EDITOR:
Fatigue of the diaphragm may contribute to the development of respiratory failure [1]. The cause is thought to be an alteration in transmembrane calcium transport [2]. We have previously shown that the calcium channel blocker nicardipine intensifies diaphragmatic fatigue [3]. We compared the effects of diltiazem, another calcium channel blocker, on diaphragm fatigability in vivo with those of nicardipine when both were given at the same dose of 5 µg kg⁻¹ min⁻¹.

After approval by the University of Tsukuba Animal Care and Use Committee, 16 healthy mongrel dogs (12 males, 4 females, 10–15 kg) were prepared as described previously [3]. Briefly, anaesthesia was maintained with pentobarbital 2 mg kg⁻¹ h⁻¹ intravenously (i.v.). No muscle relaxant was used. Each animal’s trachea was intubated and the lungs ventilated with O₂ in air (FiO₂ = 0.4) to maintain PaO₂ >13.3 kPa, PaCO₂ 4.7–5.3 kPa and pH 7.35–7.45. Arterial blood-gas tensions were measured every 30 min. Transdiaphragmatic pressure (Pdi) was measured with two thin-walled latex balloons — one positioned in the stomach, the other in the middle third of the oesophagus — connected to a differential pressure transducer and an amplifier. The phrenic nerves were exposed bilaterally at the neck and the stimulating electrodes connected. Supramaximal electrical stimuli (10–15 V, 0.1 ms, 20 or 100 Hz) were applied for 2 s. Diaphragmatic contractility was evaluated by measuring maximal Pdi during airway occlusion at functional residual capacity. Electrodes placed through a midline laparotomy recorded the electrical activity of the crural and costal portions of the diaphragm. The signal was rectified and integrated to yield diaphragmatic electromyographical activity (Edi-cru and Edi-cost, respectively).

The dogs were randomly divided into two groups of eight. After measuring baseline values of heart rate (HR), mean arterial pressure (MAP), Pdi, Edi-cru and Edi-cost, diaphragmatic fatigue was induced by intermittent supramaximal bilateral 20 Hz phrenic stimulation applied for 30 min (low-frequency fatigue) with alternating 2 s cycles of stimulation and rest [4]. During this fatigue-inducing period, the dogs in Group 1 received nicardipine 5 µg kg⁻¹ min⁻¹ i.v. and those in Group 2 received diltiazem 5 µg kg⁻¹ min⁻¹ i.v. The dose of the study drugs was chosen based on our previous study [3]. At the end of the fatigue-inducing period, the phrenic nerves were stimulated again with 20 and 100 Hz and the diaphragm responses measured. Edi-cru and Edi-cost were calculated as the percentage of baseline (%Edi-cru, %Edi-cost). Statistical analysis was performed by ANOVA for repeated measurement with Bonferroni corrections for multiple comparisons and a t-test, where appropriate. P < 0.05 was considered as statistically significant. Data were given as mean ± SD.

The results are shown in Table 1. After the fatigue-inducing period, HR had increased (P < 0.05) and MAP decreased (P < 0.05) in Group 1 (nicardipine). Transdiaphragmatic pressure decreased from baseline values after 20 Hz stimulation (P < 0.05), but not after 100 Hz stimulation. Edi was not affected by either stimulation frequency. Heart rate and MAP decreased in Group 2 (diltiazem) (P < 0.05). Pdi was decreased at both stimulation frequencies (P < 0.05), but Edi only decreased after 100 Hz stimulation (P < 0.05). The decrease of Pdi and Edi was larger in Group 2 than in Group 1 (P < 0.05).

Selective loss of force at 20 Hz stimulation was closely related to the impairment of excitation–contraction coupling [5], and selective loss of force and electromyographical activity at 100 Hz stimulation indicates the failure of neuromuscular transmission [6]. Pdi was decreased in Group 1 at 20 Hz stimulation but not at 100 Hz. Edi was unchanged at both frequencies. This was in agreement with our previous report [3].

The mechanism by which nicardipine intensifies diaphragmatic fatigability remains unclear but may be
Table 1. Changes in haemodynamics, transdiaphragmatic pressure (cmH2O) and percentage diaphragmatic electromyographical activity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Fatigue + nicardipine</th>
<th>Fatigue + diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>(Group 1)</td>
<td>(Group 2)</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats min⁻¹)</td>
<td>137 ± 10</td>
<td>146 ± 11*</td>
<td>129 ± 10†</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>125 ± 12</td>
<td>90 ± 16*</td>
<td>88 ± 14</td>
</tr>
<tr>
<td>Pdi (cmH₂O)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Hz stimulation</td>
<td>15.5 ± 3.2</td>
<td>8.9 ± 1.7*</td>
<td>7.4 ± 1.6†</td>
</tr>
<tr>
<td>100 Hz stimulation</td>
<td>20.5 ± 2.7</td>
<td>20.0 ± 2.4</td>
<td>17.5 ± 2.0†</td>
</tr>
<tr>
<td>%Edi-cru</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Hz stimulation</td>
<td>100.0 ± 0.0</td>
<td>97.9 ± 6.0</td>
<td>96.5 ± 6.5</td>
</tr>
<tr>
<td>100 Hz stimulation</td>
<td>100.0 ± 0.0</td>
<td>99.5 ± 3.3</td>
<td>90.0 ± 3.0†</td>
</tr>
<tr>
<td>%Edi-cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Hz stimulation</td>
<td>100.0 ± 0.0</td>
<td>97.5 ± 7.1</td>
<td>96.1 ± 7.2</td>
</tr>
<tr>
<td>100 Hz stimulation</td>
<td>100.0 ± 0.0</td>
<td>98.6 ± 2.6</td>
<td>89.4 ± 2.3†</td>
</tr>
</tbody>
</table>

Data are the mean ± SD. HR: heart rate; MAP: mean arterial pressure; Pdi: transdiaphragmatic pressure; Edi-cru: integrated electrical activity of the crural part of diaphragm; Edi-cost: integrated electrical activity of the costal part of diaphragm. Group 1: nicardipine 5 µg kg⁻¹ min⁻¹; Group 2: diltiazem 5 µg kg⁻¹ min⁻¹. *P < 0.05 versus baseline; †P < 0.05 versus Group 1.

associated with impairment of excitation–contraction coupling. The results in Group 2 showed a reduction of Pdi at both stimulation frequencies, but Edi only reduced at 100 Hz. This is presumably associated with the impairment of excitation–contraction coupling and the failure of neuromuscular transmission. Thus, the mechanism of diltiazem on diaphragmatic fatigability might be different from that of nicardipine.

Our results showed that diltiazem reduced Pdi more than nicardipine at both stimulation frequencies (P < 0.05) at the same dose of 5 µg kg⁻¹ min⁻¹, which suggests that diltiazem affects diaphragmatic fatigability more than nicardipine. The reason for this difference is unknown, but it may be attributed to the different mechanisms of action of these two calcium channel blockers.

As far as we are aware, this is the first report that compares the effects of diltiazem with those of nicardipine on diaphragmatic fatigability in vivo. When used at the same dose, diaphragmatic fatigue with diltiazem is more pronounced than with nicardipine in dogs. The mechanisms by which these two calcium channel blockers intensify diaphragmatic fatigability may be different. One must consider the limitations of this study. First, the dose of the study drugs may not have been equipotent. Second, diaphragm blood flow – which can affect diaphragm contractility – may have differed. However, diaphragm blood flow is autoregulated at MAP > 70 mmHg [7] and MAP was > 70 mmHg during this study indicating that blood flow to the diaphragm was maintained. Third, there is a possibility that the increase in HR during nicardipine administration may be provoked by stimulating the phrenic nerves and a decrease in HR during diltiazem administration may also be modified by it. Future studies should consider these limitations.

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References
Possible underestimation of the relative incidence of anaphylactic reactions to benzylisoquinoline neuromuscular blocking agents

EDITOR:

We report a case of a confirmed anaphylactic reaction to cisatracurium that was initially interpreted as a non-specific anaphylactoid reaction not requiring further allergological investigations.

A 62-yr-old female (weight 68 kg) was admitted for cholecystectomy. She had a history of poliomyelitis in childhood, requiring eight consecutive operations on her right leg, and hypertension treated with a β-adrenoceptor blocking agent. She had no history of atopy, allergy, asthma or previous adverse reactions during anaesthesia. Cefazolin 2 g was injected 20 min before induction of anaesthesia without any disturbance of heart rate or arterial pressure (60 beats min⁻¹, 120/70 mmHg). Fentanyl (200 µg), thiopental (500 mg) and cisatracurium (14 mg) were then injected intravenously (i.v.). The trachea was easily intubated and the lungs mechanically ventilated. Anaesthesia was maintained by isoflurane (end-tidal 0.6%) and O₂/N₂O (50/50). Heart rate and arterial pressure were stable at 65 beats min⁻¹ and 100/70 mmHg, respectively. Five minutes later, a generalized erythema appeared with a rapid but moderate decrease in arterial pressure (80/60 mmHg) and increase in heart rate (70 beats min⁻¹). No wheezing or increase in airway pressure was recorded. End-tidal PCO₂ decreased from 5.2 to 3.7 kPa. Symptomatic treatment was started by i.v. phenylephrine injections (four boluses of 6 mg each at 1 min intervals) and circulating volume expansion (1000 mL 0.9% saline) allowing a return of haemodynamic variables to the postinduction values. The erythema lasted approximately 10 min and then progressively disappeared. Haemodynamic fluctuations were initially attributed to induction of anaesthesia, and the erythema to non-specific histamine release following injection of cisatracurium. Further allergological investigations were considered unnecessary. However, colleagues suspected a true anaphylaxis, because non-specific histamine release following cisatracurium injection is uncommon. The operation was then cancelled as recommended, and blood and urine samples were collected in an attempt to establish a diagnosis of anaphylaxis [1]. The patient recovered from anaesthesia without any problems and was extubated 35 min later, and there were no further complications. Results of plasma histamine and tryptase monitoring, immunoglobulin E-specific assays as well as skin tests performed 6 weeks later are summarized in Tables 1 and 2. Skin tests were interpreted in comparison with a histamine control (histamine prick-test: IP/OP = 8/20; histamine intradermal test at a 10⁻² dilution: 20/65) by an allergologist experienced in performing and interpreting such tests with anaesthetic agents. The patient’s skin was considered highly reactive to

Table 1. Results of biological tests.

<table>
<thead>
<tr>
<th></th>
<th>At 30 min</th>
<th>At 90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum tryptase (µg L⁻¹)</td>
<td>25.9</td>
<td>24.8</td>
</tr>
<tr>
<td>Serum histamine (µg L⁻¹)</td>
<td>7.2</td>
<td>5.2</td>
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</table>

Immunglobulin E-specific assays

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<thead>
<tr>
<th></th>
<th>% of inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quaternary ammonium compounds</td>
<td>&lt;1.0: negative</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>&lt;15.0: positive</td>
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Urinary methylhistamine

<table>
<thead>
<tr>
<th></th>
<th>(nmol mmol⁻¹ creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary methylhistamine</td>
<td>184.7</td>
</tr>
</tbody>
</table>

Table 2. Results of skin tests.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>10⁻¹</td>
<td>10⁻³</td>
<td>10⁻²</td>
<td>10⁻¹</td>
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</tbody>
</table>

Intradermal reactions (IP/OP)

<table>
<thead>
<tr>
<th></th>
<th>10⁻¹</th>
<th>10⁻³</th>
<th>10⁻²</th>
<th>10⁻¹</th>
</tr>
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<tr>
<td>Prick (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vecuronium</td>
<td>Negative</td>
<td>-</td>
<td>-</td>
<td>15/23</td>
</tr>
<tr>
<td>pancuronium</td>
<td>Negative</td>
<td>-</td>
<td>-</td>
<td>10/20</td>
</tr>
<tr>
<td>rocuronium</td>
<td>Negative</td>
<td>-</td>
<td>8/25</td>
<td>na</td>
</tr>
<tr>
<td>atracurium</td>
<td>Negative</td>
<td>5/25</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>mivacurium</td>
<td>Negative</td>
<td>10/40</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>cisatracurium</td>
<td>Negative</td>
<td>8/30</td>
<td>10/50</td>
<td>na</td>
</tr>
<tr>
<td>latex</td>
<td>Negative</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>thiopental</td>
<td>Negative</td>
<td>-</td>
<td>10/30</td>
<td>-</td>
</tr>
<tr>
<td>propofol</td>
<td>Negative</td>
<td>-</td>
<td>-</td>
<td>10/15</td>
</tr>
<tr>
<td>etomidate</td>
<td>Negative</td>
<td>-</td>
<td>-</td>
<td>10/20</td>
</tr>
<tr>
<td>midazolam</td>
<td>Negative</td>
<td>-</td>
<td>-</td>
<td>10/40</td>
</tr>
<tr>
<td>fentanyl</td>
<td>Positive</td>
<td>-</td>
<td>-</td>
<td>5/35</td>
</tr>
<tr>
<td>sufentanil</td>
<td>Negative</td>
<td>-</td>
<td>-</td>
<td>8/30</td>
</tr>
</tbody>
</table>

IP/OP: injection papule diameter (mm)/oedematous papule diameter (mm) measured 20 min after injection. Intradermal tests were performed at a 10⁻¹, 10⁻³, 10⁻² and 10⁻¹ dilution if applicable. na: not applicable.
Several French surveys focusing on the incidence of peranaesthetic anaphylactic reactions confirmed that neuromuscular blocking agents (NMBAs) were the most incriminated drugs [2–5]. Interestingly, the last survey reported relevant differences among non-depolarizing NMBAs [5]. The incidence was higher with rocuronium and lower with cisatracurium. However, those surveys were based on spontaneous reports, by anaesthetists of suspected anaphylactic reactions, to GERAP. Therefore, under reporting due to misinterpretation of clinical symptoms may distort the results. Since a high percentage of patients presenting with a suspected peroperative anaphylactoid reaction do not have further allergological investigations, results may underestimate the reality [5]. This is particularly suspected in the case of atracurium [6]. Indeed, non-specific histamine release is well described following rapid bolus injections of atracurium so that distinction between a low-grade anaphylactic reaction and a non-specific anaphylactoid reaction is difficult to make clinically. A systematic allergological investigation in case of moderate variations in haemodynamic variables and the appearance of erythema following atracurium injections would be expensive and so is not recommended [1]. However, cisatracurium differs from atracurium regarding non-specific histamine release. Owing to its higher potency, lower doses of cisatracurium are required in order to reach the same depth of curarization, then minimizing histamine release in the clinical setting [7]. Logically, when using cisatracurium, the occurrence of clinical symptoms evoking histamine release should be considered a threat of real anaphylaxis. Patients should then benefit from an allergic ‘work up’ and instances should be declared both to the pharmacovigilance institute and to GERAP. This may be considered as the main clinical interest of cisatracurium over atracurium. However, as in this current description, assimilation between atracurium and cisatracurium may be made, possibly leading to under reporting of cisatracurium-related potential anaphylactic reactions. On the contrary, since rocuronium is now widely considered in France as an important anaphylactic reaction provider, declarations of even minor clinical events suggesting such a reaction are probably exhaustive. This last attitude is, of course, a good one, but it should be promoted with each agent. If not, one should be particularly suspicious that an artificially lower incidence of real anaphylaxis to cisatracurium compared with other neuromuscular blocking agents exists.

Epidemiological surveys such as the French ones are of great importance in providing relative risks of anaphylactic reactions following injections of NMBAs. To improve the veracity of the results, all suspected cases of anaphylaxis should be investigated and declared whatever neuromuscular blocking drug is used. Specifically, all clinical situations evoking histamine release following the injection of cisatracurium should be considered to be potentially real anaphylactic reactions, which facilitates the decision of proceeding or not to an allergologic ‘work up’ compared with atracurium. However, one can suspect that a parallel is often drawn between those two drugs, so that the incidence of anaphylactic reactions to cisatracurium may be underestimated due to spontaneous under reporting.

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References

Two episodes of bronchospasm during anaesthesia in asthmatic patients

EDITOR:
Tracheal intubation can trigger bronchospasm in asthmatic patients and to avoid this anaesthetists often deepen anaesthetic depth when the airway is instrumented in asthmatics [1]. We report bronchospasm that occurred after tracheal intubation and after tracheal suctioning in two asthmatic patients, despite meticulous anaesthetic care.

An 18-yr-old male (height 167 cm, weight 41 kg), with a history of allergy and bronchial asthma, was scheduled for resection of a haemangioma of the orbit. He had not suffered a severe attack of asthma for some years. He tended to feel breathless and wheezy whenever he had an upper respiratory tract infection, for which about three or four times a year he would use a nebulized β2-agonist or corticosteroids.

When the patient presented for surgery, he had not had a recent infection. His chest was clear on auscultation. His forced vital capacity (FVC) was 3.7 L (85% of predicted) and his forced expiratory volume in 1 s (FEV1.0) was 2.4 L (67%). He received intravenous (i.v.) methylprednisolone 40 mg the evening before surgery and again 2 h before he was due for surgery. He received clonidine 150 µg and famotidine 20 mg orally 90 min before induction of general anaesthesia. An i.v. infusion was started on the ward.

On arrival in the operating room, basic monitoring was established and anaesthesia induced with fentanyl 100 µg and propofol 100 mg while the patient breathed 100% oxygen. Vecuronium 6 mg was injected and the trachea intubated.

At this stage, manual ventilation became impossible because of high airway resistance. No wheezing could be heard. Manual application of 30 cmH2O produced a tidal volume <100 mL. Anaesthesia was deepened by increasing the inspired concentration of sevoflurane. Epinephrine 200 µg, aminophylline 250 mg and hydrocortisone 100 mg were injected i.v. Within a few min, manual ventilation became easier, with a little wheezing, and the improvement continued. Pulse oximetry remained normal. Arterial blood was taken for analysis while the patient was breathing 100% oxygen: PaO2 = 48.9 kPa, PaCO2 = 6.7 kPa, base excess = −4.4 mmol L−1.

After this episode, an oesophageal stethoscope was inserted and anaesthesia maintained with sevoflurane 1–2% in nitrous oxide and oxygen. After surgery was completed, bronchospasm recurred during suction of the trachea (inspired sevoflurane was 1.5%) preparatory to removing the endotracheal tube. Epinephrine 50 µg i.v. was given and manual ventilation became easy and returned to normal within a few minutes. A radiograph showed hyper-expansion of both lung fields. The endotracheal tube was eventually removed and a cuffed oropharyngeal airway (COPA®, Mallinckrodt Medical, St Louis, MO, USA) was inserted, without incident, while the patient breathed sevoflurane 1.5% in oxygen spontaneously. The concentration of sevoflurane was gradually reduced, the COPA® was removed and there were no more respiratory problems.

A 38-yr-old asthmatic female (height 156 cm, weight 52 kg), who had not had an attack for 3 years and was taking no medication, was scheduled for resection of an ovarian tumour under combined epidural and general anaesthesia. Her chest was clear on auscultation. Her preoperative FVC was 91% predicted and her FEV1.0 73% predicted.

Intravenous methylprednisolone 40 mg was given 2 h before induction of anaesthesia was due, and oral diazepam 10 mg with famotidine 20 mg 90 min before. Anaesthesia was induced with fentanyl 200 µg and propofol 100 mg and vecuronium was given to enable tracheal intubation. Immediately, manual ventilation became difficult with obvious wheezing, but it lasted only a few minutes.

We needed to remove airway secretions, so we deepened the sevoflurane anaesthesia to 2.5%. Manual ventilation again became difficult with high airway resistance and the SpO2 decreased to 90%. We gave lidocaine 50 mg i.v. and were then able to perform suction without bronchospasm. After surgery, we removed the endotracheal tube without incident while the patient breathed sevoflurane 1.5% in oxygen spontaneously.

Patients who have asthma have more than normally reactive airways and it has long been known that any instrumentation of the airways is best done under deep anaesthesia. Propofol is considered safe for asthmatic patients because of its bronchodilating effect [2] and it is worth giving corticosteroids a few hours preoperatively. Airway receptors in the lower respiratory tract are more sensitive to chemical stimulation and less sensitive to mechanical stimulation.

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It is the laryngeal and carinal regions that are most sensitive to mechanical stimulation and, as well as eliciting respiratory reflex responses as indicated in Gillespie’s chart [3], also elicit haemodynamic reflexes during anaesthesia. Tracheal intubation and carinal stimulation cause transient reflex bronchoconstriction even in non-asthmatic patients, and unsurprisingly patients with chronic obstructive airways disease are more at risk than normal patients [4]. The cardiovascular responses to mechanical stimulation can be blocked by deep anaesthesia, but respiratory responses caused by stimulation of the airway probably cannot be blocked completely just by deep anaesthesia [1]. Mechanical stimulation of the carina, such as occurs when suction catheters are used in the trachea, is likely to cause bronchospasm in asthmatic patients whatever the depth of anaesthesia.

Many drugs have been used, either i.v. or via the airway, to treat severe bronchospasm in asthmatic patients: lidocaine, β2-adrenergic agonists, atropine, theophylline and others [1]. Different responses demand different drugs. For example, i.v. lidocaine has been reported as being effective treatment for bronchospasm when there is also light anaesthesia and the patient is coughing, but lidocaine, whether i.v. or inhaled, is likely by itself to cause bronchoconstriction [5]. Intravenous lidocaine does not protect against reflex bronchoconstriction [6]. Volatile anaesthetics, especially halothane, have been used for relieving the spasm [1]. Inhaled clonidine, an α2-adrenoceptor agonist, has been reported to decrease airway reactivity [7]. The response to oral clonidine in asthmatic patients is uncertain, sensitizing to histamine in one study but not in another. An inhaled α2-adrenergic agonist, albuterol, protected against bronchoconstriction caused by tracheal intubation in patients given propofol and isoflurane [6]. Perhaps this drug would be useful in routine clinical practice in asthmatic patients.

Unsurprisingly, anaesthesia administered by facemask or laryngeal mask is less likely to cause bronchoconstriction [8]. In one of our patients, changing from an endotracheal tube to a COPA® during deep anaesthesia enabled uncomplicated emergence. Provided there is no need for tracheal suction, emergence does not cause bronchoconstriction. If suction is necessary, applying local anaesthetic to the upper airways [4] should reduce the likelihood of bronchospasm.

Prevention of bronchospasm in asthmatic patients during anaesthesia is a difficult problem. None of the drugs that can be used are guaranteed to prevent bronchospasm in these patients, and from our observations in our two patients we suggest that the best strategy may be to try as far as possible to avoid any mechanical stimulation of the airway, especially of the carinal area.

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References
EDITOR:
Indications for permanent pacemaker implantation have changed considerably in the last two decades. The American Heart Association (AHA) and the American College of Cardiology (ACC) latest guidelines [1] deny the need for permanent pacemaker implantation in moderate sinus node or conduction disturbances (e.g. asymptomatic sinus bradycardia). Other guidelines provide the indications for electrophysiological examinations, e.g. the presence of Mobitz type I atrioventricular block (AVB) [2]. Furthermore, in some cases the permanent pacemaker implantation is based on pure haemodynamic considerations when an individually programmed permanent pacemaker generator, with a short atrioventricular delay, can improve the quality of life of patients with a failing left ventricle and prolonged PQ time [3].

Frequently, the anaesthetist is the first doctor who examines the patient’s electrocardiograph recording and suspects the potential for intraoperative dysrhythmias during the preoperative visit. Some rhythm disturbances have no effect on the everyday life of the patient – nevertheless, they may present a potential danger during surgery and anaesthesia or in the postoperative period [4–6]. Therefore, it is of prime importance to select the patients who need further cardiac examination before surgery. We implemented a diagnostic algorithm for the identification of patients who might produce potentially dangerous rhythm problems during non-cardiac surgical operations (Fig. 1).

Between January 1997 and April 1999, 14 090 elective surgical operations were performed under general or regional anaesthesia in our department. Among them, 104 patients (0.17%) were identified as having either bradycardia (resting heart rate < 50 beats min\(^{-1}\)) or intraventricular conduction disturbance (first- or second-degree AVB with QRS complexes > 100 ms). Patients were subjected to an atropine test or carotid massage (Fig. 1). Twenty-four

![Figure 1. Diagnostic protocol for the selection of patients for perioperative temporary pacemaker therapy. HR: heart rate; AVB: atrioventricular block.](image-url)
patients (23%) met the criteria for the insertion of a temporary pacemaker electrode preoperatively. The distribution of dysrhythmia diagnoses is shown in Table 1. Forty-nine patients (47%) received atropine premedication (1.0 mg subcutaneously 30 min before operation) to prevent episodes of critical bradycardia (<45 beats min⁻¹) during anaesthesia. The remaining 31 patients (29%) were regarded as low risk and neither temporary pacemaker insertion nor atropine premedication were used and the standard intraoperative monitoring was considered as sufficient. Three other patients who were not subjected to the diagnostic procedure shown in Figure 1 also needed temporary pacemaker treatment: one patient had third-degree AVB and narrow QRS complexes; two had first-degree AVB and a bifascicular block.

The electrodes were inserted through the basilar vein at the antecubital fossa in nine patients and central veins were used (internal jugular or subclavian vein) in 15 cases. Following the AHA/ACC guidelines, permanent pacemakers were implanted in four patients in the postoperative period.

The negative chrono- and dromotropic effects of drugs used for the induction and maintenance of general anaesthesia can significantly worsen existing rhythm disturbances. Our protocol has to be applied cautiously since not only the dysrhythmia, but also the type of the operation, as well as patients’ comorbid conditions, need to be taken into account [7] (e.g. atropine cannot be administered to glaucoma patients, and operations with severe blood loss or thoraco-abdominal procedures require temporary pacing more frequently). The benefit of our protocol is supported by the fact that patients without permanent pacemakers did not develop any rhythm disturbances that would have needed admission to an intensive care unit. The temporary pacemakers were set to a rate limit of 60 beats min⁻¹ and all of them triggered the myocardium during the surgical intervention. Patients with temporary pacemakers had no complications related to their insertion.

We conclude that when using our algorithm, the patients scheduled for non-cardiac surgery can be classified into different risk categories for perioperative heart rhythm complications. Further prospective clinical trials are warranted to examine the false-positive and -negative results of the diagnostic protocol.

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References
Effects of sevoflurane and isoflurane on the efficacy of rewarming from hypothermic cardiopulmonary bypass

EDITOR:
The after-drop is a rapid and unavoidable reduction in core temperature that occurs after discontinuation of cardiopulmonary bypass (CPB). Because the core component is rewarmed much more rapidly than the peripheral tissues during CPB, heat is redistributed from core to periphery in the early post-bypass period. Prolonged bypass, high pump flows, heating blankets, forced air, heated humidified gases and the vasodilator sodium nitroprusside have all been used in attempts to mitigate the problem [1]. We report our experience with sevoflurane and isoflurane on this phenomenon.

We studied 44 patients undergoing coronary artery bypass grafting or valve replacement surgery. All patients received morphine 0.15 mg kg\(^{-1}\) intramuscularly and their routine cardiac medication 1 h before surgery. Arterial and venous cannulation was performed and then anaesthesia was induced with fentanyl 10–15 µg kg\(^{-1}\) and midazolam 0.1–0.2 mg kg\(^{-1}\) intravenously. Endotracheal intubation was accomplished after the administration of vecuronium 0.1 mg kg\(^{-1}\). The patients then received two different maintenance regimens to maintain anaesthesia: Group 1 (n = 21), isoflurane + fentanyl 0.1–0.15 µg kg\(^{-1}\) min\(^{-1}\) + 50% oxygen in air; and Group 2 (n = 23), sevoflurane + fentanyl 0.1–0.15 µg kg\(^{-1}\) min\(^{-1}\) + 50% oxygen in air. Isoflurane and sevoflurane concentrations were adjusted to maintain the mean arterial pressure to within 25% of baseline. Boluses of fentanyl 3–4 µg kg\(^{-1}\) were administered before skin incision and sternotomy and also during episodes of tachycardia (heart rate > 25% of baseline).

Patients were cooled during CPB to a minimum rectal temperature of about 28°C and subsequently rewarmed to a rectal temperature of at least 36.5°C. The fluid–blood temperature gradient was maintained near 8°C. The circulating water mattresses under the patients were adjusted to 37–38°C in the post-bypass period. Room temperature was maintained to between 19 and 21°C throughout the operation.

Anaesthetic vaporizers, connected to the gas supply of the oxygenator, supplied volatile agents during CPB. A fentanyl infusion 0.05–0.075 µg kg\(^{-1}\) min\(^{-1}\) and supplemental vecuronium were used in both groups. Isoflurane and sevoflurane were administered in concentrations to keep the mean arterial pressure between 40 and 60 mmHg with pump flows of 2.0–2.2 L min\(^{-1}\) m\(^{-2}\) during hypothermia. Both agents were titrated to use maximum pump flows of 2.4–2.6 L min\(^{-1}\) m\(^{-2}\) with mean arterial pressure ranging between 60 and 90 mmHg in the rewarming period. The target mean arterial pressure was increased gradually according to the rise in core temperature. Any hypotension unresponsive to titration of volatile anaesthetics and manipulations of pump flow was treated by boluses of ephedrine 5 mg.

Temperatures were measured at 5 min intervals. The core temperature was recorded from the nasopharynx, the intermediate thermal zone was monitored by a rectal thermocouple (T\(_{rect}\)) and the peripheral thermal zone was monitored by skin-surface sensors placed on the midthorax in the anterior axillary line (T\(_{chest}\)), lateral upper arm (T\(_{arm}\)), lateral thigh (T\(_{thigh}\)) and calf (T\(_{calf}\)). Mean skin temperature (MST) was calculated from four sites: 0.3 (T\(_{chest} + T_{arm}\)) + 0.2 (T\(_{thigh} + T_{calf}\)).

Data are presented as mean ± SD. The U-test, Fisher’s exact test and χ\(^{2}\)-test were used to test the significance of the difference between groups. Statistical significance was taken as P < 0.05.

Patient characteristics in both groups were similar (Table 1). Our results are shown in Table 2; none of the variables showed statistically significant differences between groups.

Nitroglycerin 0.1–0.25 µg kg\(^{-1}\) min\(^{-1}\) was administered both in the pre- and post-bypass period to 15 patients in Group 1 and to 17 patients in Group 2. Ten patients in Group 1 and eight patients in Group 2 required dopamine infusion, and 17 patients in both groups required a dobutamine infusion (5 µg kg\(^{-1}\) min\(^{-1}\)) in the post-bypass period. The number of patients treated with vasoactive agents did not differ significantly between the groups. Hypotensive episodes were treated by bolus doses of ephedrine in five patients (24%) in Group 1 and in three patients (13%) in Group 2 (P = 0.4) during rewarming.

Isoflurane and sevoflurane produced a similar after-drop after hypothermic CPB. The after-drop associated with both agents was within the range of previously reported values [2–5]. All investigators studying heat balance during open-heart surgery agreed that a certain degree of post-bypass hypothermia was unavoidable. PujoJ and colleagues [2] reported a 1.8°C after-drop in their patients who were cooled to 29°C. Deakin and colleagues reported a decrease

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in the after-drop from 2.8 to 2.5°C using nitroprusside in patients operated on at a 28–30°C core temperature [3]. Rajek and colleagues found that the after-drop was 2.3°C at a bypass temperature of 27°C [4]. In a previous study – with a bypass temperature of 28°C – we reported that isoflurane and nitroprusside produced comparable after-drops of approximately 1.4°C [5].

The contribution of volatile agents to the distribution of heat may be explained by arteriolar vasodilation related to direct relaxant actions on vascular smooth muscle or to reduction in sympathetic activity [6,7]. Although not investigated in the present study, the effects of volatile anaesthetics on systemic vascular resistance have been reported. Rödig and colleagues showed that inspired concentrations of 3% sevoflurane or 1.8% isoflurane produced 20–25% reductions in the systemic vascular resistance index during CPB [6]. Similarly, 0.5 and 1 MAC isoflurane provided dose-dependent decreases in the systemic vascular resistance index during bypass, counteracting the vasoconstriction caused by hypothermia [7]. We suggest that the use of isoflurane or sevoflurane throughout the hypothermic CPB period offers an easy way of managing core hypothermia after CPB.

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References


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**Impossibility of injection through an epidural catheter caused by an incorrect connection of catheter and connector**

**EDITOR:**

Situations where it is impossible to inject through an epidural catheter are rare. Reported causes include kinking, knotting [1,2], stretching [3] and blockade by a blood clot in the catheter [4,5]. We describe a case in which it was impossible to inject through an epidural catheter, although a preinsertion patency test had been successful.

A 53-yr-old female with degenerative osteoarthritis of the right hip was scheduled for right total hip replacement. Lumbar epidural anaesthesia was planned. An epidural catheter, which was confirmed to be patent by an injection test before insertion, was inserted through an 18-G Tuohy needle at the L2–L3 interspace using loss of resistance to physiological saline. The epidural catheter was easily threaded 3 cm into the epidural space with no unusual resistance being encountered. After removal of the epidural needle, the epidural catheter was inserted into the connector (Hakko, Nagano, Japan). No blood or cerebrospinal fluid was aspirated through the catheter, and there was a firm resistance on trying to inject a test dose of a local anaesthetic through it. Changing the patient’s body position did not allow injection of the local anaesthetic. The probability of the knotting of the epidural catheter was explained to the patient, and she accepted its removal and the insertion of another one. The original catheter was cautiously removed without resistance or paresthesia during the removal. Though neither knotting nor a blood clot were found in the removed epidural catheter, it was still impossible to inject any solution through it. Another catheter was inserted at the same lumber intervertebral space and a local anaesthetic was easily injected through the epidural catheter. Surgery proceeded uneventfully under epidural anaesthesia with intravenous sedation.

A close examination revealed that the inability to inject any solution through the catheter was caused by incorrect assembly of the catheter and connector. The connector assembly used had three components: a retaining cap into which a small rubber ball is placed, and a screw cap that pushes the ball against the retaining cap (Fig. 1a). When it is assembled correctly, an epidural catheter passes completely through the lumen of the ball, and the ball fastens it tightly by screwing the retaining and screw caps

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Cyproheptadine and the treatment of an unconscious patient with the serotonin syndrome

EDITOR:
The serotonin syndrome results from a drug-induced abnormality of serotonin metabolism. It presents with central, neuromuscular, and autonomic signs and symptoms. The presentation, differential diagnosis and management of a patient who presented with a decreased level of consciousness, neurological signs and a raised temperature are described.

A 60-yr-old female presented to the Accident and Emergency Department with an altered level of consciousness of sudden onset and a history of a seizure. Her Glasgow Coma score was 7/15 and her pupils were equal and reactive. Neurological examination revealed a generalized increase in tone, particularly the upper limbs, but no other focal signs. Her arterial pressure was 143/87 mmHg, heart rate 87 beats min\(^{-1}\), respiratory rate 24 breaths min\(^{-1}\) and core temperature 38.5°C. Pulse oximetry revealed a saturation of 98% during oxygen breathing 6L min\(^{-1}\) from a facemask. Past medical history included hypertension and depression. Her depression was treated with paroxetine 60 mg day\(^{-1}\) and risperidone 2 mg twice daily. The dose of paroxetine had recently been increased owing to worsening symptoms. There was no history of any other drug ingestion. Her trachea was intubated to protect her airway. Anaesthesia was induced with thiopental 3 mg kg\(^{-1}\), and tracheal intubation facilitated with 1 mg kg\(^{-1}\) succinylcholine. Sedation was maintained with a propofol infusion.
Arterial blood-gas status and basic blood pathology including creatine kinase were unremarkable. A brain computed tomography (CT) scan, an electroencephalogram and cerebrospinal fluid examination were all normal. Urine was sent for toxicological examination. The following day, despite discontinuing the propofol, she remained hypertonic and unresponsive. A repeat CT scan revealed no evolving pathology. The differential diagnosis included a cerebrovascular accident, an infection or a metabolic abnormality such as malignant hyperthermia, or the neuroleptic malignant syndrome. Because of the drug history, the serotonin syndrome was considered. Cyproheptadine, an anti-serotonergic drug, was commenced (8 mg by mouth, three times a day). Shortly after its introduction, the patient’s level of consciousness dramatically returned to normal, the hypertonia and temperature resolved, and the trachea was extubated. She remained symptom free and was discharged to the ward. Therapy was changed to tricyclic antidepressants and after 3 months she had had no recurrence of any neurological, autonomic or neuromuscular symptoms. Toxicology results revealed no other foreign substances. The patients has been advised to avoid selective serotonin reuptake inhibitors (SSRIs) and those doctors treating her were all informed of this fact.

The serotonin syndrome is caused by increased serotonin activity both in the brain and spinal cord. In his description of it, Sternbach [1] explained its diagnosis as being based on history and examination as there are no confirmatory tests available. The essential features to make the diagnosis are central nervous system, neuromuscular and autonomic abnormalities in the presence of serotonergic drugs and no other proven cause.

Abnormalities of serotonin metabolism have been implicated in many behavioural abnormalities [2]. This may be due to drugs that increase its secretion such as amphetamines and cocaine or those that decrease its uptake such as selective SSRIs and tramadol [3], or drugs that stimulate serotonergic receptors such as bromocriptine and lithium. It occurs when more than one agent is used at a time, the dose of one agent is changed or when one agent is commenced too soon after the cessation of another (up to 2 weeks for some agents). Symptoms may occur as soon as 1 h or up to several days after ingesting the relevant agents. The central symptoms can range from a slightly altered level of consciousness to coma and convulsions. Neuromuscular findings include incoordination, hyper-reflexia, tremors, myoclonus, rigidity, clonus and ataxia. Diaphoresis, salivation, fever, hypertension, tachycardia and shivering are manifestations of the autonomic abnormalities that occur [1]. With supportive therapy, it usually resolves in 24 h, but prolonged symptoms and progression to multiorgan system failure and death may occur. It may be underreported because it is unrecognized or, due to similar signs, misdiagnosed as the neuroleptic malignant syndrome [3].

The serotonin syndrome has many similarities to the neuroleptic malignant syndrome, which develops following an idiosyncratic reaction to several antipsychotic drugs such as the phenothiazines and butyrophenones. The neuroleptic malignant syndrome is due to dopamine receptor blockade or withdrawal of exogenous dopaminergic agonists and presents with a profound hyperthermia, altered conscious state as well as peripheral and autonomic symptoms. It differs from the serotonin syndrome in that it usually resolves over days rather than hours.

Malignant hyperthermia was excluded because the patient had no history of exposure to anaesthetic agents, her temperature did not rise above 38.5°C, her creatine kinase was not elevated and her PaCO₂ was always within the appropriate range. Although succinylcholine had been used to permit tracheal intubation, her symptoms preceded its use. Selective serotonin reuptake inhibitors block the action of the presynaptic serotonin reuptake pump and thereby increase the amount available for action at the postsynaptic receptor. All SSRIs have several similarities in that they are all hepatically metabolized and lack the multiple receptor affinity associated with tricyclic antidepressants. Their safety profile, with mild side-effects and uncommon fatality with overdose, has made them popular [4]. Although SSRIs have a very high toxic-to-therapeutic ratio, it is recommended that they are not used in combination with any other drug that affect serotonin concentrations. Our patient was also receiving risperidone, a balanced serotonin agonist–antagonist that has been used to treat many behavioural and psychological symptoms [5].

Cyproheptadine is a serotonin antagonist and antihistamine agent that has been used to treat allergies, migraines, nightmares and behavioural abnormalities [6]. It has even been used to treat sexual dysfunction cause by SSRIs. Its pharmacological action makes it an ideal agent to treat symptoms associated with increased serotonin concentrations.

Hypertensive patients, such as this patient, and those with endothelial disease may be at a greater risk of developing the serotonin syndrome. They have a reduced ability to secrete nitric oxide in response to platelet-derived serotonin [7]. Because nitric oxide is counter-regulatory to serotonin – particularly in the cerebrovascular system – inhibiting its action may cause abnormalities in serotonin metabolism and therefore cause symptoms.

In conclusion, this patient presented with symptoms, a risk factor and a drug history for a diagnosis
of serotonin syndrome to be made. Extensive investigation revealed no other cause and her dramatic recovery to the serotonin antagonist cyproheptadine seems to confirm the diagnosis. Many drugs may be responsible for the serotonin syndrome and it is probably much more common than realized. When one SSRI is prescribed, care should taken when adding further medications.

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References