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CASE REPORT

Companion or pet animals

Isoproterenol and phenylephrine infusions following external pacing failure in an anaesthetised dog with sick sinus syndrome undergoing unilateral mastectomy

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Abstract

Managing anaesthesia in dogs with sick sinus syndrome poses significant challenges due to bradyarrhythmias and life-threatening hypotension. An 8-year-old, mixed-breed dog with sick sinus syndrome underwent general anaesthesia for unilateral mastectomy. Anaesthetic drugs with minimal cardiovascular impact and a multimodal analgesic approach, including loco-regional techniques, were employed. Initially, transcutaneous pacing ensured stable cardiovascular parameters, but surgical repositioning led to pacing failure, causing a rapid drop in heart rate and mean arterial pressure. Immediate infusion of isoproterenol and phenylephrine successfully normalised the dog's haemodynamics, allowing the 100-minute surgery to proceed with stable vital parameters. The infusions were discontinued at the end of anaesthesia, leading to an uneventful recovery. This case demonstrates the effectiveness of isoproterenol and phenylephrine infusions in managing an anaesthetised dog with sick sinus syndrome, highlighting the importance of preparedness and having alternative pharmacological interventions ready for device-related challenges.

KEYWORDS

anaesthesia, canine, isoprenaline, sinus node disease, sinus node dysfunction, transcutaneous pacing

BACKGROUND

Sick sinus syndrome (SSS), or sinus node dysfunction, is a disease characterised by intrinsic sinoatrial node dysfunction and is a common cause of bradyarrhythmias in dogs.[1,2] Clinically, affected animals may show a variety of changes on electrocardiography (ECG) including sinus bradycardia, sinus arrest, atrioventricular (AV) blocks, ventricular escape rhythm and tachyarrhythmias.[1] Symptoms such as exercise intolerance and syncope are a consequence of a decreased cardiac output.[2,3] Diagnosis involves clinical signs, anamnesis and a negative response to atropine test.[2,4]

Anaesthetic management in dogs with SSS can be challenging.[5] General anaesthesia is known to depress the sympathetic drive, increasing the incidence of bradyarrhythmias further compromising the cardiac output with potential life-threatening consequences.[6] The treatment with the best long-term outcome is the surgical implantation of a permanent artificial pacemaker.[2,7] Alternatively, transcutaneous pacemaker (TCP) is a non-invasive technique used in dogs and humans for temporary cardiac pacing during anaesthesia or as emergency treatment in severely bradyarrhythmic patients.[8–10] Optimal transthoracic pads placement is needed in order to achieve effective pacing.[8,9]

Besides artificial pacing, infusion of isoproterenol appears to be effective in SSS cases.[4,11] Isoproterenol is a β1 and β2 adrenergic agonist amine with marked chronotropic and vasodilatory effects.[12] Its use in dogs with SSS increases sinus node activity and AV conduction.[11] Undesired hypotension has been reported during its administration in an anaesthetised dog with SSS.[4]

Phenylephrine is a selective α1 adrenergic agonist amine, known to increase systemic vascular resistance and blood pressure.[13] Its administration in dog to counteract isoproterenol-induced vasodilation has not yet been documented.

This report describes the successful anaesthesia of a dog with SSS undergoing unilateral mastectomy, where simultaneous infusions of isoproterenol and phenylephrine were used for the first time in a clinical patient.

CASE PRESENTATION

An 8-year-old, female, mixed-breed dog, weighing 10 kg was referred to our institution for unilateral left mastectomy.

The referring veterinarian reported unremarkable clinical examination of the patient, except for a pronounced irregular cardiac rhythm and a 2/6 holosystolic heart murmur on the right side at auscultation. Electrocardiography revealed predominant ventricular escape rhythm with long sinus pauses (up to 5 seconds) and variable heart rate (HR) (28–64 beats per minute). The atropine test (Atropinum sulfuricum 'Nycomed', Takeda Austria, Austria; 40 μg/kg intramuscularly [IM]) showed a negative response leading to the diagnosis of SSS. Haematology, biochemistry and total thyroxine levels measured upon blood collection at the referring veterinarian were within normal reference ranges. The dog had been adopted for 2 years by the current owner, and there was no medical history before this period. The owner did not report any episodic weakness, exercise intolerance or syncope. A repeated ECG examination at our institution confirmed the findings reported by the referring clinician. The owner refused the option of referring the dog elsewhere for permanent cardiac pacemaker placement.

TREATMENT

On the day of surgery, the dog was alert and bright, anxious and uncooperative during pre-anaesthetic examination. Irregular heart rhythm variating between 32 and 90 beats per minute and synchronous strong peripheral pulse at femoral arteries palpation were observed. At cardiac auscultation, heart murmur on the right side of the thorax, holosystolic and grade 2/6 was confirmed. Mucous membranes were pink and capillary refill time was less than 1.5 seconds. The patient was classified as American Society of Anaesthesiologists class III. Premedication consisted of pethidine (Alodan, G.L. Pharma; 4 mg/kg IM). Thirty minutes after injection, the sedation achieved was unsatisfactory, and the patient remained uncooperative for intravenous catheter placement. In order to avoid further stress, second IM injection of ketamine (Ketamidor, Richter Pharma; 2 mg/kg) and midazolam (Midazolam Hameln, Hameln Pharma Plus; 0.2 mg/kg) was opted. A moderate sedation was achieved 7 minutes after injection, and a 20-gauge catheter (Vasofix Safety, B. Braun) was aseptically placed on the left lateral saphenous vein. Preoxygenation via mask (3 L/min of 100% oxygen) was performed for 5 minutes before intravenous (IV) induction with etomidate (Etomidat, Lipuro, B. Braun; 2 mg/kg) and ketamine (1 mg/kg). After smooth orotracheal intubation with a cuffed polyvinyl chloride 7.5 mm internal diameter endotracheal tube (Rüschelit, Teleflex Medical), the dog was connected to an anaesthetic circuit (Uniflow coaxial breathing system, Intersurgical).

Anaesthesia was maintained with sevoflurane (Sevofluran 'Baxter' 100%, Baxter Healthcare) in oxygen. The patient was positioned in dorsal recumbency and instrumented. Pulseoximetry (SpO_2), ECG, end-tidal carbon dioxide ($EtCO_2$) and sevoflurane (FESevo), respiratory rate (fR), rectal temperature were continuously monitored using a multiparametric monitor (IntelliVue MP60 patient monitor, Philips). Data were recorded every 5 minutes. An isotonic crystalloid solution (Sterofundin ISO, B. Braun; 5 mL/kg/h IV) was administered. A forced air device (Bair Hugger, 3 M) connected to a warming blanket (MoeckWarmingSystem, Moeck) was used to maintain normothermia during the entire procedure. The lungs of the dog were mechanically ventilated and fR adjusted to maintain $EtCO_2$ between 35 and 50 mmHg. After induction, HR was 28 beats per minute with sinus pauses of up to 5 seconds. At this stage, a 22-gauge catheter (Vasofix Safety, B. Braun Melsungen) was placed on the right dorsal pedal artery, and invasive arterial systolic (SAP), mean (MAP) and diastolic (DAP) pressures were monitored and recorded. At the same time, a pair of adhesive conduction pads (Pediatric Plus Multifunction Defibrillation Electrode Pads, Philips) for TCP (M4735A Philips HeartStart XL Defibrillator/Monitor) were quickly applied to each side of the thoracic wall, between 4th and 10th ribs at the costo-chondral joints level (Figure 1). Ventricle capture was achieved after minimal position adjustments at the electrical current of 40 mA with an impulse duration of 20 milliseconds. A frequency of 60 beats per minute was able to maintain the MAP over 60 mmHg. Rocuronium (ESMERON, N.V. Organon; 0.6 mg/kg IV) was administered in order to suppress the muscular twitches generated by the electrical impulses of the TCP. Once TCP was stable, ultrasound-guided (NanoMaxx Ultrasound system SonoSite) transversus abdominis plane (TAP) block in two points (subcostal and lateral abdominal approaches) with 0.3% ropivacaine (Ropinaest, Gebro Pharma; total volume of 0.3 mL/kg per point) and superficial serratus plane (SP) block with 0.75% ropivacaine (total volume of 0.3 mL/kg) were performed on the left side. Twenty-two minutes after starting TCP, the left pad of the device was repositioned dorsally due to surgical need for mastectomy. The new position of the pad proved ineffective in pacing the heart. The HR and SAP/DAP(MAP) decreased to 36 beats per minute and 70/30(45) mmHg, respectively (Figure 2). Therefore, a pharmacological treatment with isoproterenol (Isoprenalina cloridrato monico, Monico; 0.05–0.2 μg/kg/min) and phenylephrine (Biorphen, Sintetica; 0.25–1 μg/kg/min) infusions were immediately initiated in an attempt to improve cardiovascular function. Five minutes after starting the infusions, HR and SAP/DAP(MAP) increased to 65 beats per minute and 105/55(70) mmHg, respectively. Surgical procedure started 50 minutes after induction and had a total duration of 100 minutes. FESevo remained between 1.4% and 2%, HR between 70 and 100 beats per minute and SAP/DAP(MAP) between 105/60(80) and 150/87(107) mmHg

LEARNING POINTS/TAKE-HOME MESSAGES

- Dogs with sick sinus syndrome may be anaesthetised without prior permanent pacemaker implantation in case of need.
- Simultaneous administration of isoproterenol and phenylephrine infusions may be effective in maintaining cardiovascular stability in anaesthetised dogs with sick sinus syndrome.
- Preparedness to adapt promptly in case of complications optimises outcomes in challenging cases.

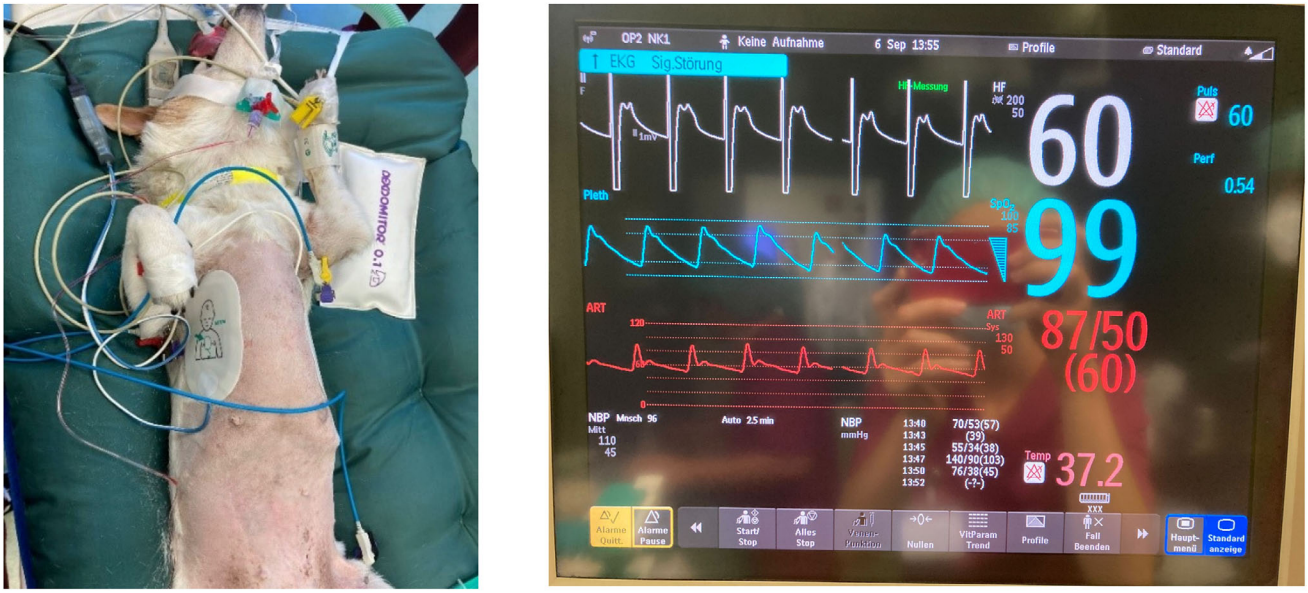

FIGURE 1 Photographs taken during the surgical preparation of an anaesthetised dog with sick sinus syndrome while transcutaneous external pacing was employed. On the left, it displays the dog in dorsal recumbency along with some of the equipments including the adhesive transcutaneous pads during effective external pacing. On the right, it shows the multiparameter monitor displaying from top to bottom electrocardiography (ECG), pulse-oximetry, invasive blood pressure and endoesophageal temperature values of the dog during effective pacing. Note the typical spiked artefact, preceding the QRS complex during ventricular capture on the ECG trace.

FIGURE 2 Graph illustrating some cardiovascular variables during the dog's anaesthetic event (marked as close dotted vertical lines) and in recovery. A long-dashed vertical line denotes the start of effective external pacing, while a red closed dashed line with an X marks the moment of external pacing failure. Vertical arrows indicate the start and end of the infusions of isoproterenol and phenylephrine. A light green rectangle highlights the surgical period. Doses of isoproterenol (ISP) and phenylephrine (PH) expressed in µg/kg/min are detailed in the upper section of the graph.

during the infusions (Figures 2 and 3). At the end of surgery, absence of residual curarisation was confirmed by stimulation of the left peroneal nerve using an accelerometer device (TOF-GUARD, Organon Teknik) through train-of-four assessment. A T4/T1 ratio over 0.9 was confirmed and the animal weaned off the ventilator. At 155 minutes after induction, a bolus of acepromazine (Temprace, Dechra Veterinary Products; 5 µg/kg IV) was administered to provide a calmer recovery period. At 160 minutes after induction, sevoflurane administration was terminated, the infusions of isoproterenol and phenylephrine were discontinued, the animal placed in lateral recumbency and continuously monitored. Within 6 minutes,

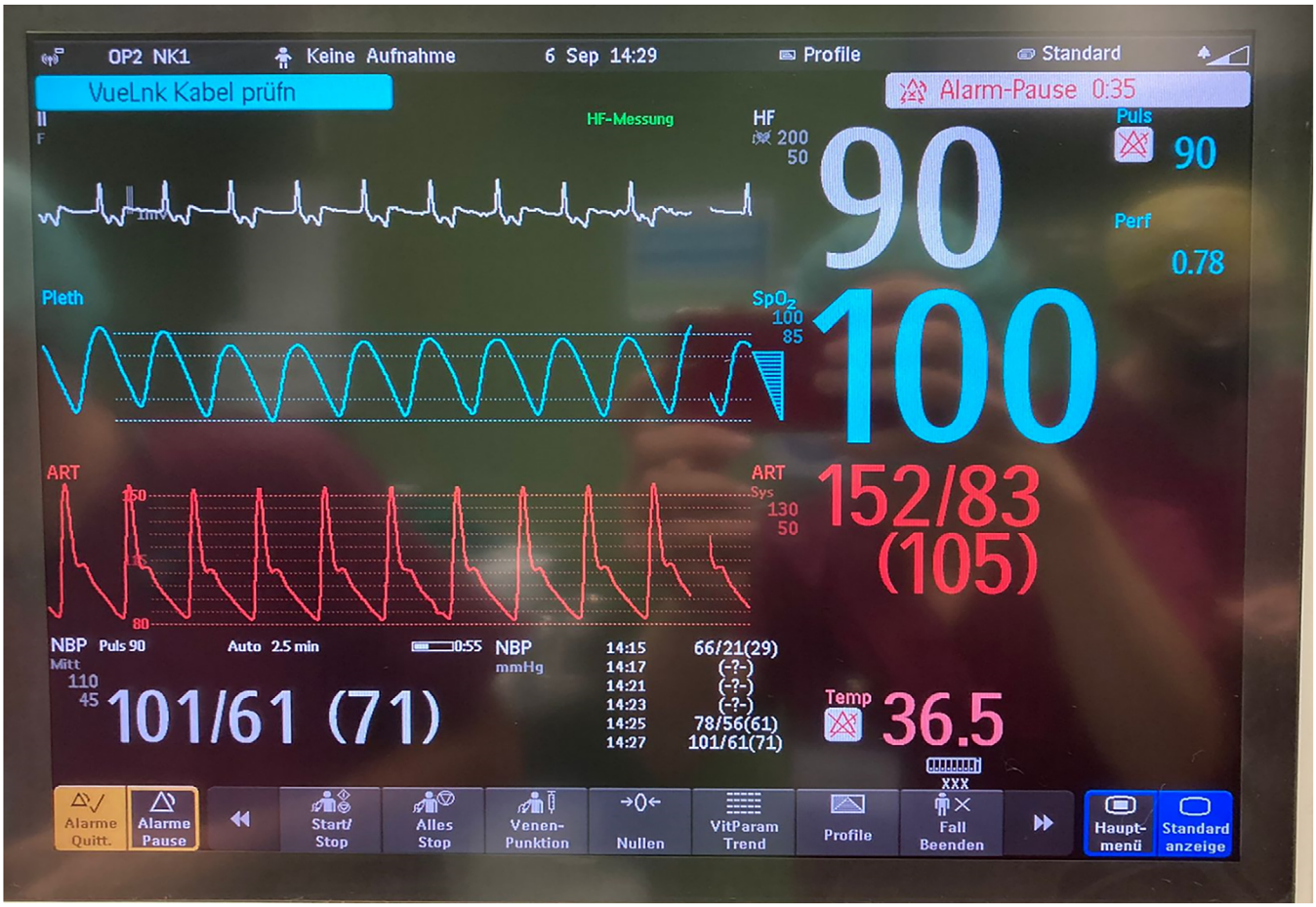

FIGURE 3 Screen's photograph of the multiparameter monitor while monitoring an anaesthetised dog with sick sinus syndrome during the simultaneous infusions of isoproterenol and phenylephrine. It displays (from top to bottom) electrocardiography, pulse-oximetry, blood pressure and endoesophageal body temperature values at that time point.

cardiovascular parameters returned to baseline values, with MAP decreasing to 57 mmHg and HR between 20 and 67 beats per minute with an irregular rhythm (Figure 2).

Eight minutes after the end of anaesthesia, the dog showed a positive swallowing reflex and its trachea was extubated. The animal was able to stand 15 minutes after the end of anaesthesia and remained hospitalised until the next day and monitored through periodic ECG and NIBP measurements. A short form of the Glasgow Composite Pain Scale (CMPS-SF) was used to assess pain postoperatively, with a score of 2 out of 24 recorded 1 hour after the end of anaesthesia and similar results in the following assessments during hospitalisation. Postoperative analgesia, initiated after the CMPS-SF first assessment, consisted of meloxicam (Metacam, Boehringer Ingelheim; 0.2 mg/kg IV, once daily), paracetamol (Paracetamol, B. Braun; 10 mg/kg IV, twice daily) and gabapentin (Gabapentin Hexal, Hexal Pharma; 10 mg/kg orally, twice daily).

OUTCOME AND FOLLOW-UP

The dog was successfully discharged from the hospital without complications 24 hours after surgery. Analgesic and anti-inflammatory therapy was continued at home. Until the time of writing this report (12 months after the event), no complications have occurred.

DISCUSSION

This case report details the successful anaesthetic management of a dog with SSS undergoing unilateral mastectomy, where, after the external pacemaker failed, bradycardia and hypotension were promptly addressed with simultaneous infusions of isoproterenol and phenylephrine.

Isoproterenol is a short-acting sympathomimetic drug used to increase HR in anaesthetised dogs affected by SSS and other forms of bradyarrhythmias.[4,11] Its β1 agonism increases cardiac inotropism and chronotropism, while its concomitant β2 agonism causes peripheral vasodilation by relaxing involuntary muscles fibres, leading to decreased DAP and potentially hypotension.[11] This side effect has been reported in a dog with SSS under general anaesthesia, where isoproterenol infusion led to hypotension.[4]

Phenylephrine, a short-acting vasopressor, induces peripheral vasoconstriction through α1-selective agonism.[13] Its cardiovascular impact has been extensively investigated in people and animals.[14–16] Interestingly, studies in people and pigs reported variable effects on cardiac output depending on the position of the heart on the Frank–Starling curve.[15,16] Moreover, phenylephrine has been clinically used to treat isoproterenol-induced hypotension in humans,[17] despite the lack of studies evaluating its efficacy for this purpose. Based on these findings, we hypothesised that phenylephrine could counteract the vasodilatory effect of isoproterenol in the dog,

thereby preventing hypotension. Our clinical use in this dog confirms that concurrent isoproterenol and phenylephrine infusions can maintain haemodynamic stability, ensuring that HR and blood pressure variables remained within the physiological range throughout the entire 110-minute infusion period. Notably, 6 minutes after discontinuing the infusions at the end of the procedure, the cardiovascular variables dropped again to baseline values.

While the outcome was successful, it is important to note that the administration of sympathomimetic and vasopressor drugs during anaesthesia carries certain risks.

The use of isoproterenol can lead to unwanted side effects, including cardiac ischaemia, due to increased myocardial oxygen demand and decreased coronary perfusion, as observed in a study in conscious dogs.[18] Additionally, isoproterenol may increase venous admixture by enhancing ventilation–perfusion mismatch due to increased cardiac output and pulmonary vasodilation, as described in a study with dogs where isoproterenol was tested at different doses, with varying ventilation techniques and inspired gas concentrations.[19] This occurs because more blood is directed through less well-ventilated lung regions, resulting in a greater mismatch.

Furthermore, in the same study, isoproterenol was also shown to increase right-to-left shunt. This shunt persisted even when ventilation was adjusted to maintain stable $EtCO_2$, most likely due to increased blood flow through physiological arteriovenous communications in the lungs, which may bypass the alveolar–capillary interface.[19] In the cited experiment, significant effects were associated with higher doses than those used in our case. Nevertheless, care should be taken when using this drug to support the heart of a dog.

To maintain normotension, other drugs may have been used instead of those employed in this case.

Dobutamine, a short-acting synthetic catecholamine that acts as a nonselective β-agonist with some α1 adrenergic affinity, may have been employed instead of isoproterenol.[20,21] Clinical studies in humans undergoing atrial fibrillation ablation surgery have shown that high-dose dobutamine alone can elicit atrial triggers similarly to isoproterenol while causing less hypotension due to its weak α1 effect.[17] Besides, this drug has been extensively studied and commonly used in dogs.[20,21] Operator familiarity and cost-effectiveness could make it a viable alternative.[17] However, the high doses often required for a consistent positive chronotropic effect in dogs, typically over 20 μg/kg/min or even up to 50 μg/kg/min, are much higher than those employed for cardiovascular support in clinical settings and might lead to severe tachycardia.[20,22]

Dopamine, a short-acting endogenous catecholamine, was previously used in an anaesthetised dog with SSS to address isoproterenol-induced hypotension.[4] Its effects on the cardiovascular system are variable due to its affinity for α, β and peripheral dopaminergic receptors, and these effects are dose-dependent. Higher doses (above 10 μg/kg/min) typically result in greater α activation and peripheral vasoconstriction.[11] However, in the mentioned case, high doses of dopamine (up to 13 μg/kg/min) did not resolve the hypotension, which is why we decided not to use dopamine for this purpose in our case. Interestingly, dopamine is considered by the American Heart Association in its cardiac life support guidelines as an emergency treatment for severe bradycardias in humans.[23] Its efficacy has been reported to be comparable to TCP in cases of atropine-unresponsive bradycardias.[24] However, a recent trial in human patients with third-degree AV block requiring emergency stabilisation has shown that dopamine is less effective than isoproterenol in increasing AV conduction.[25]

Similarly, noradrenaline, a short-acting vasopressor commonly used in humans and animals that acts as a mixed α and β1 adrenergic agonist could have been considered instead of phenylephrine to increase systemic vascular resistance. Besides, it is possible that its concomitant administration with isoproterenol may have helped in maintaining good inotropism while lowering the dose of isoproterenol needed.[26] Interestingly, recent experiments in anaesthetised dogs suggest that the increase in blood pressure induced by noradrenaline may be primarily due to enhanced inotropism rather than increased vascular resistance, especially when compared with phenylephrine.[27]

Given the complex interactions and interrelated effects of different drugs on adrenoceptor activity and susceptibility, it is crucial to evaluate the haemodynamic effects in each patient, and choose drugs and doses accordingly.

The anaesthetic protocol and techniques used in the case described aimed to prevent complications, minimise stress, ensure smooth anaesthesia, and avoid excessive cardiovascular depression of the animal. Table 1 summarises the anaesthetic drugs and techniques employed in this case, along with their rationale based on the literature. Drugs known to negatively affect HR and contractility were avoided. Premedication included pethidine for its μ opioid receptor agonistic and well-established anti-muscarinic effects,[28] ketamine for its positive sympathetic effects,[29] and midazolam for its safe cardiovascular profile and the muscle relaxation to counteract ketamine-induced rigidity.[30,31] Etomidate was chosen for induction due to its minimal cardiovascular impact.[32] Sevoflurane was preferred over isoflurane for maintenance due to its mild vasodilator and positive chronotropic effects.[33]

TABLE 1 Drugs and techniques employed in the anaesthetic management of a dog with sick sinus syndrome undergoing unilateral mastectomy including the rationale for their selection in this case.

Anaesthetic management of a dog with sick sinus syndrome	
Drug (route) or technique	**Hypothesised advantages**
Premedication (IM)	Avoid stress, smooth induction; reduced catecholamine-induced arrhythmias[31]
Pethidine (IM)	Antimuscarinic and tranquilisation[28]
Ketamine (IM and IV)	Hypnosis and sympathetic stimulation[29]
Midazolam (IM)	Anxiolytic and minimal cardiovascular depression[30]
Etomidate (IV)	Hypnosis and minimal cardiovascular depression[32]
Sevoflurane (Inhalation)	Rapid elimination; fine titration; less vasodilation than isoflurane[33]
Loco-regional anaesthesia	Analgesia perioperatively, reduction doses of anaesthetics and adverse events[34]
Acepromazine (IV)	Tranquilisation at recovery; at low doses, mild cardiovascular effects[13,31]
Paracetamol (IV) Meloxicam (IV) Gabapentin (orally)	Analgesia and anti-inflammatory; reduce the use of opioids[35–38]

Before recovery, the dog was resedated with acepromazine to avoid stress in emergence.[31] A priority in the anaesthetic management was the implementation of a multimodal analgesic approach. Loco-regional techniques, specifically TAP and SP blocks, were employed for their proven effectiveness in maintaining adequate antinociception in dogs undergoing mastectomy.[34] Postoperatively, opioids were avoided in favour of drugs with milder cardiovascular impact like paracetamol,[35] meloxicam[36] and gabapentin.[37,38] Scores on the CMPS-SF consistently remained low, indicating appropriate postoperative pain management.[39]

Despite the good outcome of the case with pharmacological treatments, it is important to remark that the gold standard treatment for dogs with SSS involves implantation of a permanent cardiac pacemaker.[2,7] Alternatively, temporary approaches like transvenous, transesophageal or TCP are recognised techniques for treating bradyarrhythmic animals including those with SSS.[2,7,8] In the described case, the owner declined permanent pacemaker implantation before the mastectomy; hence, TCP was selected to maintain cardiovascular stability. This technique has proved to be easy to apply and it is not invasive.[8,9] However, in this case, the transthoracic placement of the transdermal conduction pads, necessary for effective pacing, conflicted with the surgical field required for mastectomy, leading to pacing failure. An alternative, such as transesophageal or intravenous temporary pacing, could have been more suitable in this case, as it would not interfere with the surgical field.[40] Unfortunately, specific tools including electrophysiology-specific catheter and compatible pulse generator were not available at the authors' institution.

To the authors' knowledge, this is the first report of an anaesthetised dog with untreated SSS undergoing mastectomy in which the infusions of isoproterenol and phenylephrine were effective in maintaining physiological cardiovascular parameters.

AUTHOR CONTRIBUTIONS

Giorgio Mattaliano and **Bruna Alonso**: case management; drafting and writing of the manuscript. **Martina Mosing**: interpretation of the findings; drafting; writing and critical revision of the manuscript. **Attilio Rocchi**: supervision of the case management and critical revision of the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

The redaction of this case, being retrospective in nature, was exempt from ethical approval.

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MULTIPLE-CHOICE QUESTION

What is the rationale of using phenylephrine in an animal receiving isoproterenol infusion, and which side effect of isoproterenol might it help mitigate?

POSSIBLE ANSWERS TO MULTIPLE-CHOICE QUESTION

A) To decrease heart rate by blocking β1 adrenergic receptors and counteract isoproterenol-induced tachycardia.

B) To decrease systemic vascular resistance by activating α1 adrenergic receptors and counteract isoproterenol-induced tachycardia.

C) To increase heart rate by activating β1 adrenergic receptors and counteract isoproterenol-induced decreased cardiac output.

D) To increase systemic vascular resistance by activating α1 adrenergic receptors and counteract isoproterenol-induced vasodilation.

E) To reduce systemic vascular resistance by activating β2 adrenergic receptors and counteract isoproterenol-induced vasoconstriction.

CORRECT ANSWER

D) To increase systemic vascular resistance by activating α1 adrenergic receptors and counteract isoproterenol-induced vasodilation.

Explanation: Isoproterenol causes peripheral vasodilation and therefore possibly hypotension due to its β2 adrenergic receptor activity. Phenylephrine, an α1 adrenergic agonist, can be used to increase systemic vascular resistance, thereby potentially stabilising blood pressure.