been identified [3,4]. The detected mutations involve Ca^2+ handling, mostly in ryanodine (Ry) isoforms, less frequently in the Ca^2+-binding protein calsequestrin (CASQ2), or the integral proteins triadin 1 and junctin (JCN) [3, 4]. Defects in proteins of this junctional Ca^2+ signalling complex induce irregular Ca^2+ flow and electrical instability at the sarcoplasmic reticulum (SR) of cardiac (and muscular) myocytes. The electrical dys-function is complex and leads to a SR “perceived Ca^2+ overload”, the so called “Ca^2+ overload paradox”, with a consequent decreased threshold to Ca^2+ and predisposition to arrhythmia [3, 4]. Experts in basic research and pharmacology [3, 4] write that “technically” CPVT is not a “true” cardiac channelopathy, because it is an inherited genetic arrhythmia encoding a channel-related protein and not the channel itself. However, ryanodine receptors actually are part of the Ca^2+ channels that control Ca^2+ flow out of the SR protein and cause CPVT. Furthermore, there is a phenotypic and therapeutic overlap with long QT syndrome (LQTS) and short QT syndrome (SQTS). It is therefore clinically correct to accept CPVT as a channelopathy. CPVT is characterised by a structurally normal heart with a myocardial substrate that is highly disposed to ventricular arrhythmias, typically triggered by adrenergic stimulation, especially physical exertion or emotional stress. Patients with CPVT have an entirely normal-looking ECG at rest, but clinical exercise, or stress testing with adrenaline, may provoke several arrhythmias and ventricular tachycardia (VT), characteristically in a bidirectional or polymorphic pattern. Ventricular ectopic beats in CPVT are mediated by delayed after-depolarisation.

Case report

A 23-year-old Caucasian male patient was referred because of syncope during jogging. His first symptoms of cardiac arrhythmia began at the age of 12 years, during physical effort. There was a worrisome familial anamnesis for SCD in the paternal family. A CASQ2 mutation had been detected in the paternal family. The father, an uncle and a cousin died suddenly, at the ages of 29, 34 and 27, respectively, and an aunt had been fitted at the age of 36 with an implantable cardioverter defibrillator (ICD) for secondary prophylaxis. The patient had refused a genetic test. He was in excellent clinical conditions and jogged regularly at least twice a week. There were no classic cardiovascular risk factors. A laboratory check-up did not detect any pathology. The resting ECG was normal. At echocardiographic examination
there was no structural cardiopathy. A 24-hour dynamic ECG, recorded during jogging, detected 98 runs of tachyarrhythmia with frequent and complex atrial ectopic beats and paroxysmal atrial fibrillation, and some premature ventricular beats (fig. 1a, 1b, 1c, and 1d). The atrial ectopic beats were polymorphic and probably derived from increased automaticity. Some premature ventricular beats were also seen. Paroxysmal tachycardic atrial fibrillation was detected. A cyclo-ergometric stress test elicited marked horizontal ST down-sloping in the left precordial leads, without chest pain. The ECG (fig. 2) recorded in the post-exercise recovery phase shows VT with a rate of 125 beats/min. The VT lasted almost 2 min. The diagnosis of VT is confirmed by the atrioventricular dissociation in the second QRS complex in V4–V5. In the fifth minute of the recovery phase the ECG (fig. 3a) showed slow intraventricular conduction in the posterior fascicle, explaining the appearance of left axis deviation and a slightly broader QRS complex. In the follow-up (recovery) phase a negative T-wave was recorded in aVF and in V3–V6 (fig. 3b). The QRS morphology returned to normal after 15 min. The disappearance of the T negativity confirmed the hypothesis of T-wave memory due to VT [5, 6]. A pharmacological stress test with adrena-line would have confirmed the catecholaminergic aetiology of the arrhythmia, but in this case it was considered unnecessary.

**Treatment**

Clinical therapy for CPVT traditionally has relied on reducing precipitating circumstances (vigorous physical activity and high emotional stress must be avoided in those patients), high-dose noncardioselective β-adrenergic blockade and adhesion to therapy [3, 4]. In addition to blunting whole-body adrenergic tone,
Figure 1b: Dynamic ECG recording during jogging. Change from atrial arrhythmia to paroxysmal atrial fibrillation.

Figure 1c: Dynamic ECG recording during jogging. Paroxysmal atrial fibrillation.
β-blockers modulate the heart rate-dependent overload of Ca²⁺ in cells and may directly reduce the type-I Ca²⁺ channel current. Ca²⁺ channel blockers have also been used and have been shown in small studies to partially protect patients from exertion-induced arrhythmic events [3, 4]. This patient was treated with metoprolol retard, the dose being slowly adjusted to 200 mg/day. The patient refused to stop his sporting activity. He was instructed to adhere to the therapy and to reduce the intensity of jogging. The frequency of symptoms decreased. However, repeated dynamic ECG recording showed that arrhythmia persisted. It has been shown [4] that the Na⁺ channel blocking drug flecaïnide inhibits RyR2 activity and reduces spontaneous SR Ca²⁺ release. It also seems to have significant antiarrhythmic effects in CASQ2 models and small clinical series, suggesting that the effects of flecaïnide, the role of CASQ2 in CPVT, or both are still incompletely understood. Some patients with CPVT may require combination medical therapy, with high-dose β-blockers plus flecaïnide, verapamil, or both. However, despite polytherapy there continues to be a significant rate of cardiac events. Side-effects of medical polytherapy may be important. Our patient refused therapy with either verapamil or flecaïnide because the combined therapy had been ineffective and poorly tolerated by his relatives. The use of nonpharmacologic therapies is warranted for medically refractory cases. Minimally invasive left cardiac sympathetic denervation has been reported by several groups to be effective for selected patients with CPVT, although the numbers treated with this technique are still small. Because of the catecholaminergic nature of the disease and the patient’s worrisome familial history of SCD,
the risk of arrhythmic storm was of particular concern. The implantation of an ICD was considered and the patient accepted an invasive cardiac diagnostic procedure. At ventriculography no structural pathology was detected and biventricular function was normal. Coronarography did not detect a coronary artery disease. The patient received an ICD.
At 1-year follow-up, under therapy with metoprolol retard, recurring supraventricular and ventricular tachycardic runs occurred during jogging and were successfully treated by appropriate ICD discharges. Atrial fibrillation did not recur. Vigilant programming of ICDs and discussions to minimise medication non-compliance are vital because even an inappropriate shock can trigger an electrical storm with multiple shocks. The patient has now returned to his country of birth. He was instructed to be strictly followed up by a local cardiologist experienced in arrhythmias and ICD therapy.

**Figure 2:** Ventricular tachycardia (rate 125/min) with biphasic right bundle branch block morphology in V1 and V4–V5. The atrioventricular dissociation in the second QRS complex in V4–V5 confirms the diagnosis of ventricular tachycardia.

**Figure 3a:** ECG changes in the recovery phase of the stress test. In the fifth minute of recovery the ECG detects slow intraventricular conduction in the posterior fascicle, explaining the appearance of the left axis deviation and a slightly broader QRS complex.
Figure 3b: ECG changes in the recovery phase of the stress test. The QRS morphology returns to normal. Negative T-waves are present in aVF and V3–V6. The disappearance of the T negativity confirm the hypothesis of T-wave memory due to ventricular tachycardia.

Discussion

This patient has a CPVT and a worrisome family history of SCD and a channelopathy. Stress testing showed ST down-sloping, QRS conduction disturbances, afterrepolarisation arrhythmias and secondary (memory-induced) T negativity. These changes prove relevant catecholaminergic activation. In the absence of myocardial ischaemia and/or dilatative cardiomyopathy, similar arrhythmias are found in patients with exaggerated sympathetic stimulation, such as patients with cerebral haematoma. These ECG changes indicate a high risk for SCD.

The past 20 years have witnessed an incredible advancement in the role of genetics on cardiac arrhythmias [3, 4]. The case underlines the importance of ICD in patients with recurring syncope, a worrisome family history of SCD with a genetically proven CPVT in different family members.

Acknowledgment

The authors thank Mrs. J. Bugmann for the typographic work.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

References

Varia

Cardiology Update (11–15 February 2017)

Dr. Ruth Amstein
Zurich Heart House

Davos will once again be hosting the 22nd biennial Cardiology Update Course in February, 2017. This four-day course is among the major European meetings in cardiology that offer a comprehensive overview on the entire field of cardiovascular medicine, a scope that includes atherosclerosis, risk factors and prevention, coronary artery disease, acute coronary syndromes, revascularisation strategies, arrhythmias, cardiomyopathies, valve disease, heart failure and imaging modalities. The scientific programme was developed by the Zurich Heart House / University Hospital Zurich, the European Society of Cardiology (ESC) and the Brigham and Women’s Hospital in Boston, together with the two course directors, Prof. Thomas F. Lüscher from Zurich and Prof. Bertram Pitt from Ann Arbor, USA. A distinguished international teaching faculty contributes to an outstanding programme on the latest scientific and therapeutic developments, as well as on the newest intervention and treatment strategies in cardiology. The key educational objectives are to review and disseminate the very latest knowledge about advances in the prevention, diagnosis and treatment of cardiovascular disease, and also to provide an update on the most recent ESC Guidelines and to stimulate discussion about their impact on clinical practice. Traditional state-of-the-art lectures with discussion rounds will alternate with interactive seminars providing guidance for everyday practice. A particular emphasis will be placed on “Meet the Expert” sessions in which clinical cases will be presented and discussed with a focus on diagnostic and therapeutic decision-making in accordance with guidelines. Additionally, moderated poster sessions will provide young researchers with the opportunity to present their latest scientific findings. Also of note will be the variety of satellite symposia from industry partners, whose focus on recent developments in the drug and device industry will specifically address therapeutic innovations. Cardiovascular clinicians, internists and primary care physicians attending will derive benefit from this four-day summit on the latest scientific updates and treatment modalities in being able to better serve their patients. The new Sunday to Wednesday schedule should help busy practitioners avoid long leave of absence from the workplace. As it offers great opportunities for networking among faculty members and participants, the course promises a stimulating environment for work and learning.

Programme and registration:
www.cardiologyupdate.ch

Correspondence:
Dr. Ruth Amstein
Director
Zurich Heart House
Foundation for Cardiovascular Research
Moussonstrasse 4
CH-8091 Zürich
ruth.amstein[at]usz.ch