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**Dexmedetomidine-associated hyperthermia: A series of nine cases and a review of the literature**

**Online supplement: Detailed case reports of all patients included in the case series**

Patient #1

A 55 years old patient with dilative cardiomyopathy and prior biventricular assist device implantation was transferred to our intensive care unit (ICU) after heart transplantation (HTPL). The patient had a history of atrial fibrillation and an ischemic cerebral infarction without clinical residues. Other comorbidities were chronic renal failure and diabetes mellitus type 2.

Postoperatively cardiovascular support was provided by continuous iv administration of epinephrine (0.1 mcg/kg/min), norepinephrine (0.1-0.4 mcg/kg/min), milrinone (0.2 mcg/kg/min) and inhalational nitric oxide (20 ppm). Analgosedation for mechanical ventilation was accomplished with sufentanil iv (0.2 mcg/kg/h) combined initially with propofol iv (4 mg/kg/h). Dexmedetomidine was started on POD 1. The dose was up-titrated from 1.0 to 1.4 mg/kg/h. Seven hours after dexmedetomidine initiation the body temperature had risen from 37.4 °C to 39.2°C. Piperacillin/tazobactam and vancomycin were administered as an empiric antibiotic therapy 2 hours after the onset of hyperthermia. The insertion of an intravenous cooling device had no effect on lowering the body temperature. Dexmedetomidine was discontinued after 9 hours and propofol iv (4 mg/kg/h) re-commenced. The body temperature declined to 36.2°C over the course of six hours. Cooling was discontinued and the body temperature increased over the following 8 hours to 37.0°C. Thereafter, hemodynamical and pulmonary support could steadily be reduced and mechanical ventilation was discontinued on postoperative day (POD) 5 after the successful weaning of inhalational nitric oxide. Clonidine was administered on POD 5 and 6 without any effect on body temperature (36.5 - 37.2 °C). After extubation no signs of delirium or motoric deficits were detected but non-invasive ventilation (NIV) was required until POD 11. Microbiological sampling was repeated on POD 5 because of elevated laboratory inflammation markers. Tracheal aspirates revealed the presence of *enterobacter aerogenes* with beta lactamase properties and *stenotrophomonas maltophilia*. The antibiotic regimen was changed to meropenem and gentamycin (for the treatment of *enterobacter*) and trimethoprim/sulfamethoxazol (for the treatment of *stenotrophomonas maltophilia*). After resolution of the pneumonia the patient remained free from any new infection and all antibiotics were eventually discontinued despite trimethoprim/sulfamethoxazole. Acute on chronic renal failure required transient renal replacement therapy. The heart function remained excellent without signs of rejection and the patient was discharged from ICU on day 23.

Patient #2

A 75 years old female patient was admitted for suspected pacemaker lead infection following positive blood cultures for staphylococcus aureus. The pacemaker (PM) had been implanted 5 years ago following a third degree atrioventricular (AV) block after beta-blocker therapy for atrial fibrillation. Two years thereafter, AV node ablation was performed as therapy for recurrent episodes of symptomatic reentry tachycardia. At hospital admission, the patient was afebrile with a non-invasive blood pressure (NIBP) of 139/78 mmHg and a HR of 60 bpm. Comorbidities included chronic obstructive pulmonary disease (COPD), substituted hypothyroidism and osteoporosis with chronic back pain. Transesophageal echocardiography showed a normal heart function and a severe mitral regurgitation as a potential correlate of endocarditis. As a primary step the PM system was surgically removed and a temporary transvenous PM implanted. Delayed surgery of the mitral valve took place after two of a total of 6 weeks of antibiotic therapy with flucloxacillin and rifampicin. Annular dilation was identified as the etiology for the severe regurgitation and no signs of endocarditis were seen on visual inspection. The valve was successfully reconstructed, an epicardial left ventricular electrode was implanted for delayed definite PM implantation. Permanent atrial fibrillation was addressed by atrial cryoablation and closure of the left atrial appendage. On the first two ICU days, the patient had a convulsive status epilepticus followed by a recurrent non-convulsive epileptic activity, which resolved eventually with a continuous midazolam infusion. No recent ischemic or hemorrhagic brain lesions were detected by a computed tomography (CT). Sedation was switched to dexmedetomidine on POD 7 with a starting dose was 0.8 mcg/kg/h. Two hours later a steady increase of the body temperature was observed from 37.7°C over the course of 26 hours to 38.9°C. Tazobactam/piperacillin had been empirically commenced in the perioperative period and was changed to meropenem iv 9 hours after onset of hyperthermia. After discontinuation of dexmedetomidine the body temperature declined over a period of 11 hours to 37.5 °C. Microbiologic investigations during broad spectrum antibiotic therapy revealed only stenotrophomonas maltophilia in samples of tracheal secretions which was not specifically targeted in this immunocompetent patient. The antibiotic therapy was reduced on POD 14 to flucloxacillin iv for another two weeks after a definite PM implantation as a prophylaxis following endocarditis. Because of muscular weakness and lung disease dilative tracheotomy was performed for weaning from mechanical ventilation. Acute renal failure required temporary renal replacement therapy. On POD 28 the patient was discharged from the ICU.

Patient #3

An 86 years old female patient with a history of coronary artery disease (CAD) was admitted following a witnessed syncope and out of hospital resuscitation for 20 minutes. Cardiac fibrillation had been identified as the initial heart rhythm and return of spontaneous circulation was obtained after cardiac defibrillation. The patient was initially unconscious (GCS 3) and was intubated. On arrival, the EKG showed depressed ST segments in the anterolateral area of the left ventricle. Cardiac risk factors included arterial hypertension and type 2 diabetes mellitus, comorbidities were chronic renal failure and hypothyroidism. The coronary angiogram revealed a significant stenosis of all coronary arteries including the main left coronary artery that were not amenable for intervention. An intra-aortic balloon pump (IABP) was implanted to assist coronary blood flow. In the echocardiography, no obvious regional wall motion abnormalities were seen, the heart function was normal and a moderate regurgitation of the mitral valve was present. Despite the risk of severe neurologic damage an emergent CABG was performed. General anesthesia (GA) was provided during off pump surgery with sevoflurane, fentanyl and remifentanil iv with norepinephrine as vasopressor in the range of 0.1-0.2 mcg/kg/min. On ICU, therapeutic hypothermia (35-36°C) for 24 hours was targeted by use of an transvenously inserted cooling device and analgosedation provided with propofol iv (2-4 mg/kg/h) and sufentanil iv (0.1-0.2 mcg/kg/h). The IABP was removed on POD 1 and the sedation switched to dexmedetomidine iv (0.02-1.0 mcg/kg/h) after discontinuation of therapeutic hypothermia. During 20 hours of dexmedetomidine administration a normal body temperature around 37°C was seen and the patient was extubated on POD 2. The patient was somnolent without signs of severe neurologic injury. An increase of the body temperature to 38°C occurred around extubation with a decline towards 37.3°C over the next 10 hours when the patient was re-intubated for respiratory failure due to residual oversedation. Low dose propofol iv (1-2 mg/kg/h) was used initially, and the patient was alert and cooperative during verbal and tactile stimulation. Dexmedetomidine was re-commenced on POD 4 because of inadequate tracheal tube tolerance. The body temperature increased after dexmedetomidine initiation over 5 hours to 38.6°C with an undulating course above 37.5°C during POD 5 and declined on POD 6 after dexmedetomidine discontinuation from 38.6 over 6 hours to 37.2°C. An empirical antibiotic therapy with amoxicillin/clavulanic acid had been commenced for assumed aspiration pneumonia before the initiation of dexmedetomidine. Microbiologic sampling did not reveal any microorganisms. The pulmonary and neurologic function permitted the extubation of the patient on POD 5. The patient recovered without any neurologic sequelae and was discharged from ICU on day 9.

Patient #4

A 60 years old male patient under therapy for chronic heart failure due to dilative cardiac myopathy presented in the cardiologic ambulatory care unit of the UHZ with dyspnea (NYHA III) and weight gain of 5 kg despite increase of his oral diuretics dose. Due to a previous echocardiography left ventricular function was severely reduced (LV-EF 24%) with a moderate regurgitation of the mitral and tricuspid valve. Vital parameters were in the patients’ normal range (NIBP 101/60 mmHg, heart 69 bpm, body temperature 36.4°C, SpO2 99%). Cardiac risk factors included DM type II, obesity (BMI 36.3 kg/m²), arterial hypertension, dyslipidemia. In his past medical history, a CRT-D had been implanted after AV-node ablation for permanent atrial fibrillation with change of the impulse generator for a low battery state one year ago. For the past two weeks, a localized edema with warming of the skin overlying the CRT implantation site had been noted by the patient. Of the laboratory inflammation markers, only CRP was mildly elevated (13 mg/l). A fluid collection around the CRT pulse generator was seen by ultrasound and surgically evacuated. Staphylococci epidermidis was found in the fluid, antibiotic therapy with vancomycin and rifampicin initiated and the complete transvenous CRT system switched to an epicardial CRT system one week later. After surgery, the patient was transferred to the ICU where mechanical ventilation was discontinued on the same day after a stable course of hemodynamics. Clonidine was administered twice to ameliorate a mild agitation state. On POD 1, however, the patient exhibited a hyperactive delirium that was addressed initially by 5 mg haloperidol iv and then by dexmedetomidine iv (0.1-1.2 mg/kg/h). The body temperature at dexmedetomidine initiation was 37.5°C, increased over the next 10 hours steadily to 38.8 °C and undulated between 39°C and 40°C and returned to below 37.5°C only after 14 days. The focus of infection being targeted by antibiotics, drug fever was assumed as differential diagnosis in the first 48 hours of hyperthermia. Thereafter with declining lung function and necessity of NIV an assumed hospital acquired pneumonia was empirically targeted by piperacillin/tazobactam iv. Dexmedetomidine for hyperactive delirium was discontinued after 5 days when the sudden onset of severe cardiovascular instability necessitated the restart of mechanical ventilation. Endocarditis was ruled out by transesophageal echocardiography. A CT scan revealed a hematoma at the initial CRT removal site that was evacuated but microbiologic investigations did not reveal any infective organism. Under empirical therapy with meropenem, daptomycin and rifampicin a stabilization of hemodynamics and decline of laboratory inflammation markers eventually developed. Ongoing delirium was treated with pipamperone and clonidine and then for a second time by dexmedetomidine during POD 13 to15. Hyperthermia (38.8°C) was already present when dexmedetomidine was initiated this time, decreased over the course of 24 hours to 36.6 °C and remained between 37° to 38°C until the discontinuation of dexmedetomidine on POD 15. Due to COPD, the weaning process from mechanical ventilation was successful this time only after dilative tracheotomy. Metabolic toxic encephalopathy and continuous low dose vasopressor support prolonged ICU care thereafter to a total of 45 days.

Patient #5

A 67 years old patient with a history of dilative arteriopathy was admitted to the UHZ for aortic repair of an asymptomatic thoraco-abdominal aortic aneurysm (TAAA) with a maximal diameter of 5.7 cm. The patient had normal vital signs (NIBP 138/90 mmHg, a HR 72 bpm, normal body temperature) and a BMI of 20.7 kg/m2. His past medical history consisted of CAD and COPD (risk factors: tobacco smoking, occupational dust exposure) with an intermittent need for supplemental oxygen at home. In the past the patient had undergone multiple abdominal operations (appendectomy, femoral and umbilical hernia repair) and widespread intraperitoneal adhesions had been described during a recent elective cholecystectomy. A complete endovascular aortic repair (EVAR) was therefore planned and in a first step endovascular reno-visceral rebranching and EVAR below the left subclavian artery performed. The procedure was technically challenging with both femoral and the left subclavian artery (LSA) as EVAR access sites and took 7 hours and 50 minutes to complete with a significant blood loss. GA was provided by propofol and remifentanil iv. Hypovolemia and coagulopathy due to intraoperative blood loss were corrected with 4500 ml crystalloids, 2500 ml colloids, 284 ml blood from the cell saver, 6 packs of erythrocyte concentrates, 8 g of fibrinogen, 1250 U of factor XIII and 500 U of prothrombin complex. Vasopressor support with norepinephrine was in the range of 0.2-0.4 mcg/kg/min. The patient was postoperatively transferred to the ICU to closely monitor for spinal cord and abdominal organ ischemia after EVAR. Ischemia of kidneys and liver was ruled out by ultrasound Doppler. Weaning the patient from mechanical ventilation was complicated by inadequate tolerance to the endotracheal tube during the reduction of propofol iv. Dexmedetomidine iv (0.1-0.8 mcg/kg/min) was used as supplementary sedation agent and the patient thereafter successfully weaned and extubated 4 hours later. During dexmedetomidine administration hyperthermia (max. body temperature 38.6°C) occurred and resolved over the course of 5 hours. After the onset of hyperthermia microbiologic sampling was performed. The patient was still under the routine perioperative antibiotic prophylaxis for 24 hours with cefuroxime. Pseudomonas aeruginosa was identified in tracheal secretions but was regarded as a COPD related bronchial colonization and not targeted by specific antibiotic therapy. Laboratory inflammation markers declined steadily after peaking on POD 3. Neurologic deficits and signs of visceral organ ischemia remained absent and the patient was discharged from ICU on POD 1. EVAR of the TAAA proximal to the LSA with endo-debranching of the supra-aortic vessels occurred in a second step 8 months later and was performed without any of the procedure related complications.

Patient #6

A 66-year-old male with a past medical history of mechanical aortic valve replacement for aortic stenosis 9 years ago presented after a two weeks’ episode of productive cough and dyspnea (NYHA III-IV) without fever to his local cardiologist. The patient had no signs of angina pectoris. Cardiac risk factors were arterial hypertension, dyslipidemia and prior use of tobacco products (20 pack years). His medication consisted of a beta-blocker, an ACE inhibitor, a calcium antagonist, a statin and an oral vitamin K antagonist. Laboratory inflammation markers were in the normal range and of the cardiac biomarkers only troponin slightly elevated. The EKG showed a heart rate of 88 bpm in sinus rhythm, a bifascicular AV block and no signs of ischemia. A transesophageal echocardiography revealed a normal prosthetic valve function, a mild to moderately reduced left ventricular function (EF 45%) with diffuse regional wall motion anomalies and no signs of endocarditis. A thoracic CT scan showed no pulmonary infiltrates and no pulmonary embolism. Exercise EKG testing was inconclusive because of the patients’ exercise intolerance. A subacute NSTEMI was assumed and the patient scheduled for coronary angiography which 4 weeks later revealed a significant stenosis of the main left coronary artery and a new severe paravalvular aortic leak that was confirmed by echocardiography. The patient had no clinical signs of infection and normal laboratory inflammation markers (CRP, leucocytes) but an endocarditis was suspected and the patient admitted to the University Hospital Zurich (UHZ) for emergent aortic valve surgery and CABG. Staphylococcus epidermidis was eventually identified in blood cultures and targeted by antibiotic therapy with vancomycin, rifampicin and temporarily with gentamycin; the antibiotics were determined to last for at least 6 weeks. During cardiac surgery endocarditis was confirmed by an abscess cavity in the aortic root. The aortic valve was replaced, CABG performed and additionally the mitral and tricuspid valve reconstructed for annular dilation with moderate regurgitation. The postoperative persistence of an AV block III° was addressed by pacing via routine temporary epicardial pacemaker leads. After transfer to the ICU the patient was initially sedated with propofol and sufentanil. Signs of delirium developed after discontinuation of propofol on POD 1 and the sedation was switched to dexmedetomidine iv. A rise in body temperature to 38.8°C from an elevated baseline of 38°C was observed in the hours thereafter. The patient suffered a convulsive status epilepticus and dexmedetomidine was switched to midazolam iv (0.05 - 0.1 mg/kg/h) for the suppression of epileptic brain activity. Sampling on POD 2 did not reveal any microorganisms. Cardiovascular drugs (epinephrine, milrinone, noradrenaline) and mechanical ventilation could be successfully weaned and the patient did not exhibit any signs of focal neurologic deficiency after sedative discontinuation. In absence of clinical signs of active infection and declining laboratory inflammation markers, a definite pacemaker with epicardial leads was eventually implanted. The echocardiography revealed a normal prosthetic valve and mildly reduced left ventricular function. The patient recovered well from the endocarditis and was discharged from ICU on POD 6.

Patient #7

A 72 years old female with a severe aortic valve stenosis and a CAD was admitted for elective aortic valve replacement and CABG of the LAD and RCA. Dyspnea NYHA grade III had been present for 6 months. She had a history of chronic renal failure and had undergone a right sided carotid endarterectomy and a resection of a non-metastasized melanoma on her lower thigh 3 years ago. During the preoperative examinations, a urinary tract infection with multi-sensible E. coli was identified and targeted by a single dose of fosfomycin po. GA for cardiac surgery was conducted with sevoflurane, fentanyl iv (20 mcg/kg) and remifentanil iv (0.15 mcg/kg/min). The surgery was technically uneventful but bleeding after ECC and heparin reversal with protamine required the transfusion of 2 packs of RBC. The blood coagulation was optimized according to our institutional guidelines by administration of fibrinogen, factor XIII, desmopressin and prothrombin complex. The heart function was excellent (LVEF 65%) and vasopressor support with norepinephrine in the range of 0.1 mcg/kg/min. Several hours thereafter on ICU, a massive bleeding occurred and the patient was resuscitated because of hypovolemic shock. After emergent re-sternotomy, the bleeding was under control. Following a stabilization of hemodynamics with additionally dobutamine iv (4 mcg/kg/min) the sedation with propofol was repeatedly reduced for a neurologic evaluation but the patient was found only to fight mechanical ventilation without any adequate reaction to verbal stimulation. Clonidine bolus administration did not have any effect and dexmedetomidine was commenced on POD 2, where after the body temperature increased steadily from 37.5 °C during the following 35 hours to a maximum of 39°C. The function of the lung was uncompromised but because of yellowish tracheal secretions pneumonia was assumed and tazobactam / piperacillin iv empirically commenced. The results of the microbiologic investigations were negative for microorganisms and in absence of a clinical infection focus drug fever was suspected. Dexmedetomidine was discontinued and a combination of continuous clonidine and midazolam iv for sedation commenced to target the patients persisting intolerance to mechanical ventilation. The change of the sedative drugs was followed by a decrease of the body temperature over the next 5 hours to 37°C without any hyperthermia thereafter. Because of the patients prolonged inadequate neurologic response to weaning from the sedation postoperative cerebral lesions were ruled out by a CT scan and a non-convulsive status epilepticus excluded by an EEG. Eventually, on POD 7 the patient recovered neurologically and was extubated. The patient was discharged from the ICU after 9 days.

Patient #8

A 64 years old female was diagnosed with a severe aortic valve stenosis and CAD following a diagnostic workup of dyspnea NYHA grade II-III. The usual cardiac risk factors (hypertension, diabetes mellitus type II, dyslipidemia, obesity (BMI 36,8 kg/m2) and nicotine abuse) were present. Her comorbidities included a combination of a severe osteoporosis with Paget disease in parts of the spine, sacrum, right hemi pelvis, proximal left femur and left scapula. During the uneventful cardiac surgery, the aortic valve was replaced and CABG performed while GA was provided with sevoflurane, fentanyl and remifentanil. No bleeding occurred after heparin reversal with protamine and vasopressor support with norepinephrine was in the range of 0.05 mcg/kg/min at the end of the surgery. Postoperative discontinuation of mechanical ventilation on the ICU was particularly challenging in this patient. Every reduction of propofol (3-4 mg/kg/min) resulted in a highly uncooperative patient fighting the ventilator with concomitant oxygen desaturation and necessity of immediate re-sedation and administration of muscular relaxation to regain hemodynamic stability. Additional clonidine iv with a cumulative dose of 900 mcg over 12 hours had no positive influence on the patients’ response to the reduction of sedation. On POD 1 dexmedetomidine iv (1 mcg/kg/h) was initiated and the sedation with propofol and clonidine discontinued. Over the course of following 10 hours the body temperature increased from 37.5 °C to 38.9 °C without signs of hemodynamic instability and undulated around 38.2 °C until POD 4. Dexmedetomidine, however, was discontinued on POD 2 when the patient was sufficiently cooperative to be extubated. Because no focus of infection could be identified and signs of hemodynamic instability were absent an empirical antibiotic trial was not commenced. Furthermore, no microorganisms were detected in samples of body fluids. On POD 3 a hyperactive delirium was treated with pipamperone po (cumulative 60 mg) resulting in a deeply sedated patient with partial pulmonary failure. NIV was initiated and bilateral pleural effusions revealed by a chest x-ray. After evacuation of the left pleural cavity the pulmonary function was much better and NIV could be discontinued after the patient was responsive again. Because of the possibility of aspiration pneumonia and continuously elevated body temperature around 38 °C empirical tazobactam/piperacillin was commenced on POD 4. Hemodynamics were in a stable range without the need for vasopressors. The patient was discharged on POD 5 to the intermediate care where the patient gradually recovered from the hyperactive delirium under pipamperone po (20-40 mg/day).

Patient #9

A 72 years old male patient was admitted for an elective mitral valve repair because of a prolapse of P2 of the posterior leaflet with severe mitral regurgitation. Under torasemide po the patient was in a cardiopulmonary compensated state. Because of a severely dilated left atrium atrial fibrillation was present. Heart rate control was accomplished by bisoprolol and anticoagulation by rivaroxaban. Cardiac risk factors were arterial hypertension and smoking (20 PY). However, a significant CAD had been excluded by a recent coronary angiography. Transesophageal echocardiography after induction of GA revealed a LVEF of 65% and a normal right ventricular function before cardiac surgery. Intraoperatively, after successful mitral valve repair (dpmean 3 mmHg, no regurgitation) and separation of the patient from the ECC suddenly a severe hemodynamic instability occurred with right ventricular failure and systolic anterior movement (SAM) of the anterior mitral valve leaflet with the need of open heart resuscitation. The ECC was emergently reinstalled and after 30 minutes of reperfusion a second separation from the ECC was possible under high dose norepinephrine (0.3 mcg/kg/min), epinephrine (0.15 mcg/kg/min), milrinone (0.15 mcg/kg/min) and inhalational nitric oxide (20 ppm). Sedation with propofol iv was changed postoperatively to midazolam iv (0.15 mg/kg/h) in the ICU because of persistent hemodynamic instability with norepinephrine iv in a range of up to 0.5 mcg/kg/min. Tazobactam/piperacillin and vancomycin were commenced empirically on POD 1. The right ventricle had regained its function and the SAM phenomenon had declined due to increased left ventricular filling on POD 2. As hemodynamics stabilized continuous midazolam was switched during weaning from mechanical ventilation to sevoflurane on POD 2 and then to dexmedetomidine on POD 5. The baseline body temperature at dexmedetomidine initiation was 37.5°C and hyperthermia > 38.5°C was noted 17 hours later. In absence of a clinical focus of infection, negative results from microbiological investigations of body fluids, established broad-spectrum empirical antibiotic therapy and declining laboratory inflammation markers, drug fever was assumed and dexmedetomidine discontinued 36 hours after its initiation. The temperature declined over the course of 24 hours to < 37.5°C. Because of the patients’ poor endotracheal tube tolerance propofol sedation was recommenced and following several unsuccessful attempts of reducing sedation a dilative tracheotomy was performed on POD 9. A nocturnal, hyperactive delirium developed thereafter that was initially treated by continuous midazolam iv (0.05 mg/kg/h) and then by pipamperone po. The weaning from the ventilator was further complicated by bilateral pleural effusions which were evacuated on POD 12 and a hospital acquired pneumonia on POD 14 with Klebsiella pneumoniae and Citrobacter koseri initially targeted by meropenem and then by tazobactam/piperacillin for 10 days. Following structured weaning from the ventilator the patient was decannulated on POD 27 after 48 hours of spontaneous breathing. Neurologic deficits were absent, the echocardiography revealed a normal heart function with a fully functional repaired mitral valve and the patient was discharged from the ICU after 29 days.

**Glossary (alphabetical)**

BMI body mass index

CABG coronary artery bypass grafting

CAD coronary artery disease

COPD chronic obstructive pulmonary disease

CT computer tomography

ECC extracorporeal circulation

EKG electrocardiogram

EEG electroencephalogram

EVAR endovascular aortic repair

GA general anaesthesia

GCS Glasgow Coma Scale

HR heart rate

ICU intensive care unit

IV intravenously

LAD left anterior descending coronary artery

LVEF left ventricular ejection fraction

NIBP noninvasive blood pressure

NIV noninvasive ventilation

NYHA New York Heart Association

PO per orally

POD postoperative day

PPM parts per million

PY pack years

RBC red blood cells

RCA right coronary artery

UHZ University Hospital Zurich