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Prevention, epidemiology, and prognosis of perioperative myocardial injury

Erin N. Sloan, Erin E. Morley, Philip J. Devereaux

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Summary

Annually over 200 million adults undergo noncardiac surgery worldwide. Myocardial ischaemia is a frequent cause of perioperative cardiac morbidity and mortality. Approximately 8 million patients will suffer a myocardial injury after noncardiac surgery (MINS) each year. MINS is defined as a prognostically important myocardial injury due to ischaemia that occurs during, or within 30 days after, noncardiac surgery. The diagnostic criterion for MINS is an elevated troponin measurement resulting from myocardial ischaemia. MINS is a strong, independent predictor of 30-day and 1-year mortality. The majority of patients suffering MINS would go undetected without troponin monitoring since >80% of these patients do not experience ischaemic symptoms. Intensification of pharmacotherapy may reduce 30-day mortality in patients who have experienced MINS. This paper will review the epidemiology, prevention, prognosis and treatment of MINS.

Key words: perioperative medicine; cardiovascular events; myocardial ischaemia; myocardial infarction; troponin elevation; myocardial injury after noncardiac surgery; noncardiac surgery; epidemiology; prevention; prognosis; treatment; perioperative management; perioperative care

Epidemiology

Worldwide over 200 million adults undergo noncardiac surgery annually [1, 2]. Conservative estimates suggest that at least 100 million adults undergoing noncardiac surgery are in an at-risk age group for major perioperative vascular events [3]. Approximately 8 million of these patients will suffer a myocardial injury after noncardiac surgery (MINS) [4] and, as a result, over 1 million adults will die within 30 days of noncardiac surgery worldwide annually [1, 2]. The magnitude of this problem is predicted to increase owing in part to an aging population, a rise in the incidence of cardiovascular related problems, and a trend toward surgical intervention in elderly patients.

Myocardial infarction (MI) is defined in the Third Universal Definition of Myocardial Infarction, an expert consensus document by the global Myocardial Infarction Task Force [5] (table 1). While MI is the cardiac endpoint in many perioperative studies, it is important to differentiate MINS from MI as a multitude of factors limit the ability to diagnose an MI in the perioperative period (table 1).

Typically, postoperative patients receive some form of analgesia. This is often an opioid or similar agent, which can effectively mask chest pain from myocardial ischaemia [6]. Furthermore, patients who are sedated or intubated postoperatively are unable to effectively communicate and thus perioperative ischaemia may be overlooked. The majority of troponin measurements and ECGs are ordered on the basis of ischaemic symptoms [7], therefore acute perioperative MI or MINS may be missed in patients receiving analgesia or in patients whose communication is impaired. Based on the VISION Study (a prospective, international, cohort study involving 40 000 patients, ≥45 years of age having noncardiac surgery), the majority of patients (87%) with MINS experienced the ischaemic

Table 1: Definition of myocardial infarction (MI) and myocardial injury after noncardiac surgery (MINS).

<table>
<thead>
<tr>
<th>MI</th>
<th>Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Symptoms of ischaemia</td>
<td></td>
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<tr>
<td>- New or presumed new significant ST-segment–T wave changes or new left bundle-branch block</td>
<td></td>
</tr>
<tr>
<td>- Development of pathological Q waves in the ECG</td>
<td></td>
</tr>
<tr>
<td>- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality</td>
<td></td>
</tr>
<tr>
<td>- Identification of an intracoronary thrombus by angiography or autopsy [5]</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>MINS</th>
<th>A prognostically relevant myocardial injury due to ischaemia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The diagnostic criterion for MINS is troponin T ≥0.03 ng/ml due to an ischaemic aetiology within 30 days of noncardiac surgery.</td>
<td></td>
</tr>
<tr>
<td>- Ischaemic ECG changes are not required.</td>
<td></td>
</tr>
<tr>
<td>- Ischaemic cardiac symptoms are not required [4].</td>
<td></td>
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</tbody>
</table>
injury within the first 3 days after surgery [4]. A mere 15.8% of patients who developed MINS experienced ischaemic cardiac symptoms [4]. Therefore, without postoperative troponin monitoring, 84.2% of MINS events would go undetected [4]. Furthermore, in VISION, all patients with an elevated troponin measurement had an ECG. Only 34.9% of patients had ischaemic ECG changes and a minority (41.8%) of patients suffering MINS fulfilled the universal definition of MI (fig. 1) [4].

115–129 mm Hg were randomised to antihypertensive drugs or placebo [9]. The follow-up period was 18 months. At the time, many experts believed that hypertension was essential for brain perfusion. The primary outcome included death, dissecting/ruptured aortic aneurysm, cerebral haemorrhage / disabling stroke, MI, congestive heart failure (CHF), retinal haemorrhage, papilloedema and rapidly progressive renal failure [9]. Thirty-nine percent of the placebo group versus three percent of the antihypertensive group experienced the primary outcome. The relative risk reduction for antihypertensive drugs was 93%, p = 0.00000003 [9].

Historically, physicians did not believe that nonvalvular atrial fibrillation was a risk factor for stroke, but rather simply a nuisance for patients who experienced palpitations [10, 11]. Currently, it is recognised that both valvular and nonvalvular atrial fibrillation carry a significant risk of embolic stroke. This historical perspective suggests that physicians can overlook important diagnoses. Evidence suggests that MINS is prognostically important and overlooked by most physicians. This is primarily due to a lack of perioperative troponin monitoring. In addition, the fragmented nature of perioperative follow-up likely facilitates physicians’ underappreciation of the impact of MINS.

**Prognosis**

VISION demonstrated that MINS is not a benign entity and it independently predicts major vascular events and mortality at 30 days (table 2) [4, 12]. Levy et al. performed a systematic review and meta-analysis evaluating the intermediate and long-term prognostic value of troponin and creatinine kinase-MB measurement after noncardiac surgery. The findings demonstrate that an elevated troponin after noncardiac surgery strongly predicts mortality at 1 year [odds ratio (OR) 6.7, 95% confidence interval (CI) 4.1–10.9] [13]. Based on its high prevalence, asymptomatic nature and substantial influence on perioperative mortality, MINS has been classified as a “silent killer” [14].

MINS is associated with an adjusted hazard ratio (HR) of 3.87 (95% CI 2.96–5.08) for 30-day mortality and MINS has the highest population-attributable risk (PAR) (34%) compared with other postoperative complications that predict death at 30 days after surgery (table 3) [4]. The PAR represents the proportion of all deaths potentially attributable to the relevant risk factor (e.g., MINS) if causality was proven [12].

Higher levels of postoperative troponin T elevation correlate with increased risk of mortality. In VISION,
The incidence of 30-day mortality was 1.0, 4.0, 9.3 and 16.9% in patients with peak troponin T values of 0.01, 0.02, 0.03–0.29, and ≥ 0.30 ng/ml, respectively (fig. 2) [12]. Higher levels of postoperative troponin elevation also correlate with lower median days to death. A peak troponin T value of 0.03–0.29 ng/ml was associated with median time to death of 9.0 days [interquartile range (IQR) 3.5–16], whereas the median time to death for a peak troponin T value of ≥0.3 ng/ml was 6.5 days [IQR 1.5–15] [12]. The median time from discharge to death was 11 days [IQR 4–15 days] and 26.6% of the patients who died, did so after hospital discharge [12]. Therefore, MINS may serve as a “red flag” or foreshadowing of a more serious vascular event to follow in the next 30 days and up to 1 year after noncardiac surgery [12, 13].

Pathophysiology of perioperative MI and MINS

The precise pathophysiology of perioperative MI and MINS has not yet been clearly defined. The two predominant theories involve myocardial oxygen supply–demand mismatch [15], and coronary artery thrombosis [1, 16]. Multiple factors may increase myocardial oxygen demand perioperatively including fluid shifts, catecholamine surges, hypotension, anaemia, pain, hypothermia and hypoxia [17]. In coronary arteries with high-grade lesions, the inability to respond adequately to increased myocardial oxygen demand may lead to supply–demand mismatch resulting in myocardial ischaemia [1]. Thus, preexisting coronary artery disease (CAD) is an intuitive culprit. However, in an angiographic study involving vascular surgery patients, the majority of MINS occurred in myocardium supplied by arteries without high-grade stenosis [18]. The landmark CARP Trial (510 patients) demonstrated no reduction in perioperative MI with preoperative revascularisation for coronary stenosis ≥70% [19]. The coronary computed tomographic angiography (CTA) VISION Study performed coronary CTA on 955 patients before noncardiac surgery. This study showed that while the majority (72%) of perioperative MIs occurred in patients with obstructive or extensive-obstructive CAD, 24% and 4% of the perioperative MIs occurred in patients with nonobstructive disease or a normal preoperative CTA, respectively [20].

Table 3: Postoperative variables predicting death at 30 days after surgery.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
<th>Adjusted HR (95% CI)</th>
<th>PAR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MINS (TnT ≥0.03 ng/ml)</td>
<td>1200 (8.0)</td>
<td>3.87 (2.96–5.08)</td>
<td>34.0 (26.6–41.5)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>812 (5.4)</td>
<td>7.18 (5.17–9.97)</td>
<td>30.5 (23.7–37.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>81 (0.5)</td>
<td>3.50 (2.05–5.97)</td>
<td>4.5 (1.3–7.8)</td>
</tr>
<tr>
<td>PE</td>
<td>95 (0.6)</td>
<td>6.11 (3.18–11.74)</td>
<td>3.5 (0.9–6.2)</td>
</tr>
</tbody>
</table>

A number of factors contribute to death at 30 days after noncardiac surgery. While sepsis and PE have higher adjusted HR compared to MINS, the PAR for MINS is higher because the incidence of MINS is substantially higher.


![Figure 2: Kaplan-Meier estimates of 30-day mortality based on peak troponin T values.](image_url)
In contrast to CARP, a recent trial randomised 426 patients to preoperative coronary angiography followed by selective percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) versus no preoperative coronary angiogram or revascularisation before elective carotid endarterectomy [21]. This trial demonstrated a reduction in the risk of MI in the group allocated to preoperative coronary angiography ($p = 0.01$). Although this represents encouraging data, there were only six perioperative MIs and thus the results require cautious interpretation because of the fragility of this finding [22].

Evidence also supports coronary artery thrombus as a potential culprit for perioperative MI. Sympathetic activation in the perioperative period promotes a hypercoaguable state by up-regulating platelets and down-grading fibrosis [23–25]. This hypercoaguable state, coupled with increased shear wall stress, may lead to plaque fracture and subsequent thrombus formation [1, 16]. Small autopsy studies in <70 patients who suffered a fatal perioperative MI found intracoronary thrombus in one third of patients [26]. However, given the late timing of autopsy relative to the MI, it is possible that resolution of additional intracoronary thrombus occurred prior to the time of examination [26].

More recently, a study evaluated 120 consecutive patients who suffered a perioperative acute coronary syndrome (PACS) after noncardiac surgery and subsequently underwent coronary angiography [16]. The angiography results of the PACS patients were compared with the angiographic results of a group of 120 patients who suffered a nonoperative ACS (recruited from the emergency room on randomly selected days) and 240 patients with stable CAD (who were recruited prior to angiography on randomly selected days). Angiography in the PACS group showed that 45% of patients had Ambrose’s type II lesions (i.e., findings strongly associated with a disrupted plaque) versus 56.7% in the nonoperative ACS group and 16.4% in the stable CAD group ($p <0.001$) [16]. Both PACS and nonoperative ACS patients had more complex lesions (i.e., intraluminal filling defect, plaque ulceration, plaque irregularity/haziness, or TIMI flow <3) than patients in the stable CAD group (56.7 vs 79.2 vs 31.8%, respectively; $p <0.001$) [16]. These results suggest that a substantial proportion of patients suffering MINS have angiographic evidence that it was due to a thrombotic event, and that the frequency of these findings is similar to that in patients suffering a nonoperative MI.

It seems probable that both intrinsic and extrinsic factors influence patients’ risk of adverse cardiovascular events. It is possible that the underlying mechanism for MINS may vary among patients with different risk factors. The perioperative period is fraught with a multitude of stressors including increased sympathetic stimulation, hypercoaguableity, bleeding, inflammation, hypotension, tachycardia, hypothermia, hypoxia and pain [1, 8]. These stressors, superimposed on preexisting chronic conditions such as renal insufficiency, CAD, peripheral vascular disease, cerebrovascular disease, diabetes, CHF, atrial fibrillation, hypertension, advanced age, male sex [4] and severe aortic stenosis [27], may lead to increased susceptibility to cardiovascular complications. Patients with recent high-risk CAD [4, 28, 29], recent coronary artery stent [28, 29], recent stroke [29], acute trauma (e.g., hip fracture) [30] and the need for urgent or emergency surgery [4] are at particularly high risk of complications including MINS, CHF, nonfatal cardiac arrest, and cardiovascular death [4].

**Perioperative prevention of MINS**

**Clinical risk assessment, noninvasive risk stratification and biomarkers**

Accurate preoperative risk assessment serves a number of important purposes for both physicians and patients. Accurate risk estimates provide physicians with guidance for selection of surgical approach and anaesthetic techniques, as well as the location and intensity of postoperative care [31]. For patients, accurate risk assessment may assist with informed decision-making about the appropriateness or timing of the proposed surgery [31]. For example, patients may forgo an operation if they deem the risk of a major perioperative cardiac complication unacceptable, or they may opt to defer the procedure (e.g., to experience an important life event) [31]. MINS is an independent predictor of death [12], and the risk remains elevated up to a year postoperatively [13]. Therefore, in addition to immediate perioperative complications, patients and clinicians should consider the risk implications for the coming year.

Many surgical patients may have occult cardiac disease, but owing to their underlying disease states (e.g., arthritis, cancer, peripheral vascular disease), their activity level may be insufficient to exhibit symptoms [31]. Thus, for patients undergoing major noncardiac surgery, clinical cardiovascular risk assessment tools have only modest predictive power [17]. Noninvasive cardiac testing (e.g., dobutamine echocardiography, dipyridamole myocardial perfusion scan) may provide some additional predictive value beyond clinical variables [32]; however, data are limited and these investigations are costly and time-consuming. Biomarkers, spe-
pendent predictor of cardiovascular events in the first 30 days after noncardiac surgery [31]. Given that NT-proBNP is more accurate, efficient and less costly than measurement of BNP or NT-proBNP is a powerful, independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery [31]. The preoperative BNP measurement was an independent predictor of perioperative cardiovascular events (death, cardiovascular death, or MI) [OR 44.2, 95% CI 7.6–257.0, P 51.6%] [31]. These results suggest that an elevated preoperative measurement of BNP or NT-proBNP is a powerful, independent predictor of cardiovascular events in the first 30 days after noncardiac surgery [31]. Given that NT-proBNP is more accurate, efficient and less costly than a preoperative noninvasive cardiac stress test suggests that this biomarker is the preferred preoperative cardiac test.

Evidence-based perioperative pharmacology
Increased sympathetic drive increases a patient’s heart rate and hence myocardial demand, which may lead to myocardial oxygen supply–demand mismatch. Moreover, it can also induce a hypercoagulable state [23–25] and catecholamine release that increases shear stress [33]. This may trigger plaque rupture and acute coronary syndromes (ACS) perioperatively [33]. Thus, in an attempt to prevent MINS or major adverse cardiac events (MACE) in the perioperative setting, various agents including β-blockers, α2-adrenergic antagonists, statins and aspirin (acetylsalicylic acid, ASA) have been trialed to reduce the sympathetic response [8, 34], stabilise coronary plaque [35] or to inhibit platelet function [8, 36].

Beta-blockers
Beta-blockers were proposed as a potential cardioprotective agent in the perioperative period [37]. A small trial in the 1990s found that β-blockers had a large effect in preventing perioperative MI; however, it had methodological limitations including not performing an intent-to-treat analysis [37]. Two later trials of moderate size with fewer limitations did not show a benefit of perioperative β-blocker use [38, 39]. POISE, a large international randomised controlled trial (RCT), compared metoprolol with placebo initiated on the day of surgery [8]. The results showed decreased MI (HR 0.73, 95% CI 0.60–0.90, p = 0.002) but a significantly higher risk of stroke (HR 2.17, 95% CI 1.26–3.74, p = 0.005) and death (HR 1.33, 95% CI 1.03–1.74, p = 0.002) [8]. More patients in the metoprolol group experienced clinically important hypotension (HR 1.55, 95% CI 1.38–1.74). Subsequently, a meta-analysis of high-quality trials found that beta-blockade resulted in a 27% relative risk (RR) (95% CI 1.01–1.60, p = 0.04) increase in 30-day mortality, increased stroke risk (RR 1.73, 95% CI 1.00–2.99, p = 0.05) and hypotension (RR 1.51, 95% CI 1.37–1.67, p <0.00001) [40]. Given the association with increased mortality and stroke, current guidelines no longer recommend initiation of β-blocker therapy in the perioperative period [8, 40–42].

Aspirin
Noncardiac surgery is associated with platelet activation [43]. ASA inhibits thrombus formation and observational data had suggested that discontinuation of ASA prior to surgery would result in increased thrombotic risk [44, 45]. A systematic review and two small RCTs showed mixed results but with a potential decreased risk of vascular events in patients on ASA in the perioperative period [46–48]. In contrast, the PEP trial, involving 13356 patients undergoing hip surgery, demonstrated more cardiac ischaemic events (death due to ischaemic heart disease or nonfatal MI) in patients randomised to ASA versus placebo (HR 1.33, 95% CI 1.00–1.78) [49]. There was also an increased risk of bleeding (6 per 1000 patients) [49]. In 2014, POISE 2 (an international, multicentre RCT of 10 010 patients) found a significant increase in major bleeding risk for patients randomised to ASA [36]. ASA-naive patients were randomised to initiation of ASA or placebo, starting on the morning of surgery and continued for 30 days; patients on chronic ASA therapy were randomised to restart ASA or to placebo on the day of surgery and for 30 days thereafter [36]. Patients who had been taking ASA chronically on average stopped it 7 days before surgery. ASA had no significant effect on the primary outcome of death or MI at 30 days (7% in ASA group vs 7.1% in placebo group; HR 0.99, 95% CI 0.86–1.15, p = 0.92). Major bleeding, however, was more common in the ASA group than with placebo (4.6% vs 3.8%; HR 1.23, 95% CI 1.01–1.49, p = 0.04). Major bleeding was defined as a significant drop in haemoglobin requiring red blood cell transfusion or intervention (i.e., embolization, superficial vascular repair, nasal packing); or bleeding in a high risk location (i.e., intraspinal). The authors theorised that while ASA may have prevented some MIs due to coronary artery thrombus, it may have contributed to MI via supply–demand mismatch from bleeding and hypotension, giving rise to an overall neutral MI signal [36]. In summary, the largest trial in this area, with the power to
detect changes in outcome, shows that continuing ASA in the perioperative period causes more harm than benefit [36].

**Statins**

There is overwhelming evidence for the benefit of statin use in secondary prevention for patients who have suffered an MI. Statins may also prevent perioperative complications through pleiotropic mechanisms like plaque stabilisation, anti-inflammatory effects and improved endothelial function [1, 35]. A Cochrane review of three vascular surgery RCTs (178 patients) found a nonsignificant decrease of death and MI at 30 days [50]; two recent systematic reviews, predominantly in vascular noncardiac surgery, found a decrease in MI and all-cause mortality in patients taking statins [35, 51]. However, because of the limited number of cardiac events in dedicated RCTs, there remains uncertainty as to the degree of support for recommendations for perioperative statin use [35, 41, 42, 50].

The VISION study compared 18.4% of patients on statin therapy with 29% of controls. Preoperative statin use was associated with a lower risk of the composite primary outcome (all-cause death, MINS or stroke at 30 days) (HR 0.83, 95% CI 0.73–0.95, p = 0.007) [52]. This was driven by a statistically significant lower risk of MINS and death [52]. This relative effect corresponded to an absolute risk reduction of 2.0% (95% CI 0.5–3.2%, p = 0.005). VISION is the only study to look at the association of statin use with MINS, and the results are hypothesis generating in that preoperative statin use may reduce the risk of adverse perioperative cardiac outcomes [52]. A large RCT is required to evaluate these findings further.

**Alpha-2 adrenergic agonists**

Results of small RCTs initially suggested that clonidine (an α2-adrenergic agonist) may prevent MI [53, 54] by blunting central sympathetic outflow with associated anxiolytic, and anti-inflammatory effects [54, 55]. However, these trials were small (<300 patients) with few events [53–56]. A meta-analysis of 12 RCTs looking at α2-adrenergic agonists in noncardiac surgery showed no difference in overall mortality or MI in the entire study population; however, a decrease in MI and death was found in the vascular surgery subgroup [57]. These findings were driven largely by a trial from 1999 that used mivazerol, an α2-adrenergic agonist [56, 57].

More recently, POISE 2, found that clonidine did not reduce the rate of death or nonfatal MI at 30 days (HR 1.08, 95% CI 0.93–1.26, p = 0.29) [34]. It did, however, increase the rate of nonfatal cardiac arrest (HR 3.20, 95% CI 1.17–8.73, p = 0.02) and clinically important bradycardia (HR 1.49, 95% CI 1.32–1.69, p <0.001) and hypotension (HR 1.32, 95% CI 1.24–1.40, p <0.001). While enhanced heart rate control may be protective [8], perioperative hypotension is an independent risk factor for perioperative MI [34, 58]. Thus, in the largest trial in this area, α2-adrenergic agonists were not protective and increased the risk of significant perioperative hypotension and bradycardia [34].

**Perioperative hypotension**

POISE demonstrated that clinically significant hypotension (defined as systolic blood pressure <90 mm Hg requiring intervention) had the largest PAR (37.3%) for perioperative death and the largest PAR for stroke (14.7%) [8]. In POISE 2, more patients in the clonidine group had clinically important hypotension, bradycardia and an increased risk of nonfatal cardiac arrest [34]. Prospective observational studies have suggested an association between intraoperative hypotension with myocardial injury [59, 60] and 30-day mortality [58]. A recent cohort study on perioperative hypotension assessed adults ≥60 years of age undergoing vascular surgery with routine troponin monitoring on postoperative days 0–3 [59]. The authors found that intraoperative hypotension (defined as decrease of 40% from preinduction mean blood pressure for >30 minutes) was associated with increased postoperative myocardial injury (RR 1.8, 95% CI 1.2–2.6, p <0.001) [59]. The association of hypotension with adverse cardiac events has important implications for perioperative management of antihypertensive agents. In POISE 2, clinically important hypotension occurred more often after patients left the postanaesthetic care unit (PACU). In the clonidine group, the median intraoperative period of hypotension was 15 minutes and on the first postoperative day it was 180 minutes [34]. This highlights the need for caution regarding the use of antihypertensives in the perioperative setting, including consideration of omitting some or all antihypertensive agents on the day of surgery, careful reintroduction of antihypertensives postoperatively, and close monitoring of vital signs once the patient has returned to the ward after surgery. Future studies are required to assess whether close monitoring for postoperative hypotension with rapid, protocol-driven intervention may be cardioprotective.

**Treatment options for MINS**

Data that informs on the optimal treatment for MINS patients is limited; however, extrapolation from the ACS literature [61, 62] and other recent perioperative work [52, 63, 64] provides the modern day clinician...
with a reasonable strategy until future RCTs provide further guidance. Examination of the placebo arms from ACS studies demonstrates that some patients survive, and may do well clinically, despite not being on the active agent [65]. However, at the time of the acute event, it is not possible to predict with precision which patients will benefit from the drug and which patient will not and thus clinicians err on the side of caution by prescribing a standard cocktail of cardiac medications to each ACS patient.

Multivariable regression analysis among patients suffering MINS from the original POISE Trial identified two drugs that were associated with reduced 30-day risk of death: ASA [adjusted odds ratio (aOR) 0.54, 95% CI 0.29–0.99] and statin [aOR 0.26, 95% CI 0.13–0.54] [8]. In a propensity-matched study on 1-year outcomes (death, MI, coronary revascularisation, or CHF requiring hospitalisation), 66 MINS patients were compared with 132 matched non-MINS patients (controls) [64]. Among the MINS patients, 43 received therapeutic intensification of ≥1 of four cardiac medications [ASA, statin, β-blocker, angiotensin-converting enzyme inhibitor (ACE inhibitor)], while 23 patients did not receive therapeutic intensification after MINS. MINS patients not receiving therapeutic intensification had a hazard ratio of 1.77 (95% CI 1.13–2.42) while MINS patients receiving therapeutic intensification had a hazard ratio of 0.63 (95% CI 0.11–0.19) [64]. These data suggest that secondary cardiac prevention interventions may benefit MINS patients.

MANAGE (an international, multicentre RCT) is currently evaluating the impact of an anticoagulant (dabigatran 110 mg b.i.d) versus placebo on major vascular complications in patients suffering MINS [66]. INTREPID (an open-label, randomised pilot study) is currently evaluating the impact of ticagrelor (anti-platelet agent, 90 mg bid) versus ASA (81 mg) on the rate of cardiovascular events in patients with elevated troponin levels after major, noncardiac surgery [67]. More treatment-focused RCTs are needed, but until these trials are conducted, the evidence in the available literature suggests that pharmacological intensification for MINS patients may prove beneficial and possibly even life-saving. At the very least, these patients need to be identified and referred to internal medicine or cardiology departments for close outpatient follow-up, preferably within 1 week of discharge given that the median time to death following MINS was found to be 11 days [12].

A cost-consequence study analysed the cost associated with postoperative troponin monitoring, including the assumption that every patient will have an echo-cardiogram and therapeutic cardiac medication intensification [68]. This study demonstrated that postoperative troponin monitoring, which predicts death within 30 days, is profoundly less expensive than cancer screening which typically predicts death within several years.

Conclusion

MINS is common and is associated with poor outcomes. One in ten patients suffering from MINS will die in 30 days after noncardiac surgery [12]. Failure to monitor troponin after noncardiac surgery will miss over 80% of MINS events [12]. The current model of perioperative patient care lacks continuity of care, and it is easy to assume that patients do well postoperatively if they are not followed longitudinally. Clinicians are unlikely to attribute a MI occurring 6 weeks after surgery to a complex cascade of inflammation and hypercoagulation that was first initiated during the perioperative period. However, there is strong evidence to support the conclusion that MINS is an important and clinically relevant entity with a profound impact on perioperative mortality [4, 12, 13]. Dismissal of asymptomatic perioperative troponin elevation as “troponitis” comes at a risk to patients. Clinicians should recognise MINS as a marker of increased risk of perioperative morbidity and mortality. Furthermore, clinicians should be proactive in monitoring troponin postoperatively for patients with elevated cardiovascular risk [4, 12]. Offer MINS patients cardiac medications for secondary prevention (including ASA, statin, plus consideration of an ACE inhibitor and potentially a beta-blocker) [52, 63, 64] and arrange timely patient follow-up with internal medicine or cardiology departments after hospital discharge.

A shared care model that integrates anaesthesia, internal medicine, cardiology and surgery would be a step forward in helping to ensure the continuity of perioperative patient care while providing potentially life-saving risk stratification and secondary prevention.

Disclosure statement

Dr Devereaux is a member of a research group with a policy of not accepting honorariums or other payments from industry for personal financial gain. They do accept honorariums/payments from industry to support research endeavours and to participate in meetings. Based on study questions Dr Devereaux has originated and grants he has written, he has received grants from Abbott Diagnostics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Coviden, Octapharma, Philips Healthcare, Roche Diagnostics and Stryker. Dr Devereaux has participated in an advisory board meeting for GlaxoSmithKline and an expert panel meeting with AstraZeneca and Boehringer Ingelheim.

References

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


A pragmatic approach based on current guidelines and point-of-care platelet function testing

Antiplatelet therapy before cardiac surgery

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Introduction

Bleeding complications and perioperative acute coronary events after coronary artery bypass grafting (CABG) are strongly influenced by the management of pre- and postoperative antithrombotic therapy. Haemorrhagic events needing transfusion of blood products increase perioperative morbidity and mortality and compromise the long-term benefits of CABG [1, 2].

In the last decade, antithrombotic therapy has become more effective and reliable, particularly in the catheter laboratory. Indeed, the success of percutaneous transluminal coronary angioplasty (PTCA) in the context of an acute coronary syndrome (ACS) has improved with the availability of new antiplatelet compounds [3].

Approximately 10% of ACS non-ST-elevation myocardial infarction (NSTEMI) patients will require urgent CABG during their acute hospitalisation, with or without a stent already implanted [4]. These patients evoke a decisional challenge on many levels because of the delicate balance between effective antiplatelet treatment and risk for major bleeding: choice of the right platelet inhibitory drug, timing of surgery, diagnostic and therapeutic strategy before, during and after CABG. There are some published data confirming the high bleeding rate under double antiplatelet therapy (DAPT) [5, 6]. There is, however, a lack of prospective, randomised clinical trials testing and revealing the best strategy in this regard.

The clinical significance of this issue urged the various scientific societies and associations involved to issue guidelines on how to deal with DAPT and the need of CABG based on best available evidence and clinical knowledge.

The aim of this review is to summarise these guidelines and their recommendations according to a generally accepted methodology [7] and to suggest a tailored and applicable approach to these difficult clinical decisions.

Overview of antiplatelet agents and their mechanisms of action

Several platelet inhibitory drugs with different mechanisms of action and routes of administration are nowadays available on the market. These treatments are routinely employed to prevent myocardial infarction in cases of ACS or thrombosis after coronary stent implantation. Mechanisms of action, doses and recovery times after withdrawal of the therapy to prevent perioperative bleeding risk during surgery are briefly summarised in figure 1 and table 1.

Review of current guidelines

Back in 2009 the Canadian Cardiovascular Society recommended that “all ACS patients should be considered for dual antiplatelet therapy with ASA [acetylsalicylic acid] and clopidogrel at the earliest opportunity, despite the possibility of a need for urgent CABG.”
For patients who have received clopidogrel and ASA, and require CABG: those at high risk of an early fatal event (e.g., with refractory ischemia despite optimal medical treatment), and with high-risk coronary anatomy (e.g., severe left main stenosis with severe right coronary artery disease), should be considered for early surgery without discontinuation of clopidogrel.

In patients with a high bleeding risk (e.g., previous surgery, complex surgery) who are also at high risk for an ischemic event, consideration should be given to discontinuing clopidogrel for three to five days before surgery. Patients at a lower risk for ischemic events...
(most patients) should stop clopidogrel five days before surgery. The risk of major bleeding in patients undergoing CABG within five days of treatment with clopidogrel and ASA can be minimized by applying multiple strategies before and during surgery” [8]. Besides the differentiated management of antiplatelet therapy, which will be discussed in this paper, surgical strategies aiming to minimise bleeding should also be applied. Avoiding extracorporeal circulation (ECC) could be one of those. Should complete surgical revascularisation be technically difficult in an “off pump” scenario, a culprit-centered surgical approach completed by PTCA – during the same procedure or (preferably) deferred – should be discussed and planned with the interventional cardiologists (hybrid revascularisation). In the case of an “on pump” procedure, coated ECC circuits permit the use of less heparin and can have a positive impact on blood activation. This can reduce the amount of shed blood and activation of fibrinolysis during surgery [9, 10]. The use of anti-fibrinolytic agents such as tranexamic acid can also reduce intra- and postoperative fibrinolysis and reduce overall bleeding [11, 12].

The Society of Thoracic Surgeons, in a 2012 guideline update on use of antiplatelet drugs in patients having cardiac and noncardiac operations, suggested that aspirin could or should be discontinued before elective CABG in patients without ACS (Class IIa, Level B). The same guideline [13] stated: “Discontinuation of P2Y12 inhibitors for a few days before cardiovascular operations is recommended to reduce bleeding and blood transfusion, especially in high-risk patients. Stopping antiplatelet drugs before operation is associated with reduced bleeding, blood transfusion, and reoperation but not with increased postoperative death, myocardial infarction, or stroke. The interval between discontinuation of antiplatelet drugs and operation is uncertain and depends on multiple factors mostly related to patient drug responsiveness and thrombotic risk. This recommendation was given a Class I, Level B level of evidence” [13]. There was no recommendation on the exact number of days before surgery to discontinue DAPT, since “the interval between discontinuation of anti-platelet drugs and operation is uncertain and depends on multiple factors mostly related to patient drug responsiveness and thrombotic risk” [13]. However, the same guidelines state that for patients on DAPT who require urgent operation “it is reasonable to make decisions about surgical delay based on tests of platelet inhibition rather than arbitrary use of a specified period of surgical delay (Class IIa, Level B)”.

In the most recent guidelines issued by the American Heart Association and American College of Cardiology and developed in collaboration with the Society for Cardiovascular Angiography and Interventions and Society of Thoracic Surgeons [14], a specific section was dedicated to the timing of urgent CABG in patients with NSTEMI type of ACS, depending on the patient’s cardiac risks as well as on pharmacokinetic and pharmacodynamic properties of antiplatelet drugs:

Non-entrant-coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG (Class I, Level B). In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery (Class I, Level B) and prasugrel for at least 7 days before surgery (Class I, Level C). In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding (Class I, Level B). In patients referred for CABG, short-acting intravenous glycoprotein (GP) IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion (Class I, Level B). In patients referred for urgent CABG, it may be reasonable to perform surgery less than 5 days after clopidogrel or ticagrelor has been discontinued and less than 7 days after prasugrel has been discontinued (Class IIb, Level C).

The recent guidelines are completed by the “Expert Position Paper” of the European Society of Cardiology published in 2014 [15]: there is a Class I (Level C) recommendation regarding low-dose ASA: “low-dose ASA (75–160 mg) should be maintained in patients undergoing CABG surgery.” However, and similar to the STS guidelines, for patients with increased bleeding risk and for those who refuse blood transfusion, withdrawal of ASA 3–5 days before surgery is recommended, based on individualised assessment of ischaemic and bleeding risks [15]. Regarding the use of P2Y12 inhibitors in patients needing CABG, it is recommended to postpone surgery for 5 days after interruption of ticagrelor or clopidogrel, and 7 days for prasugrel, unless the patient is at high risk of ischaemic events (Class I, Level B) [15].

The same position paper expresses important additional recommendations:

Heart team assessment and platelet function monitoring

1 The risks of bleeding and thrombosis, and decision-making regarding DAPT and timing of surgery should be assessed by the heart team prior to CABG surgery (Class I, Level C).

2 It is reasonable to base timing of surgery on platelet function monitoring rather than arbitrary use of a specified period of delay in patients on DAPT (Class IIa, Level C).
Bridging therapy
1 Bridging with cangrelor, if available, is recommended in high-risk patients (Class I, Level B recommendation).
2 Bridging with short-acting intravenous GPIIb/IIIa inhibitors may be considered in patients at high risk for ischaemic events (Class IIb, Level C).

Point-of-care platelet function analysis approach: tailoring of decision-making

Several methods for platelet function testing are available nowadays [16–19]. Most of them, as for example light transmission aggregometry, which is still considered the reference method and "golden standard", must be performed on centrifuged platelet-rich plasma in a laboratory setting. These in-laboratory tests can be complex, time-consuming and require special laboratory training. Point-of-care (POC) tests on whole blood were recently developed. These new analyses can be performed outside a classical laboratory, in a near patient setting, for example in the operating theatre or in the intensive care unit [20]. Potential advantages of this kind of test could be readily available results, simplified workflow (rapid turnaround time, no transport of sample to laboratory) and targeted management of coagulation disorders. Of this newly available technology, two devices (VerifyNow® and Multiplate®) are the more routinely employed to assess efficacy and intensity of DAPT in cardiac patients. VerifyNow® (Accumetrics, San Diego, CA, USA) is a fully automated device not requiring any pipetting. A citrated tube containing the blood sample is directly inserted within the mixing chamber of special disposable cartridges. Cartridges contain fibrinogen-coated polystyrene beads and specific platelet activators [arachidonic acid (AA) or adenosine diphosphate (ADP)]. Stimulated platelets activate GPIIb/IIIa receptors on their surface, which bind fibrinogen on the beads. Agglutinated beads and platelets complexes fall out of the solution, which becomes more transparent. Light transmittance through the mixing chamber is continuously measured by the device and directly correlated.

Figure 2: Working mechanism of VerifyNow® system (modified from [37], with permission of Springer).
to the proportion of platelet activation. Direct pharmacological blockade of receptors or decrease of their expression by inhibitor drugs diminishes platelet aggregation and therefore light transmittance (fig. 2).

The Multiplate® analyser (Roche Diagnostics, Rotkreuz, Switzerland) is a whole-blood assay that utilises electrical impedance aggregometry to measure platelet function [21]. Impedance aggregometry is based on the principle that platelets are nonthrombogenic in their resting state, but change shape and expose receptors on their surface when activated, allowing them to adhere to vascular injuries and artificial surfaces. The Multiplate® analyser provides a disposable test cuvette containing two independent sensor units, each consisting of two highly conductive metallic wires. A small quantity of whole blood anticoagulated with hirudin is mixed with a saline solution and incubated briefly. A specific platelet activator is then added to the solution (e.g., AA, ADP or thrombin-receptor-activating peptide [TRAP]). Activated platelets adhere to and aggregate on sensor electrodes immersed in blood. This leads to an enhanced resistance between sensor metallic wires, which is continuously recorded (over a 6-minute period) and expressed as aggregation units (fig. 3).

In conclusion, light transmittance aggregometry (VerifyNow®) and impedance aggregometry (Multiplate®) are two bedside platelet function analysis devices able to measure, in whole blood, specific drug-induced platelet inhibition. Resistance (high on-treatment platelet reactivity) to some antithrombotic therapies (e.g., clopidogrel) or strong inhibition associated with increased risk of bleeding can nowadays be quickly and easily measured in the perioperative setting. It has to be noted, however, that platelet aggregation by itself might be inadequate to assess the bioavailability of an antiplatelet agent [22] and its potential effects on clinically relevant thrombotic or bleeding events.

**Discussion**

Drug-eluting stents were introduced more than 10 years ago with a main aim to counteract the significant rate of restenosis occurring with bare metal stents. The antiproliferative properties of the eluted drugs were...
proved to be effective against the proliferation of smooth muscle cells. At the same time, however, they inhibited and delayed new endothelialisation, resulting in longer exposure of thrombogenic material to the bloodstream [23]. The need to increase the intensity and specificity, as well as to prolong the duration, of DAPT was the direct consequence and the right choice to protect patients from deleterious acute stent thrombosis [24]. There are still more aspects of midterm DAPT to be clarified for every specific stent subcategory, but the tendency seems, however, to be towards longer periods of DAPT therapy.

In the acute setting, especially NSTEMI-type of ACS, and with special regard to patients needing urgent (or emergent) CABG surgery, the right strategy is more difficult to standardise. Clinical instability can impose an earlier than foreseen operation, which in turn can cause significant bleeding despite best efforts to treat coagulopathy during and after surgery. Here the individualised concept of the POC measurements can eventually help us with the decision.

In cardiac surgery, especially on pump, bleeding can be associated with multifactorial causes. Preoperative strong antiplatelet-drug-induced inhibition is an important contributory factor that is correlated with increased postoperative bleeding and platelet transfusion requirement [2, 25–30]. Preoperative platelet function analysis can, therefore, be helpful to assess bleeding risk before cardiac surgery in patients treated with DAPT. A clear cut-off value of platelet function that avoids severe perioperative bleeding has not been identified so far.

Two single-centre retrospective studies using impedance aggregometry (Multiplate®) showed a relationship between intensity of preoperative thienopyridine inhibition of the P2Y12 receptor and severity of perioperative bleeding [26, 31]. In the first study, published in 2011, the primary endpoint was severe postoperative bleeding defined as more than 800 ml chest drain blood loss in the in first 12 postoperative hours. A cut-off value for the ADP test at 31 U predicted postoperative severe bleeding quite accurately. In a second retrospective study, published by the same group in 2014 and including a larger cohort of 361 patients, severe bleeding was defined in a more restrictive way using the Universal Definition of Perioperative Bleeding in

**Figure 4:** Preoperative decisional flow-chart as used currently at the Cardiocentro Ticino.

ADP = adenosine diphosphate; TRAP = thrombin receptor activating peptide.
adult cardiac surgery (severe bleeding defined as drain fluid loss >1000 ml in the first 12 postoperative hours, or need of surgical re-exploration, or need of >5 units of red blood cells or fresh frozen plasma). In this study the ADP threshold was lower than in the first publication. A threshold of 22 U yielded a negative predictive value for severe postoperative bleeding of 94%. Thrombin platelet activation capacity (via protease-activated receptor stimulation) was also assessed using the thrombin receptor activating peptide (TRAP) test. A TRAP test result of ≥75 U was associated with a negative predictive value of 95% for severe postoperative bleeding [31].

POC coagulation assessment was introduced 5 years ago by anaesthesiologists in our centre and since then has been routinely used to check perioperative haemostasis. Impedance aggregometry on whole blood (Multiplate®) was locally chosen by us as platelet function analyzer on the basis of highly correlated results and good agreement with the in-laboratory reference method (light transmission aggregometry on centrifuged platelet-rich plasma [32, 33] despite some conflicting cross-comparisons [34, 35]). Furthermore, Multiplate® showed satisfactory validity in the perioperative cardio-surgical setting [36]. Notwithstanding little widely confirmed scientific evidence, we locally decided to develop a simple individualised decision-making preoperative algorithm based on platelet function for cardio-surgical patients on DAPT. This algorithm is intended to help us to determine the time of surgery and management of perioperative antiplatelet therapy. Platelet function is assessed in our centre by impedance aggregometry on whole blood (Multiplate®). Our local algorithm (fig. 4) is based on the few published studies presented above. It has to be stressed that this approach is not further validated and needs to be confirmed by appropriate trials or at least registries reporting on bleeding rates, particularly if the operation took place earlier than recommended, based on the POC result. In order to limit as much as possible the risk of bleeding of our surgical patients, we decided to keep in our algorithm the most protective ADP test cut-off of 31 U [26], even after publication of the second study of Ranucci et al. [31]. Simultaneous TRAP testing is also always assessed and a recovery of more than 75 U is mandatory to confirm an adequate response to thrombin-mediated activation of the platelets and to further decrease the risk of severe bleeding.

POC coagulation assessment can be a useful adjunct in our decisional armamentarium when we are called on to operate on patients under DAPT. Carefully designed and monitored randomised studies are needed to verify the validity of this approach.

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

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The full list of references is included in the online article at www.cardiovascmed.ch.
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Coronary artery status assessed with coronary computed tomography angiography

Five-year prognosis in patients with normal coronary arteries

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Known, even if in the CONFIRM trial these patients are doing well in the long term [4]. It has recently been reported that coronary artery disease severity on CCTA is strongly correlated with the occurrence of major adverse cardiac events (MACE). Most of these studies are limited because of the short follow-up (no longer than 2 years) and the heterogeneity of the studied population. In addition, no long-term data are available on the value of CCTA in patients with suspected ischaemic heart disease and normal coronary arteries. Accordingly, the aim of the present study was to evaluate the long-term prognostic role of normal CCTA findings in a cohort of patients with suspected ischaemic heart disease.

Materials and methods

Patients and study protocol

The screened population consisted of consecutive patients who presented to our outpatient clinic for cardiac evaluation (exercise electrocardiogram, stress echocardiography or invasive coronary angiography) between April 2005 and March 2007 because of suspected coronary artery disease. Ischaemic heart disease was suspected on the basis of the patient history (new-onset chest pain), a high-risk profile, or abnormal or inconclusive stress test. In all patients, CCTA was performed in addition to the standard clinical workup in order to clarify the diagnosis of possible coronary artery disease. Some patients were excluded because they met at least one of the following exclusion criteria: unwillingness to participate or high probability of loss in follow-up, allergy to iodine contrast agents, known cardiovascular disease and coronary artery disease on CCTA. Thus, the analytical study population consisted of 200 patients with normal CCTA. Normal CCTA was defined as well visualised coronary arteries without any calcifications, narrowing or wall abnormalities (fig. 1). Patients with soft plaques were also excluded. The study was approved by our institutions’ scientific and ethical committees, and all patients gave informed consent.

Key words: cardiac computed tomography; normal coronary arteries; ischaemic heart disease; coronary stenosis
A structured interview was conducted and a clinical history acquired. The following cardiac risk factors were assessed before CCTA: diabetes mellitus, hypercholesterolaemia, hypertension (blood pressure over 140/90 mm Hg or use of antihypertensive medications), positive family history of coronary artery disease, and current tobacco usage. Pretest probability of ischaemic heart disease was calculated based on the standard recommendations of the American Heart Association, and the Framingham cardiovascular disease (CVD) score was calculated [5–6].

Patient preparation, scan protocol and image reconstruction
Up to 20 mg of metoprolol was intravenously administered before CCTA in patients with heart rates >90 beats/min. In all patients, CCTA was performed using a 64-slice scanner Toshiba Aquilion (64 0.625-mm collimation, 330-ms gantry rotation time, VCT, Toshiba Medical Systems, Tokyo, Japan). Dose modulation was attained with “electrocardiographic gating” for a maximum gantry delivery between 40 and 80% during the R-R interval. Reconstructions were retrospective. A bolus of 80 ml of high concentration contrast (Iomeron 400 mg/ml, Bracco Imaging, Milan, Italy) was administered intravenously at 5 ml/s, followed by 50 ml of saline injected at the same infusion rate. The scan was initiated according to the bolus-tracking technique.

CCTA procedure
Two expert assessors unaware of the patients’ clinical status evaluated all CCTA examinations. In the case of disagreement, a joint reading was performed and a consensus decision was reached. Coronary arteries were divided into 16 segments according to the American Heart Association classification [7]. Each segment was classified as interpretable or not. Patients were excluded when a proximal segment, mid-segment or more than three segments were uninterpretable. If a segment contained calcific plaques, the patients were excluded from the study. Coronary arteries were defined as normal provided no calcium was present along the complete artery. Reconstructions were performed at the time of the CCTA testing.

Follow-up
Follow-up, either clinic visit or telephone interview, was performed by two trained research nurses. A standardised questionnaire was used. Prognosis was measured as an endpoint of cardiac fatal event and nonfatal event. Patients were contacted by telephone and in the event of doubt their general practitioner was contacted. Finally, 42% of the patients had a clinical visit at time of follow-up. Patients were followed up for the occurrence of: (1) cardiac death, (2) nonfatal myocardial infarction, (3) unstable angina requiring hospitalisation, and (4) revascularisation. Follow-up was performed during the month following the end of the 5th year after the baseline CCTA. Patients were regularly followed up by their general practitioner and once a year by the research nurse in charge of the follow-up. In an unclear clinical situation the patient was evaluated by a cardiologist. At follow-up, deaths were reviewed and classified as cardiac (death caused by acute myocardial infarction, ventricular arrhythmia or refractory heart failure) or noncardiac. Myocardial infarction was defined as recommended by the European Heart Association [8]. The diagnosis of nonfatal myocardial infarction was based on the presence of typical chest pain, elevated cardiac enzymes, and typical ECG changes.

Statistical analysis
Statistical analysis was performed using SAS (SAS Institute Inc., Cary, North Carolina). Continuous variables are presented as mean ± standard deviation, and discrete variables as absolute numbers and percentages.

Results
Of the 506 patients prospectively screened, 306 were excluded because CCTA images showed clear coronary
artery disease or calcifications in 292 patients (95%) or were uninterpretable in 12 patients (4%). Two patients (1%) were excluded because of lack of consensus between the readers (table 1 and 2). Among these 306 patients, 146 (48%) had plaque with insignificant coronary stenosis and 160 (52%) showed significant coronary stenosis which was further confirmed by invasive coronary angiography. In the 200 patients with normal CCTA, the pretest probability of coronary disease at 10 years using the Framingham score was 25 ± 15%, although in the 200 patients with normal coronary arteries it was 13 ± 4%. Demographic data are shown in table 1. Of the 200 remaining patients, follow-up was available for all (100%). Incidence of MACE during follow-up was 2% and two patients died (1%). Cause of death was chronic obstructive pneumopathy in one patient and sepsis in the other. Nonfatal endocarditis occurred in one patient (0.5%) and one patient underwent percutaneous closure of a septum secundum atrial septal defect. No patient experienced myocardial infarction or acute coronary syndrome, or developed chronic angina pectoris. The mean radiation exposure was 10 ± 4 mSv in our patients.

### Discussion

CCTA is considered a reliable method for ruling out coronary artery disease and detecting obstructive coronary stenosis [9–10]. However, data supporting the long-term prognostic value of CCTA, especially in patients with strictly normal coronary arteries, are limited. Prior studies have demonstrated a good predictive value of CCTA for mortality and morbidity from coronary artery disease [11–12]. Severity of coronary artery disease at CCTA has predictive value at 16 months, as recently shown [13], and this was also confirmed by the CONFIRM registry [4]. Our study had a longer follow-up in a very selected and completely homogeneous cohort of patients. We specifically demonstrated that patients without coronary artery stenosis had excellent long-term prognosis at 5 years with no occurrence of coronary events recorded. Pretest coronary artery disease probability was rather low at 25% in this group of patients. This is not surprising since all patients had normal coronary arteries.

The main message of our study is that patients with normal coronary arteries have a very favourable 5-year prognosis. Indeed none of our 200 patients experienced major adverse cardiac events during the follow-up period. In this group of patients, at relatively low risk, CCTA has a good prognostic value. In agreement with other studies with shorter follow-up of enrolled patients [14], our study confirmed that the absence of coronary artery disease at CCTA is associated with a high event-free survival rate for all cardiac events at 5 years. This is certainly owing to the absence of plaque at inclusion more than control of risk factors. We believe that this diagnostic modality can be safely used to exclude coronary artery disease in patients with suspected coronary artery disease and especially to reassure patients with intermediate results of stress tests, scintigraphy or stress echocardiography, without the need for an invasive coronary angiogram. A major concern of CCTA in comparison to stress echocardiography and stress test is radiation exposure. However, different approaches in the use of CCTA have been shown to reduce radiation exposure considerably [15, 16]. Our data also confirm the excellent survival of patients with a normal CCTA as it has also been shown for patients with normal invasive coronary angiography [17–19]. However, at 7–10 years the survival rate is lower for patients with normal coronary angiography than for patients with normal CCTA. This reflects the difference between CCTA and invasive angiography in the assessment of normal coronary arteries, CCTA being probably more accurate to demonstrate “normal coronary arteries”. In these cited studies, some patients were

### Table 1: Characteristics of the study population.

<table>
<thead>
<tr>
<th>Patients with normal coronary angiogram (200 pts)</th>
<th>Patients with abnormal coronary angiogram (306 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Age (years)</td>
</tr>
<tr>
<td>64 ± 17</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>126 (63%)</td>
<td>240 (78%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td>28 (14%)</td>
<td>68 (20%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>Smokers</td>
</tr>
<tr>
<td>72 (36%)</td>
<td>103 (34%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>88 (44%)</td>
<td>182 (60%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>Dyslipidaemia</td>
</tr>
<tr>
<td>102 (51%)</td>
<td>235 (77%)</td>
</tr>
<tr>
<td>Heredity</td>
<td>Heredity</td>
</tr>
<tr>
<td>54 (27%)</td>
<td>92 (30%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Dyspnoea</td>
</tr>
<tr>
<td>26 (13%)</td>
<td>36 (12%)</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>Atypical chest pain</td>
</tr>
<tr>
<td>110 (55%)</td>
<td>60 (19%)</td>
</tr>
<tr>
<td>Typical chest pain</td>
<td>Typical chest pain</td>
</tr>
<tr>
<td>32 (16%)</td>
<td>180 (59%)</td>
</tr>
<tr>
<td>Routine check-up</td>
<td>Routine check-up</td>
</tr>
<tr>
<td>32 (16%)</td>
<td>30 (10%)</td>
</tr>
<tr>
<td>Framingham score</td>
<td>Framingham score</td>
</tr>
<tr>
<td>13 ± 4%</td>
<td>25 ± 15%</td>
</tr>
</tbody>
</table>

### Table 2: Disposition of the patient population.

<table>
<thead>
<tr>
<th>506 patients screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>202 patients with coronary disease</td>
</tr>
<tr>
<td>214 patients</td>
</tr>
<tr>
<td>12 patients with uninterpretable CT</td>
</tr>
<tr>
<td>202 patients</td>
</tr>
<tr>
<td>2 patients refused to participate</td>
</tr>
<tr>
<td>200 patients included</td>
</tr>
</tbody>
</table>
classified as having “normal coronary arteries”, based on invasive coronaryography; small plaques might have been present, but not diagnosed, with an impact on long-term prognosis. These patients would certainly not have been attributed to the “normal coronary arteries” group when evaluated by CCTA. Radiation exposure could be a concern. However, it was a rather low dose in our cohort of patients and with modern CT machines the dose dramatically decreases from 4 to 6 times to a total dose of 1 to 2 mSv. Some limitations must be considered. This was a single-centre study with a significant but limited number of patients. The cohort of patients as selected does not represent the daily practice of cardiologist since most of the patients have more typical symptoms than the ones included in this trial. However, our results show that in selected patients with normal coronary arteries CCTA is a very good diagnostic tool to exclude coronary artery disease and gives major information on long-term prognosis.

Conclusions
CCTA provides very helpful information in patients with unknown coronary artery disease and provides important prognostic information in patients with normal coronary arteries showing excellent long-term prognosis without coronary events. CCTA is useful in patients with a low pretest probability of ischaemic heart disease, atypical symptoms and in whom definitive exclusion of the disease is required.

Disclosure statement
None to declare.
This work was supported by the “Fonds scientifique cardiovasculaire, Fribourg”.

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A novel device for treatment of ventricular arrhythmias and prevention of sudden cardiac death

The subcutaneous implantable cardioverter-defibrillator: pros and cons

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Summary

The subcutaneous ICD (S-ICD) has recently been introduced as an alternative to transvenous devices. The system preserves venous access and reduces risk of lead issues and of systemic infection. However, pacing for antitachycardia, antibradyarrhythmia and cardiac resynchronisation therapy is not available, and the risk of inappropriate shocks is relatively high (although it is improving). This article provides an overview of this novel therapy and discusses its advantages and shortcomings.

Key words: subcutaneous; implantable cardioverter defibrillator; indications

Introduction

Since the first implantable cardioverter-defibrillator (ICD) was implanted in a human in 1980 [1], technological advances have made these devices the most effective treatment option for the prevention of sudden cardiac death in both primary [2, 3] and secondary [4, 5] settings. Currently, the vast majority of implanted devices are transvenous ICDs (TV-ICDs), with one or more leads implanted in the heart via the venous system and connected to a pulse generator located most frequently in the subcutaneous or submuscular tissue in the pectoral region. These systems are prone to a certain number of complications, both acute (pneumothorax, lead dislodgment, cardiod perforation, tamponade) and chronic (systemic infections, venous stenosis or occlusion and lead failure). For example, the rate of implant-related complications is estimated to be around 2–3% with TV-ICDs [6, 7], rising to 6% in the case of cardiac resynchronisation therapy-defibrillator (CRT-D) devices [8]. However, it is the rate of chronic complications, most notably lead failure, that is the most troublesome, with rates of surgical revision of 2.5% at 5 years [9] and with potentially dramatic consequences such as inappropriate shocks (IAS), ineffective therapy and loss of pacing. Young, active patients are especially at risk of lead failure owing to their longer life expectancy and the increased mechanical stress placed on the leads. Moreover, lead failure constitutes, with device infection, one of the main indications for device extraction, a procedure itself linked to a relatively high morbidity (up to 2.4%) and mortality (up to 1%), as recently shown by the Electra registry [10]. In effect, lead integrity seems to be the Achilles heel of TV-ICD devices.

For these reasons, interest has grown in developing alternative novel ICD systems that reduce or eliminate vascular injury, minimise lead mechanical stress and vascular interaction, and may be more practical to implant than epicardial systems. Attention turned to subcutaneous systems, at first in the paediatric population, with initial systems consisting of standard TV-ICD leads implanted in a subcutaneous position [11], but necessitating epicardial sensing and pacing leads [12, 13]. Finally, a dedicated subcutaneous ICD system (S-ICD system, Cameron Health, San Clemente, CA, USA) has been recently developed and approved for use in Europe in 2009 and the USA in 2012 [14]; such a device represents a possible alternative to TV-ICDs in patients without an indication for bradycardia pacing or cardiac resynchronisation therapy (CRT), or the need for antitachycardia pacing (ATP).

Description of the therapy

The S-ICD device

The S-ICD, now in its second version (Emblem S-ICD model, fig. 1) and manufactured by Boston Scientific (Marlborough, MA, USA), consists of a pulse generator and a tripolar subcutaneous lead. The current pulse generator is 20% smaller than the initial model (SQ-RX), weighing 130 g and occupying 59.5 cc of volume, and has a greater durability, with an estimated life of 7.3 years. The tripolar lumenless lead is made of polyurethane and consists of an 8 cm shocking coil banked by distal and proximal sensing electrodes. There is a dedicated tablet-format programmer with
relatively simple programming options. The device is enabled for wireless remote monitoring.

Implantation procedure
The procedure is performed under either local or general anaesthesia. Briefly, the pulse generator is placed either in the subcutaneous tissue or the intermuscular plane between the serratus and latissimus dorsi muscles, overlying the sixth rib in between the mid-axillary and anterior axillary lines (fig. 2). The electrode is tunneled to a position of maximum 1 to 2 cm to the left of and parallel with the sternal midline via one to two parasternal incisions, one (optional) distally at the manubriosternal junction (second rib) and one proximally at the xiphoid process. Electrode stability is assured with an optional distal suture on the periostial fascia above the sternum and ribs, and with the use of an anchoring sleeve proximally at the xiphoid process. The whole implantation procedure is realised with the use of anatomical landmarks and usually without the need for fluoroscopy (<1% in the IDE study sanctioned by the US Food and Drug Administration [15]). Average procedural time in the largest worldwide registry (EFFORTLESS registry [16]) was 69 ± 27 minutes. Figures 3A and B show a patient on the day following implant, figures 3C and D the cosmetic result at 6-month follow-up.

Preimplantation screening
The screening procedure is an important step in assuring eligibility of the patient and potentially reducing the incidence of unwanted events such as IAS. Initial patient selection is based around the absence in the S-ICD system of durable bradycardia pacing, CRT and ATP therapy. In this respect, patients with an actual or anticipated bradycardia indication should be excluded, as well as patients fulfilling the criteria for CRT. Patients who could benefit from ATP therapy, such as those with known monomorphic ventricular tachycardia (VT) or with pathologies conferring a high risk of VT (e.g., sarcoidosis and arrhythmogenic right ventricular dysplasia) should be considered for TV-ICD. Selected candidates should undergo an electrocardiogram (ECG) screening test with a screening tool provided by the manufacturer (fig. 4A). Standard cutaneous electrodes are placed in three positions representing the two sensing electrodes and the can of the S-ICD device: 1 cm to the left of the xiphoid process (representing electrode B in the S-ICD), 14 cm cranial to the xiphoid process on the chest wall (representing electrode A), and either the fifth or sixth intercostal space on the left mid-axillary line (representing the can position) (fig. 2). ECG recordings in the three derivations mimicking the S-ICD sensing vectors are recorded, and the screening tool is used to verify suitability of these recordings (fig. 4B). The manufacture recommends at least one adequate vector (standing and supine) before considering S-ICD implantation, but it is desirable to have at least two adequate vectors, which will facilitate reprogramming in the event of sensing issues. Potential sources of failure include, most frequently, large or late peaking T-waves and, less frequently, low-amplitude QRS complexes that are too small to fit in the smallest window of the tool, and thus are likely to be undersensed by the device itself.
Particular attention should be paid to those cardiac disorders in which dynamic changes of the R-T wave relationship are expected, such as hypertrophic cardiomyopathy or Brugada syndrome. Indeed, vector change may cause dynamic R-wave undersensing or T-wave oversensing, to which the device cannot automatically adjust. In this particular setting, therefore, it is important to use pharmacological challenges in order to unmask potential issues and to assess precisely the most stable sensing vector, as recently demonstrated by Conte et al. [17].

Arrhythmia detection
As mentioned, the S-ICD system uses three sensing electrodes: the distal electrode (A) located in the upper sternum, the proximal electrode (B) located at the xiphoid level and the active can (CAN) located in the lateral fifth or sixth intercostal space (see fig. 2). Three sensing vectors can be created from these electrodes: a primary vector, from electrode B to the can (resembling surface ECG lead DI), a secondary vector from electrode A to can (resembling lead DII) and, finally, an alternate vector from electrodes A to B (resembling lead aVF). The most appropriate vector to avoid noise, QRS double counting and T-wave oversensing is chosen automatically by the device, but can be manually overridden. Once the vector is chosen, detection occurs in several successive steps, depending on whether programming includes a single shock-only zone or (preferably) dual zones with both conditional and shock zones [18].

An algorithm to avoid oversensing is used, comprising threshold adaptation to the R-wave, a decay function and three double detection algorithms to avoid T-wave oversensing and double counting. A rate-based analysis is undertaken, using an average of the four last beats to detect tachyarrhythmia. In the case of rates above the programmed shock zone threshold, detection stops at this step and therapy is delivered. In the case of programming with a conditional zone, the system uses three further steps to decide on appropriateness of therapy. A static waveform analysis of the QRS complex compares the current beat with a stored template, using up to 41 points to assess correlation. A correlation of >50% classifies the rhythm as supra-
ventricular and prevents therapy. This cutoff is lower than for TV-ICDs (e.g., 94% in Boston Scientific’s Rhythm ID algorithm) because of the greater number of points analysed (approximately eight points in transvenous systems). In cases of noncorrelation, a dynamic waveform analysis assesses the correlation between the current tachycardia beat and the previous three tachycardia beats. In the case of polymorphism, the rhythm is classified as ventricular, whereas in the case of monomorphism, the device moves to the third and final step of morphology analysis, which analyses QRS width in relation to the stored template. In the event of prolonged QRS duration >20 ms, the rhythm is classified as ventricular.

The device uses an 18/24 beat duration criterion before charging the capacitors, with automatic extension to allow spontaneous resolution of unsustained events and with a confirmation algorithm at the end of capacitor charging before delivering therapy. The shock zone is programmable between 170 and 250 bpm, and the conditional zone between 170 and 240 bpm. Although programming is variable in the different published studies, many used a shock zone at around 200–220 bpm [19–21].

**Shock delivery**

Only a single shock energy of 80 J is programmable in the S-ICD, except during defibrillation threshold (DFT) testing, where shock energies of 10–80 J at 5 J intervals are programmable. DFT testing is recommended at 65 J to ensure a margin of safety [22], although the necessity of DFT testing in the S-ICD has not been studied, and some centres do not perform it systematically. Standard shock polarity is from coil to can, but the device automatically reverses polarity in the case of unsuccessful therapy, with a maximum of five shocks available. The S-ICD system has a limited post-shock pacing function, with the possibility of delivering demand pacing at 50 bpm for up to 30 seconds after a shock in the case of asystole longer than 3.5 seconds. The system uses a 200 mA biphasic transthoracic pulse for this function. The current S-ICD model can store up to 40 treated and untreated episodes.

**Advantages and disadvantages of the S-ICD**

Table 1 shows other advantages and disadvantages of S-ICDs compared with TV-ICDs. Preservation of vascular access in young patients is a major advantage. Another major advantage is the low risk of systemic infection, which is of particular interest in patients with high infectious risk such as the immunocompromised and holders of artificial valves. Another population who are likely to benefit are those with chronic kidney disease, especially those requiring dialysis, as they have a greater risk for infection and more lead extraction-related complications as a result of increased calcification around implanted leads. Concerning the issue of myocardial damage, despite higher energy shocks compared with TV-ICDs, it is estimated that only approximately 10% of this energy reaches the myocardium when delivered subcutaneously. Moreover, there seems to be less myocyte damage, as indicated in swine models showing an elevated troponin level after TV-ICD shocks but not after S-ICD shocks [23]. Finally, the lack of transvenous lead extraction and associated risks makes the S-ICD an attractive option for young active patients, especially those at low risk of bradycardia or monomorphic VT, such as patients with Brugada syndrome, long QT syndrome and hypertrophic cardiomyopathy. Amongst the list of disadvantages, the absence of ATP therapy seems to be an important hurdle, as it has proven to be safe and effective for the treatment of fast VTs [24], as well as increasing quality of life and possibly lowering mortality [25]. Patients with known monomorphic VT, history of prior effective ATP therapy or at high risk for VT should not receive an S-ICD.
However, it is likely that in the future, the S-ICD will be able to communicate with leadless pacemakers to deliver ATP, if such therapy is found to be required. Leadless pacemakers may also be a solution for patients who develop a requirement for antibradycardia pacing, although this is only available as a VVIR system for the time being.

The absence of an atrial lead is also a potential disadvantage as atrial arrhythmias (which are prevalent in this patient population) will not be diagnosed. However, algorithms allowing diagnosis of atrial fibrillation (AF) based on ventricular rhythm irregularity may allow diagnosis in single-chamber devices in the future. Battery longevity, although improved compared with the previous version, is still less that reported for TV-ICDs produced by the same manufacturer. Finally, the system is currently not magnetic resonance imaging-conditioned (contrary to most of the current TV-ICD systems), but will become so in the future.

**Indications for the S-ICD**

The 2015 European Society of Cardiology guidelines on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [26] state that the S-ICD is a class IIa (level of evidence C) recommendation as an alternative to TV-ICDs in patients who have an ICD indication but do not require antibradycardia pacing, CRT or ATP. The guidelines also state that S-ICDs are a class IIb (level of evidence C) indication as an alternative to the TV-ICD in patients with venous access problems, after removal of a TV-ICD for infection, or in young patients who require long-term therapy.

As mentioned above, patients at high risk of systemic infections (e.g., patients on dialysis or with valve prosthesis, etc.) are also good potential candidates.

### Current evidence

Current evidence is based on a certain number of regulatory studies [15, 22] as well as several post-marketing studies, mostly multicentric [16, 19, 21, 27–29]. Follow-up remains relatively short, the longest being the pooled analysis of the EFFORTLESS and IDE registries with a mean follow-up of less than 2 years [20]. Also of note, all the studies published to date tested the previous generation S-ICD (SQ-RX generator and Q-TRAK electrode). The PRAETORIAN study, the only prospective randomised trial of S-ICD versus TV-ICD, is currently recruiting patients [30]. Below are some results from published studies evaluating the S-ICD.

### Eligibility for S-ICD implantation

Several studies have evaluated the use of the ECG screening test, with rates of failure of approximately 7–8% for one adequate vector [31, 32] and 15% for two vectors [33]. Each study identified specific predictors for failure, but apart from QRS duration, no two studies found the same predictors, despite the very similar populations in the studies of Groh and Olde Nordkamp. Examples of failed test predictors were: negative T-waves in surface ECG leads I, II and aVF (45% positive predictive value for failure), increased bodyweight (odds ratio [OR] of 1.5 per 10 kg overweight), hypertrophic cardiomyopathy (OR 12.6), prolonged QRS duration (especially right bundle-branch block, with an OR of 1.5 per 20 ms prolongation) and R/T ratio <3 on the surface ECG (OR 14.6). Of the three vectors tested, the primary and secondary vectors had a similar success rate of approximately 80%, whereas the success rate was only 40–50% for the alternate vector, probably because of the latter’s perpendicular nature causing low QRS amplitude.

Interestingly, according to one retrospective cohort study [34], 55% of patients with TV-ICDs are in fact potentially eligible for an S-ICD based on the absence (after 3.4 years of follow-up) of pacing indication.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Less risk of lead failure (e.g., no subclavian crush, simpler lead design)</td>
<td>No antibradydycardia pacing (other than directly after a shock)</td>
</tr>
<tr>
<td>Preservation of vascular access</td>
<td>No antitachycardia pacing</td>
</tr>
<tr>
<td>Lower risk of systemic infection</td>
<td>No cardiac resynchronisation</td>
</tr>
<tr>
<td>No risk of pneumothorax, pericardial effusion, etc.</td>
<td>Shorter battery life</td>
</tr>
<tr>
<td>No fluoroscopy at implantation</td>
<td>Magnetic resonance imaging conditionality not yet validated</td>
</tr>
<tr>
<td>Ease and predictability of implantation</td>
<td>No atrial lead for diagnosis of atrial arrhythmias</td>
</tr>
<tr>
<td>No risk of transvenous lead extraction</td>
<td>Higher overall risk of inappropriate shocks</td>
</tr>
<tr>
<td>Less myocardial damage linked to subcutaneous shocks</td>
<td>Limited programming options</td>
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<td>Higher cost</td>
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### Table 1: Advantages and disadvantages of the S-ICD device compared with transvenous ICDs.
episodes of ATP without subsequent shock and upgrade to CRT-D. Considering an 8% rate of failure of the ECG screening test, overall approximately 50% of all ICD patients without a pacing indication could be potentially eligible for an S-ICD.

### Sensitivity and specificity of arrhythmia detection
The sensitivity of the S-ICD system, or its ability to correctly diagnose ventricular tachyarrhythmias has been excellent, approaching 100% in the different studies [15, 18, 21], although it must be stated that prospective, long-term data are lacking. Regarding specificity (i.e., ability to correctly distinguish supraventricular arrhythmias from VT), this was reported to be 98% in the START study, which used a library of induced ventricular and supraventricular arrhythmias with simultaneous recording of intracardiac and surface ECG tracings (simulating subcutaneous recordings), and even compared favourably to TV-ICDs [18]. In the EFFORTLESS registry [16], of the 166 delivered shocks, only 10 (6%) were due to supraventricular arrhythmias, and all of these were due to the rates falling in the zone without discriminators.

### Shock efficacy
Shock efficacy has been impressive in DFT tests, with rates of conversion ≥95% at 65 J or more. These rates are comparable to those reported with TV-ICD devices [35, 36]. Mean DFT thresholds were 36.6 ± 19.8 J versus 11.1 ± 8.5 J for the TV-ICD devices [22]. During spontaneous episodes, first shock efficacy on average ranged between 88 and 92%, rising up to ≥96% after up to five shocks [15, 16]. Because of the advanced detection algorithm, time to therapy in S-ICD systems has proven to be substantially longer than in TV-ICD systems. In the pooled analysis of the EFFORTLESS and IDE studies, comprising 882 patients, the largest collection of S-ICD recipients analysed to date, mean time to therapy for spontaneous episodes was 19.2 ± 5.3 seconds. Whereas this might be considered a disadvantage, studies show that the delay allows many ventricular arrhythmias to self-terminate, thus avoiding the need for therapy from the device. In the aforementioned analysis, out of 314 ventricular events detected, 125 (40%) were episodes of unsustained VT/VF that self-terminated before therapy delivery, with no associated syncope or mortality. These findings are in accordance with recent studies in TV-ICD patients that show a lower rate of inappropriate therapy and mortality with prolonged detection times [37]. One study reported a 100% success rate of post-shock pacing in 184 cases out of 728, but in general data are scarce [15].

### Inappropriate shocks
IAS remain a major problem in all types of ICDs. Modern programming seems to have greatly reduced the rate of IAS in TV-ICDs to around 2–3% over 1 year [37–39]. Regarding S-ICDs, in five multicentric studies, the rate of IAS was 9.2% after a mean follow-up of around 1 year [19, 27–29, 40]. In the EFFORTLESS registry, the IAS rate was 7%/year [16]. The rate of IAS is therefore higher with S-ICDs than with current TV-ICDs. Several important points should be mentioned. In general, whereas cumulative rates of IAS in TV-ICDs tend to increase over the years, largely owing to lead failure, rates of IAS in some S-ICDs studies such as the EFFORTLESS registry decreased after first IAS owing to more appropriate programming of sensing vectors. Despite initial concerns about the S-ICDs susceptibility to external sources of oversensing (noise, myopotentials, electromagnetic interference), their rate seems relatively low (8% of all cases of IAS in the pooled study [20]) due to effective filters, whereas the vast majority of IAS are caused by oversensing of cardiac signals, notably T-wave oversensing and low-amplitude signals (60% of cases in total). In contrast to TV-ICDs, misclassification of supraventricular arrhythmias in the conditional zone only accounted for 1% of IAS. These differences can be explained by the fact that the subcutaneous signal is richer than traditional intracardiac electrograms, with the advantage of offering better morphology discrimination, but also providing larger T-waves, which are more difficult for the device to ignore without risking ventricular fibrillation underdetection. The ongoing UNTOUCHED study will test a programming scheme designed to minimise inappropriate and unnecessary shocks in patients who have an indication for primary prevention of sudden cardiac death and low ejection fraction. The primary objective of the study is to assess the 18-month incidence of shocks in subjects implanted with Emblem S-ICD programmed with zone cutoffs at 200 and 250 bpm. The 18-month incidence rate will be compared with an objective performance criterion derived from TV-ICDs programmed to minimise shocks in the MADIT RIT study. The secondary objective is to assess perioperative complications.

### Strategies to reduce IAS
A proven strategy to reduce IAS has been the adoption of dual zone programming, with addition of a conditional zone exploiting the advanced morphology discrimination algorithm of the device [41]. This has reduced IAS rates from around 25% to approximately 10% [20, 41]. Other potentially useful strategies to reduce T-wave oversensing (TWOS) and IAS include...
increasing the recommended number of suitable vectors on screening to more than one, as well as utilising exercise testing for screening purposes and also once the device is implanted (the reference template may even be acquired during exercise in the case of significant changes compared with during rest). In one prospective study [42], all TWOS episodes occurred during exercise or rapid AF, and exercise-testing optimisation of sensing vector and template acquisition resolved the problem in seven out of eight patients. The authors recommend achieving a maximal heart rate of at least 150 bpm, as the sensitivity of the S-ICD automatically increases at a heart rate of 148 bpm. It is important to update the template at each follow-up, as this is currently not done automatically. Finally, a recently proposed modification to the S-ICD detection algorithm reduced the rates of TWOS by nearly 40% in an experimental study [43].

**Safety and complications**

Potential complications of S-ICD implantation include parasternal lead migration, pocket infection, device extrusion and haematomas. Overall complication rates vary amongst studies, but remain relatively high compared with TV-ICDs, with rates reaching 14% after 18 months in the Dutch cohort [28]. Several points should be discussed. Firstly, as with all novel devices, a certain degree of learning curve is to be expected and has been described in some studies. In the Dutch study [28], for example, rates of complications diminished from 17 to 10% after the first 15 implantations, and in the IDE study [15], all infections occurred in the first third of patients. Secondly, although the rates of complications in some studies have been relatively high, the actual severity of complications seems to be less important than with TV-ICDs. The rate of acute major procedure-related complications (haematoma, lead or device malpositioning/displacement) in the pooled study was 2%, comparing favourably with the rate of major in-hospital complications in TV-ICDs (1.9% for single chamber and 2.9% for dual-chamber devices [44]). Concerning infection, a dreaded complication of TV-ICD systems, no cases of systemic infection with bacteraemia have been described to date with the S-ICD, and many infections could be managed conservatively. In the pooled analysis, the rate of infection was 4.8%, but only 1.7% of patients required device removal for this indication [20]. Moreover, operators describe device extraction as a much simpler process than with TV-ICDs. The use of two incisions rather than three may lower the risk of infection, although this has not been studied. Finally, one must remember that no long-term data exist concerning lead durability.

**S-ICD in Switzerland**

The S-ICD was introduced in Switzerland in November 2012, and is reimbursed by healthcare insurance. In total, 40 systems have been implanted in 12 centres (as of 1 October 2015). The relatively slow uptake may be explained by the requirement for specialised training and selection of “ideal” patients, as well as the drawbacks mentioned in table 1. However, with the recent advent of the second generation S-ICD, which has a slimmer profile, increased longevity and new algorithms with reduced risk of IAS, as well as increasing confidence with this therapy, it is likely that the numbers of implantations will increase. Boston Scientific is planning to introduce a leadless pacemaker, which will offer new possibilities in terms of antibradycardia and antitachycardia pacing in conjunction with the S-ICD, as mentioned above.

**Conclusions**

The S-ICD has proven to be a safe and effective device for the treatment of ventricular arrhythmias and the prevention of sudden cardiac death in patients not requiring pacing. Its unique disposition allows excellent sensitivity for discriminating supraventricular and ventricular arrhythmias, as well as good shock efficacy. Conversely, the rate of inappropriate therapy, notably a result of T-wave oversensing, remains high, and further research is needed to determine better eligibility criteria and appropriate strategies to lower this rate. The main drawbacks of the device are absence of durable pacing, resynchronisation and ATP therapy, although development of hybrid systems could potentially address some of these issues. Further research is needed to define the target population better, especially prospective, randomised studies (the PRAETORIAN study is underway) as well as studies in specific target groups (chronic kidney disease, for example). All in all, the S-ICD remains a promising device, and its attractiveness may rise with further technological advances.

**Disclosure statement**

N.D. has no conflicts of interest to report; H.B. has received institutional fellowship support and consulting fees from Boston Scientific; C.S. has received consulting fees from Boston Scientific; A.A. has received consulting fees and speaker fees from Boston Scientific.

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The full list of references is included in the online article at www.cardiovascmed.ch
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A patient with coeliac disease and complete atrioventricular block

Cardiac sarcoidosis with coeliac disease

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Summary

This case of cardiac sarcoidosis started with manifestation of a complete atrioventricular block in a 42-year-old female without other cardiac dysfunction. Two years later, the patient presented with acute heart failure symptoms at the Emergency Department. Echocardiography at admission showed thinning and hyperdensity of the basal interventricular septum, which is a rare but typical echocardiographic sign of cardiac sarcoidosis. Endomyocardial biopsy, positron emission tomography–computed tomography and transbronchial biopsy confirmed the clinical suspicion of sarcoidosis. Of note, the patient also had coeliac disease, which can occur conjointly with sarcoidosis. After 5 months of immunosuppressive treatment with methylprednisolone and azathioprine the burden of inflammatory lesions was significantly reduced and the patient had improved to New York Heart Association class I.

Key words: sarcoidosis; granulomatous myocarditis; acute heart failure

Case report

The long history of the 44-year-old woman included two uneventful pregnancies, dust-mite-induced asthma treated by occasional inhalation of β2-adrenergic receptor agonists, and a suspicion of coeliac disease based on an intestinal biopsy obtained 2 weeks before admission with acute heart failure. In 2013, she had presented with complete atrioventricular (AV) block with a ventricular escape rhythm at 40 bpm treated with implantation of a double-chamber pacemaker; cardiac magnetic resonance imaging (MRI) and Lyme serology were negative at that time. Between 2013 and 2015, her New York Heart Association (NYHA) class increased from I to II and left ventricular ejection fraction (LVEF) decreased from normal to 40% with global hypokinesia. In April 2015, she was admitted to the Emergency Wards for palpitations, reduced exercise tolerance, tiredness and prolonged recovery from exercise. Clinical examination revealed bilateral ankle oedema and a positive hepatojugular reflux. The laboratory results showed elevation of N-terminal pro-brain-type natriuretic peptide (NT-proBNP) (2018 ng/l), D-Dimers (2151 ng/ml), high sensitive troponin (16 ng/l) and creatinine (93 μmol/l). The echocardiogram showed a non-dilated left ventricle (LV) with global hypokinesia, a LVEF of 35%, and basal thinning of the interventricular septum (fig. 1); the ejection fraction (EF) of the non-dilated right ventricle (RV) was severely reduced. A pacemaker interrogation demonstrated a ventricular stimulation rate of 98.9% and therefore pacemaker-induced dysfunction initially entered into the differential diagnosis. Computed tomography (CT) angiography in the Emergency Department excluded pulmonary embolism but showed bilateral hilar adenopathy. The ECG revealed recurrent unsustained polymorphic ventricular tachycardia (VT), for which low-dose β-blocker therapy was started. In the following night, a haemodynamically tolerated sustained VT was successfully treated with 300 mg intravenous amiodarone; thereafter the patient was given an oral loading dose of 10 g amiodarone with subsequent decrease in the incidence of VT episodes. Work-up was negative for metabolic, endocrinological, rheumatological and infectious disorders, C-reactive protein and erythrocyte sedimentation rate were normal. However, titres of antitransglutaminase and
antigliadine IgA antibodies were elevated (84 U/l and 31 U/l, respectively) in accordance with the coeliac disease diagnosed in a duodenal biopsy obtained 10 days before admission. Late gadolinium sequences of cardiac MRI showed subepicardial enhancement of anterior, septal and inferior segments and a mid-ventricular sign in the inferior septum. The coronary angiogram was normal, but haemodynamic measurements revealed a low cardiac index (1.5 l/min/m²). Endomyocardial biopsies of the RV septum revealed non-necrotizing granulomatous myocarditis (fig. 2) and ruled out cardiac desmosomal disease (right ventricular dysplasia). 18fluorodeoxyglucose (FDG) PET-CT showed multiple hypermetabolic lesions especially in the heart, the lung, the spleen and multiple lymph nodes in the axillary, supraclavicular, mediastinal, hilar and retroperitoneal positions (fig. 3A and B). Bronchoalveolar lavage showed a mild alveolar lymphocytosis; transbronchial biopsies demonstrated granulomatous lymphadenitis. After exclusion of other aetiologies associated with non-necrotising granulomas (tuberculosis, Churg-Strauss vasculitis), the diagnosis of systemic sarcoidosis combined with celiac disease was established. In fact, both disease entities are linked to class II haplotype HLA-DR3, DQ2, and B8 expression, which result in an increased susceptibility to both diseases [1].

Corticosteroid treatment was initiated as 1 mg methylprednisolone/kg body weight and after 3 weeks of corticosteroid treatment the patient received a first dose of 50 mg methotrexate aiming at a more rapid reduction of corticosteroid treatment. The next day the patient consulted urgently for palpitation and dizziness starting a few hours previously. The ECG showed sustained VT of inferior origin with a frequency of 170 bpm, which spontaneously converted to sinus rhythm at the Emergency Wards. Only 3 hours later a VT with a frequency of 141 bpm originating from the right ventricular outflow tract occurred, for which reason the patient received an additional 6 g of amiodarone loading (800 mg/d) and a maximum dose of carvedilol was given. Despite of disappearance of sustained VT thereafter, her DDD pacemaker was upgraded to a cardiac resynchronisation therapy-defibrillator (CRT-D) because of the underlying severe cardiac pathology. As methotrexate was suspected to promote ventricular dysrhythmias [2], treatment with azathioprine was started with a consecutive taper of corticosteroid therapy to 0.5 mg/kg body weight. At 3-month follow-up, an echocardiogram showed a moderate LVEF improvement from 35 to 41% and at 5-month follow-up, the patient was in functional NYHA class I without any clinical signs of systemic sarcoidosis. A 18FDG-PET-CT showed significant reduction/disappearance of the previously described lesions (fig. 3C and D).

**Cardiac sarcoidosis**

Sarcoidosis is a multisystem granulomatous disease of unknown cause often seen in young adults. Age-
adjusted incidence rates in the United States are 35.5/100,000 for African-Americans and 10.9/100,000 for whites with an overall prevalence of 20/100,000. Cardiac manifestation is present in 20–27% of sarcoidosis patients in the United States but up to 58% in Japan [3].

**ECG in sarcoidosis**
Almost 70% of patients with cardiac sarcoidosis have ECG abnormalities. Most common are first-degree, second-degree or complete AV block (23–30%). Complete AV block tends to present at a younger age than idiopathic heart block. Unsustained VT is the second most common manifestation of cardiac sarcoidosis, and VT in combination with complete AV block accounts for almost two thirds of sudden deaths.

**Echocardiography in sarcoidosis**
Usually, dilated cardiomyopathy with regional wall motion abnormalities due to scattered granulomas are observed. Whereas there is initial wall thickening, wall thinning due to scarring and fibrosis occurs eventually. Thinning of the basal anterior septum in a young patient with dilated cardiomyopathy is rare but highly suggestive of sarcoidosis [3] (table 1).

**Endomyocardial biopsy in sarcoidosis**
Endomyocardial biopsy is the gold standard for diagnosis of cardiac sarcoidosis. However, its sensitivity is low, as shown by Ardehali et al., who reported that only 7 out of 28 patients with presumed cardiac sarcoidosis had positive biopsy results [4]. In accordance, in 50–80% of patients with extracardiac sarcoidosis and clinical signs of cardiac manifestation biopsies are negative (table 1).

**PET in sarcoidosis**
Tissue affected by sarcoidosis shows increased uptake of ¹⁸F-Glu, which correlates well with histological disease activity. PET-based perfusion images also depict the extent of fibrogranulomatous replacement in the whole heart. Overall, PET sensitivity is reported to be as high as 82–100% [3] (table 1).

**Cardiac magnetic resonance imaging**
Cardiac MRI visualises infiltration in late gadolinium-enhanced images and local inflammation with oedema in T₂-weighted images, in addition to functional and morphological characterisation. A cardiac MRI study from The Netherlands demonstrated in 58 patients with cardiac sarcoidosis a sensitivity of 100%, a specificity of 78%, and positive predictive value and negative predictive values of 55 and 100%, respectively. Since rare cases of congestive heart failure due to right ventricular dysplasia may mimic cardiac sarcoidosis, MRI should be always performed to rule out right ventricular dysplasia if cardiac sarcoidosis is suspected (table 1).

**Management**

**Immunosuppressive therapy**
Corticosteroids are the main therapy for cardiac sarcoidosis despite lack of confirmatory evidence. In one large retrospective study of 95 patients with cardiac sarcoidosis, patients treated with corticosteroids had a 5-year survival rate of 75% as compared with 10% in untreated patients [3]. The standard recommendation is to start with high doses (1 mg methylprednisolone/kg bodyweight and day) followed by progressive tapering. However, the starting dose is debated since reports show similar long-term survival when patients are started with prednisolone ≤40 mg/d, maintained for a minimum of 6 months, with progressive tapering to 5–15 mg/d over the following 12 months. If prolonged high-dose corticosteroid treatment is necessary for control of disease activity, implementation of supplementary methotrexate, ciclosporin, cyclophosphamide, as well as azathioprine treatment may be discussed in order to decrease the dose of corticosteroids. Methotrexate is the most studied alternative to steroids but its cardiac efficacy is not established.
Cardiac pharmacological therapy
Heart failure treatment even when caused by cardiac sarcoidosis remains based on recommendations in guidelines. In particular, angiotensin converting-enzyme inhibitors or angiotensin receptor blockers are recommended in all patients with impaired systolic function.

Arrhythmias
No prospective trials have tested the efficacy of β-blockers or amiodarone treatment. The secondary effects of amiodarone treatment are of concern; in particular, pulmonary fibrosis may contribute to further deterioration of lung function in patients with pulmonary sarcoidosis.

Implantable cardioverter defibrillator
Cardiac arrest or sudden cardiac death (SCD) may be the first manifestation of cardiac sarcoidosis, therefore implantation of an implantable cardio defibrillator (ICD) should be strongly considered once the diagnosis of cardiac sarcoidosis is established. However, evidence from prospective trials is lacking. Therefore, attention should be given to symptoms such as syncope, heart failure status, LV function and spontaneous or induced ventricular arrhythmias to make individualised decisions about primary prevention of SCD [3].

Radiofrequency ablation
The effectiveness of radiofrequency ablation in prevention of recurrent arrhythmias in patients with cardiac sarcoidosis is limited. In a single-centre experience, ablation therapy was effective in controlling arrhythmias in only two of eight patients with recurrent monomorphic VT [3].

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

References
Limb lead reversal giving a potentially misleading ECG

Topsy-turvy ventricular tachycardia

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Case presentation

We present the case of a 72-year-old male with a history of coronary artery disease and an inferior myocardial infarction 19 years previously, when the occluded right coronary artery was percutaneously revascularised. A DDD pacemaker had been implanted 3 months before because of complete atrioventricular (AV) block. The chief complaint upon presentation was fatigue, and the patient denied chest pain or dyspnoea. No clinical signs of congestive heart failure were noted on physical examination. Haemodynamic parameters were stable. The ECG on admission is shown in figure 1A.

Questions

1. What is the rhythm?
2. Where is the origin of the arrhythmia?

Comment

Figure 1A shows a regular wide complex tachycardia with a heart rate of 150 bpm. A diagnosis of ventricular tachycardia (VT) was made, based on the known persistent complete AV block and a QRS morphology compatible with VT with a Q in V1. Owing to the transition between V1 and V2 and the inferior axis, an anterior origin of the VT in the left ventricle was suspected, not compatible with the location of the scar after inferior myocardial infarction.

As a result of the recurrent VT documented on telemetry at the given rate, catheter ablation of the VT was attempted. At the beginning of the electrophysiological study, spontaneous premature ventricular contractions (PVCs) were present. In the precordial leads, the PVC morphology was almost identical to the VT on the initial ECG, but the limb leads showed a superior axis. A VT with the morphology of the PVCs was easily and reproducibly inducible using isoprenaline. The cycle length and QRS morphology in the precordial leads were almost identical to the VT at presentation, but the VT had a superior axis (fig. 1B). Haemodynamic parameters were stable. The VT terminated spontaneously and was often nonsustained.

After transseptal puncture, electroanatomical voltage mapping with a 3D mapping system and remote magnetic navigation (CARTO 3, Stereotaxis) showed a local-
ised endocardial infero-septo-basal scar. Pacing at that site accurately reproduced the morphology of the VT. Ablation at that site eliminated the VT. After ablation, no further VT could be induced with programmed ventricular stimulation.

With the given history, a left ventricular ejection fraction of 35–40% and optimised medical treatment (angiotensin converting-enzyme inhibitor, β-blocker and aldosterone receptor antagonist) the patient subsequently underwent an upgrade to a DDD implantable cardioverter defibrillator. He was arrhythmia-free during a follow up of 6 months.

Discussion

This case nicely illustrates the potential implications of incorrectly placed leads in the surface 12-lead ECG. Incorrect lead placement may have clinically relevant consequences [1]. A large retrospective study of 11,432 ECGs showed a rate of incorrect lead placement of 2% [2]. In a study analysing the detection capability of cardiologists with regard to incorrect lead placement, the right arm lead was switched with the right leg on purpose. Of the 25 experienced cardiologists, none was able to detect the ECG abnormality [3]. Incorrectly placed leads may lead to a bizarre QRS-axis, low voltage in leads I, II or III, or generally findings that do not correlate with the patient’s history, clinical or echocardiographic examination. Based on the number of electrodes used during electrocardiography, a plethora of possible displacement “options” exist (contralateral interchange, homolateral interchange, cross-over interchange, clockwise and counterclockwise interchange). A helpful overview on different ECG patterns and how to recognise the most common lead reversals is provided elsewhere [4, 5].

In our patient, the suspected localisation of the clinical VT was in the anterolateral aspect of the left ventricle, but this was not in accordance with the patient’s history of inferior myocardial infarction. Since lead reversal (reversal of left arm and left leg) was suspected because of spontaneous PVCs with a nearly identical QRS morphology in the precordial leads but a superior axis based on the limb leads, the subsequently induced VT (with morphology identical to the spontaneous PVCs) could be found and eliminated in an infero-septo-basal scar zone.

The presented case shows that limb lead reversal may confuse the clinician not only when occurring during sinus rhythm but also, and probably even more so, when an arrhythmia is present. Failure to recognise limb lead reversal in this case could lead to several consequences including a prolonged ablation procedure with mapping focusing on and possibly even ablation of clinically irrelevant sites in the left ventricle.

Disclosure statement

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

References


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Figure 2: 3D electroanatomic voltage map of the left ventricle showing an infero-septo-basal scar. The purple areas correspond to areas with normal endocardial voltage, the red areas correspond to sites of endocardial scar, and the remaining colors correspond to the transition zone. The green tag denotes the site with a perfect pace-map (12/12). The dark red dots denote ablation sites. The bright red dots denote sites with no matches based on pace-mapping.
A rare, but correctable, malfunction of a pacemaker

An unusual case of upper rate behaviour

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Case report

A 67-year-old patient was admitted because of sudden onset of dyspnoea during physical exertion. Six years ago, the patient was implanted with a dual-chamber pacemaker [Saint Jude Medical Zephyr™ XL DR, Saint Jude Medical (SJM), Inc., St. Paul, MN 55117, USA] because of high-degree atrioventricular (AV) block due to Lyme

Figure: Tracing A: ECG at exercise stress test with sudden onset of a 2:1 block and occasional appearance of late coupled beats with a different QRS morphology (most likely delayed afterdepolarisations) at a heart rate of 135 bpm. Tracing B: Pacing in VVI mode (maximum output of 7.5 volts and maximum pulse width of 1.5 milliseconds) with loss of 1:1 ventricular capture and onset of first 3:2 followed by 2:1 ventricular capture at heart rate of 140 bpm.
carditis. An exercise stress test revealed a sudden onset of a 2:1 block at a heart rate (HR) of 135 bpm (fig. 1, tracing A). Interrogation of the pacemaker revealed normal and stable parameters for atrial and ventricular sensing, pacing thresholds and lead impedances. The maximum tracking rate (MTR) was programmed at 160 bpm and the total atrial refractory period (TARP) to 340 ms (corresponding to a HR of 176 bpm). Pacing in DDD and VVI mode at different HR (unipolar and bipolar pacing up to maximum output of 7.5 volts and maximum pulse width of 1.5 milliseconds) revealed loss of 1:1 ventricular capture at HR above 140 bpm (figure, tracing B). However, using the noninvasive programmed stimulation (NIPS) module of the pacemaker with the same output settings, 1:1 ventricular capture could be observed at any HR up to the shortest tested stimulation cycle length of 300 ms (corresponding to a HR of 200 bpm). With the support of the pacemaker manufacturer, the pacemaker’s software was reset, which restored normal function of the device.

Discussion

In dual-chamber pacemakers loss of 1:1 AV conduction at fast HR, also called upper rate behaviour, is determined by the MTR and the TARP [1]. In the present case, however, the symptomatic rate drop during exercise was due to an error in the device’s software, which prevented 1:1 delivery of the electrical impulse at HR above 135 bpm. With technical support from SJM, the reason for the error was found in a random memory corruption of the pacemaker’s software which set the runaway protection (RAP) value to 132.3 bpm. The RAP circuit is a fail-safe mechanism that defines the maximum pacing rate and prevents inappropriate delivery of rapid pacing pulses at extremely short cycle lengths. When the required pacing rate exceeds the RAP value, the RAP circuit prevents the pacemaker from delivering pacing pulses and so generates “exit block”. The device continues to display ventricular pace markers on the ventricular channel but will deliver pacing pulses only when the RAP circuit timer has recovered [2]. When the device is initially manufactured the RAP value is at 132.3 bpm (reset value) and then is programmed typically to a nominal value of approximately 190 bpm. The RAP value is not reported by the device and can be altered when the memory is corrupted by electromagnetic interference [2]. The RAP value can only be reprogrammed via a password-protected engineering interface on the standard programmer, as performed in our case. Up to now only five cases with this specific problem have been reported to the pacemaker manufacturer and occurred in SJM Zephyr™, Victory™, and Identity™ devices.

Disclosure statement

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

Authors’ contribution

SAM wrote the initial manuscript. MM and AM edited the manuscript. All authors were responsible for the patient’s care. All authors read and approved the final manuscript.

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A travelling Port-a-Cath in a 2-year-old

A patent foramen ovale may be dangerous ... even in childhood

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A 2-year-old boy was diagnosed with acute lymphatic leukaemia. For treatment a Port-a-Cath system was implanted surgically in standard fashion via the right subclavian vein (fig. 1).

In the catheterisation laboratory, transvenous removal of the catheter was easy and uneventful; it was caught with an Amplatz Goose Neck snare from the proximal end in the right atrium and the distal end in the upper left pulmonary vein, the catheter tip is seen just protruding outside the radiological heart shadow.

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After the end of treatment and uneventful follow-up it was decided to remove the Port-a-Cath system surgically. A chest X-ray was performed prior to the intervention (fig. 2), which showed that, in the meantime, asymptomatic disconnection of the canula from the box of the system had occurred.

The catheter embolised into the heart, with one end of the canula being in the right atrium just above the tricuspid valve while the other end passed a patent foramen ovale (PFO) and remained stuck in the ostium of the upper left pulmonary vein, as also verified by echocardiography.

In the catheterisation laboratory, transvenous removal of the catheter was easy and uneventful; it was caught with an Amplatz Goose Neck snare from the proximal end in the right atrium and brought out through a 8F Mullins long sheath. No resistance was felt when it was removed from the left pulmonary vein and through the PFO.

Had the canula completely crossed the PFO and embolised into a sensitive vascular bed like that of the brain the incident could have found a fatal end.

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