

Cardiac electrophysiological effects of remifentanil: study in a closed-chest porcine model

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Background. Remifentanil has been implicated as causing intraoperative bradyarrhythmias, but little information is available regarding its cardiac electrophysiological effects. Thus, we evaluated the cardiac electrophysiological properties before and after remifentanil in a closed-chest porcine model.

Methods. Eighteen Landrace–Large pigs were premedicated with ketamine and anaesthetized with propofol (4.5 mg kg⁻¹ bolus followed by 13 mg kg⁻¹ h⁻¹). After instrumentation, an electrophysiological evaluation was performed under propofol and repeated after remifentanil (bolus of 1 µg kg⁻¹, followed by an infusion of 0.5 µg kg⁻¹ min⁻¹). We evaluated sinus node function [sinus node recovery time (SNRT) and sinoatrial conduction time (SACT)], atrioventricular (AV) nodal function [AH intervals during sinus rhythm (SR) and atrial pacing, Wenckebach cycle length (WCL), and effective refractory periods (ERP)], atrial, His–Purkinje, and ventricular conduction and refractoriness. Significant changes between ‘propofol protocol’ and ‘propofol+remifentanil protocol’ were evaluated.

Results. Remifentanil caused a significant increase in sinus cycle length (21%, $P=0.001$) and a significant prolongation of SNRT (43%, $P=0.001$), corrected SNRT (136%, $P=0.003$), SACT (40%, $P=0.005$), AH interval during SR (17%, $P=0.02$), AH interval during atrial pacing (25%, $P=0.01$), and ventricular ERP (12%, $P=0.004$). There was a tendency towards a prolongation of WCL and AV nodal refractoriness. Similar significant changes were observed in a reference group of seven animals in which sevoflurane was used instead of propofol. No significant changes were observed in atrial parameters, His–Purkinje function, parameters of intraventricular conduction, and QT intervals.

Conclusions. Remifentanil depresses sinus node function and most parameters of AV nodal function. This contributes to an explanation for clinical observations of remifentanil-related severe bradyarrhythmias.

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Remifentanil is a selective μ -opioid receptor agonist with an analgesic potency similar to that of fentanyl. Because of remifentanil's rapid systemic elimination, with a half-life of 8–10 min, it has pharmacokinetic advantages in clinical situations where a rapidly titratable potent opioid effect is desirable with a predictable offset of action without prolonged respiratory depression.¹

The haemodynamic response to remifentanil has been extensively studied and is characterized by decreases in arterial pressure, cardiac output, and systemic vascular resistance.^{2–4} In contrast, despite some clinical reports of severe remifentanil-associated bradyarrhythmias including asystole,^{5–7} little information is available regarding its cardiac electrophysiological effects.⁸

The aim of this study was to characterize the effects of remifentanyl on the electrophysiological properties of normal cardiac structures, using a standard intracardiac electrophysiological approach in a closed-chest porcine model with minimal instrumentation. Our hypothesis was that remifentanyl exerts a general depressant effect on the cardiac conduction system, altering the majority of electrophysiological parameters in the majority of individuals. Although results from animal experiments can never be extrapolated to humans, we used doses similar to those used in clinical practice to make such extrapolation more plausible.

Methods

The study was approved by the committee of the medical laboratory of experimental medicine, and the animals were cared for in accordance with the guidelines of the Animal Research Committee of the hospital.

Study design

Study group

Figure 1 provides a summary of the experimental protocol. After premedication and anaesthesia induction with propofol, the animals were instrumented and an electrophysiological evaluation was performed (propofol protocol). Remifentanyl was then infused i.v., and an identical electrophysiological evaluation was performed (propofol+remifentanyl protocol). This allowed intraanimal comparison of each parameter.

Reference group

To exclude a possible electrophysiological interaction between propofol and remifentanyl, a smaller group was added (reference group $n=7$) with a similar experimental protocol, but substituting propofol by sevoflurane 1 MAC [1 MAC=2.66%]⁹ to analyse the electrophysiological effects that were noted to change more strikingly in the study group.

Animal preparation

Eighteen hybrid Landrace–Large white pigs (16–60 kg) were investigated. The animals were housed indoors with access to food and water, except during a period before anaesthesia usually lasting 17 h when they were allowed water only. The animals were premedicated with ketamine 20 mg kg⁻¹ i.m., this is the appropriate dose recommended for swine sedation before percutaneous cannulation of superficial vessels.¹⁰ Ten minutes after premedication, the pigs were provided with oxygen 100% via a facial mask, and a 20 G cannula was inserted into an ear vein, and anaesthesia was induced by injection of propofol (4.5 mg kg⁻¹). To minimize pharmacological interaction and eliminate possible confounding factors affecting electrophysiological effects of remifentanyl, no neuromuscular blocking agents or other sedative medications were administered during the entire course of the study. After intubation, the animal was connected to a volume-controlled ventilator (Engström Respirator ER-300, LKB, Medical AB, Switzerland). Anaesthesia was maintained with propofol at a rate of 13 mg kg⁻¹ h⁻¹, this dose was chosen according to parameters obtained from the literature and because it has been previously used in swine and shown to provide adequate anaesthesia, particularly in cases in which neuromuscular blocking agents are not administered.^{11 12} Intermittent positive-pressure ventilation was used during the procedure with pure oxygen, and a ventilatory frequency intended to maintain normocapnia. All animals received an infusion of saline solution of 8 ml kg⁻¹ h⁻¹.

The anaesthesia depth was assessed closely with physiological variables (heart rate and arterial pressure) and with evaluation of reflexes (palpebral and corneal), lacrimation, and spontaneous movements. Adequate anaesthesia was considered if the animal had stable physiological parameters, as arterial pressure and heart rate and unresponsiveness to painful stimuli during femoral vessels cannulation and cardiac stimulation.

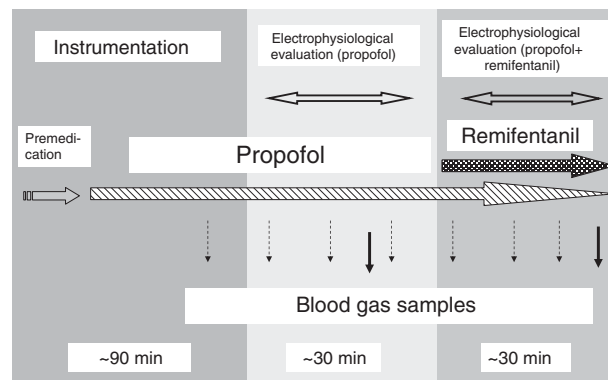


Fig 1 Study design with the mean duration time of the different phases of the protocol. Electrophysiological evaluations are performed during propofol infusion alone, and during both propofol and remifentanyl. Arrows represent blood gas sampling times blood gas samples. Thick arrows represent additional blood gas samples after each electrophysiological evaluation. These latter measurements are used for statistical comparisons, and systolic and diastolic pressure measurements at this time are also used for statistical comparisons in Table 1. In the reference group, sevoflurane was used instead of propofol.

After instrumentation and a stabilization period, an electrophysiological evaluation under propofol infusion (propofol protocol) was performed. After, remifentanyl was administered as a bolus of $1 \mu\text{g kg}^{-1}$ followed by an infusion of $0.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$, followed by another electrophysiological evaluation (propofol+remifentanyl protocol).

Instrumentation

Three quadripolar catheters (Bard®, Medtronic®) were used for stimulation and intracardiac recordings (filtered between 70 and 500 Hz). These catheters were inserted into the right femoral vein (generally percutaneously, and under local anaesthesia with mepivacaine 1%), and advanced under fluoroscopic guidance, to the high right atrium, to the His bundle recording area, and to the right ventricular apex.

Monitoring

The ECG was continuously monitored in all animals and arterial pressure was registered through the femoral artery, by means of an intraarterial catheter (Arrow®, Monitor: Life Scope G. Nihon Kohden®). Blood samples were obtained for gas analysis every 15 min and after each electrophysiological evaluation.

Electrical stimulation and recordings

Electrical stimulation was bipolar, consisting of square pulses of 1 ms duration at five times diastolic threshold, delivered by a custom-made programmable stimulator. Atrial stimulation protocol included pacing trains at a fixed cycle length and the extrastimulus technique with extrastimuli preceded by 8-beat pacing trains. Ventricular stimulation protocol included the extrastimulus technique in a similar manner. Two cycle lengths were used for basic atrial and ventricular stimulation, 600 and 400 ms whenever possible. If the sinus cycle length (SCL) was shorter than 600 ms, the longest possible cycle length was used.

Electrophysiological and electrocardiograph measurements

Electrophysiological measurements included:

- (i) SCL.
- (ii) Sinoatrial conduction time (SACT): the time taken for a sinus node impulse to conduct through the sinus node complex to the adjacent atrial tissue. It was estimated by Narula's method.¹³
- (iii) Sinus node recovery time (SNRT): the time required for return of spontaneous sinus node activity after rapid atrial pacing. Rapid pacing was performed as 30 s pacing trains starting at a cycle length 50 ms less than the SCL and decreasing the paced cycle length by 50 ms intervals until a cycle length of 250 ms was reached. A 1 min resting period was allowed between pacing trains.

- (iv) Corrected sinus node recovery time (CSNRT): the difference between SNRT and basic SCL.
- (v) Atrioventricular (AV) nodal effective refractory period (AVNERP): the longest coupling interval at which atrial extrastimuli fail to conduct to the His bundle area, measured at the atrial electrogram closest to the AV nodal area.
- (vi) Wenckebach cycle length (WCL): the longest atrial paced cycle at which 1:1 atrio-His conduction is lost
- (vii) Right atrial effective refractory period: the longest coupling interval of a premature atrial impulse after an 8-beat pacing train not resulting in a propagated response. It was determined with two different paced cycle lengths.
- (viii) Right ventricular effective refractory period: the longest coupling interval of a premature ventricular impulse after an 8-beat pacing train not resulting in a propagated response. It was determined with two different paced cycle lengths.
- (ix) AH interval: the time interval from the onset of the atrial electrogram in the His bundle area to the onset of the His deflection. It was measured during sinus rhythm and during atrial pacing at a paced cycle length of 400 ms.
- (x) HV interval: the time interval from the onset of the His bundle deflection to the onset of ventricular activation.
- (xi) Paced QRS duration: measured from the pacing stimulus to the QRS offset, at a paced cycle length of 400 ms.
- (xii) QT interval: the QT interval was measured during sinus rhythm and corrected to rate (QTc interval) using Bazett's formula. The QT interval was also measured during ventricular pacing.

After completing the experiment, all animals were killed after a bolus injection i.v. of propofol 200 mg with KCl 30 mmol.

Statistical analysis

All values were expressed as mean (sd). Haemodynamic data and blood gas analysis were presented and compared at the end of each electrophysiological evaluation. After testing for normal distribution with Kolmogorov–Smirnov, significant changes between values for the 'propofol protocol' and the 'propofol +remifentanyl protocol' were evaluated by Student's *t*-test for paired data. Statistical significance was defined as $P < 0.05$. In the reference group, the differences were evaluated with a Wilcoxon test. All statistical analyses were performed with the SPSS-11 software package.

Results

The experimental model was completed successfully in all 18 animals, with an electrophysiological evaluation during

both drugs in all animals. The mean animal weight was 34 (SD 13) kg. Haemodynamic data, blood gas analyses, and electrolytes are given in Table 1. There was a significant decrease in heart rate after remifentanyl infusion, whereas systolic and diastolic arterial pressures were similar compared with baseline measurements. Arterial blood gases were maintained within physiological ranges throughout the procedure, although there was a statistically significant but clinically irrelevant increase in Pa_{CO_2} after remifentanyl infusion in the study group.

Sinus node and AV nodal function

There was a significant increase in all electrophysiological parameters of sinus node function after remifentanyl, including SCL (by 21%) (i.e. a decrease in heart rate), SACT, SNRT, and CSNRT (by as much as 136%) (Table 2). Figure 2 shows an example of a significant prolongation of the SNRT.

Remifentanyl significantly prolonged specialized AV conduction times: AH interval increased by 17% during

SR and by 25% at a paced cycle length of 400 ms (Fig. 3); it also increased the WCL (by 20%) and tended to increase AV nodal refractoriness.

Atrial, His-Purkinje, and ventricular function

Remifentanyl had no significant effect on the atrial refractory period (Tables 2 and 3). It did not have significant effects on the mean HV interval. However, infra-Hisian block in response to atrial extrastimuli after remifentanyl was observed in one pig (this was seen before remifentanyl). This particular animal also had a slight increase in HV interval during SR after remifentanyl, from 30 to 40 ms. Remifentanyl significantly prolonged ventricular refractoriness at the longer paced cycle length and tended to do so at the shorter cycle length. It had no significant effect on the paced QRS duration. There were no changes in the QTc intervals.

Reference group (sevoflurane)

Haemodynamic data are given in Table 4. There were similar differences in sinus and AV nodal function in the sevoflurane group as in the study (propofol) group (Table 5), with increases in SCL (23% vs 21%), SACT (55% vs 40%), CSNRT (225% vs 136%), WCL (21% vs 20%), and AVNERP-400/600 (16% and 12% vs 5% and 9%) (Tables 2 and 5).

Discussion

The main finding of this study is that remifentanyl, in doses typical of clinical practice in humans and added to propofol, depresses sinus node and AV nodal function, and prolongs ventricular refractoriness, in comparison with propofol alone, in a closed-chest porcine model. Similar findings were noted substituting propofol by sevoflurane,

Table 1 Haemodynamic data, arterial blood gases, and electrolytes. Study group ($n=18$). Values are mean (SD), measured at the end of propofol and propofol+remifentanyl electrophysiological evaluation. DAP, diastolic arterial pressure; HR, heart rate; SAP, systolic arterial pressure

	Propofol	Propofol+remifentanyl	P-value
SAP (mm Hg)	115 (17)	115 (22)	0.9
DAP (mm Hg)	73 (18)	69 (19)	0.3
HR (beats min^{-1})	101 (21)	85 (18)	0.003
pH	7.55 (0.07)	7.51 (0.06)	0.054
Pa_{O_2} (mm Hg)	464 (127)	458 (132)	0.7
Pa_{CO_2} (mm Hg)	27 (6)	31 (5)	0.02
HCO_3^- (mmol litre^{-1})	25 (2)	25 (2)	0.1
BE (mmol litre^{-1})	3 (2)	3 (2)	0.3
Sa_{O_2} (%)	100	100	0.3
Na^+ (mmol litre^{-1})	138 (2.6)	138 (2.4)	0.2
K^+ (mmol litre^{-1})	3.5 (0.4)	3.6 (0.4)	0.2
Ca^{2+} (mmol litre^{-1})	1.34 (0.06)	1.34 (0.1)	0.8

Table 2 Electrophysiological parameters of the sinus node, right atrium, and atrioventricular node. All values in milliseconds except otherwise indicated. Study group ($n=18$). AH, atrio-His interval; AH-400, atrio-His interval during atrial pacing at a basic cycle length (BCL) of 400 ms; AVNERP, atrioventricular nodal ERP at a BCL of 400 and 600 ms; CSNRT, corrected sinus node recovery time; RAERP, right atrial effective refractory period at a BCL of 400 and 600 ms; SACT, sinoatrial conduction time; SCL, sinus cycle length; SNRT, sinus node recovery time; SR, sinus rhythm; WCL, Wenckebach cycle length

	Propofol	Propofol+remifentanyl	Mean % difference	P-value
Sinus node function				
SCL	614 (110)	734 (165)	21 (23)	0.001
SACT	36 (12)	50 (24)	40 (44)	0.005
SNRT	753 (146)	1111 (492)	43 (38)	0.001
CSNRT	142 (66)	353 (303)	136 (137)	0.003
Atrioventricular nodal function				
AH during SR	81 (18)	93 (21)	17 (26)	0.02
AH-400	120 (31)	141 (21)	25 (37)	0.01
WCL	235 (40)	280 (94)	20 (37)	0.05
AVNERP-400	250 (27)	261 (35)	5 (10)	0.09
AVNERP-600	287 (30)	315 (76)	9 (17)	0.06
Atrial function				
Atrial threshold (mA)	0.65 (0.5)	0.53 (0.4)	-6 (61)	0.29
RAERP-400	152 (24)	156 (28)	3 (16)	0.48
RAERP-600	154 (27)	157 (39)	2 (17)	0.40

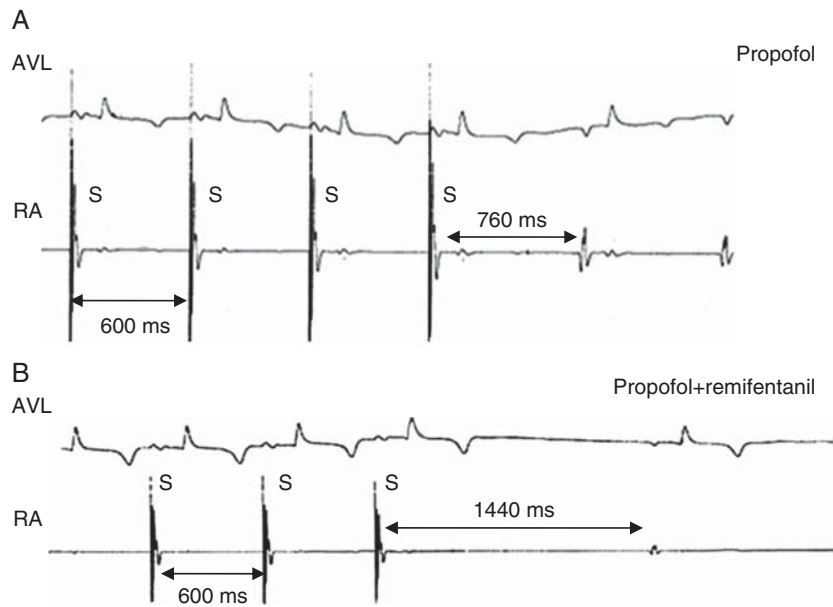


Fig 2 A representative example of SNRT measurements. Both panels show one ECG lead (aVL) along with one intracardiac recording from the right atrium of the same animal. Both panels show the end of a pacing train at a cycle length of 600 ms (S, electrical stimuli). (A) Electrophysiological evaluation on propofol. SNRT=760 ms. (B) Electrophysiological evaluation on propofol+remifentanyl. SNRT=1440 ms.

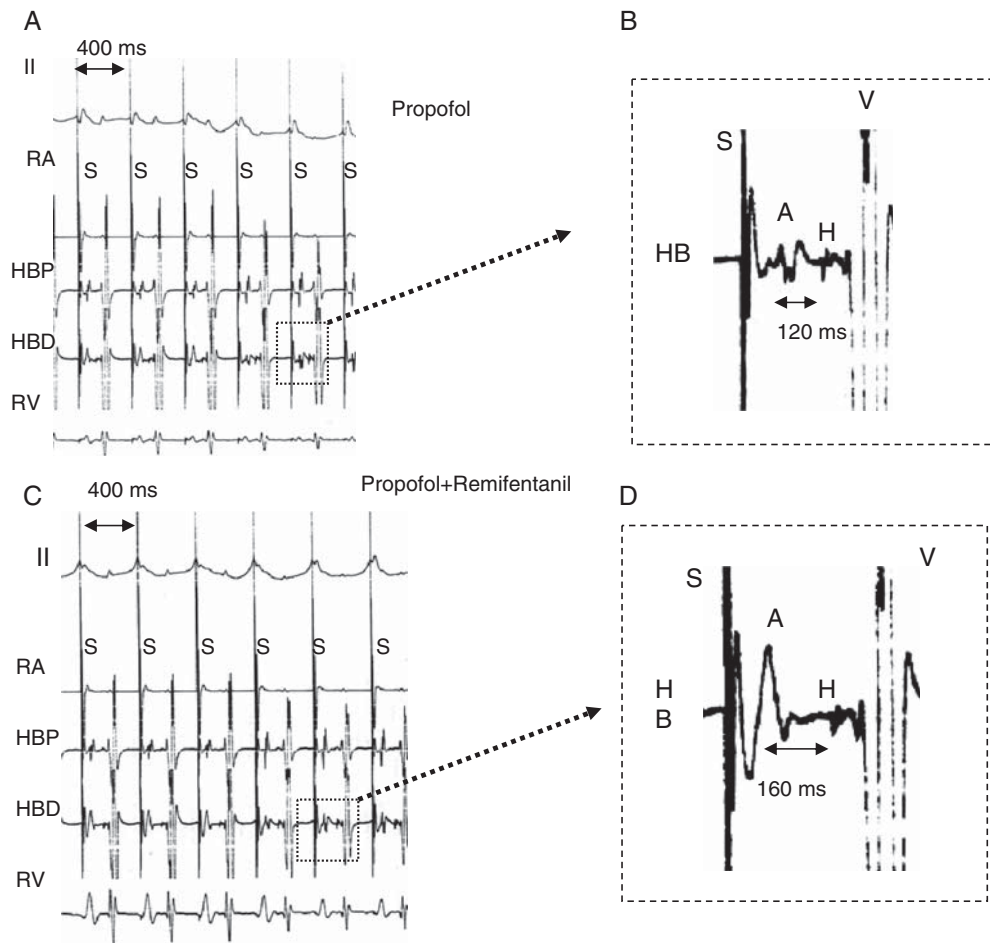


Fig 3 Representative example of influence of remifentanyl on AV nodal conduction time. (A) and (C) show one surface ECG lead along with intracardiac recordings from the right atrium (RA), proximal and distal His bundle recordings (HBP and HBD), and right ventricle (RV) during rapid atrial pacing. S, electrical stimulus. (A) was obtained during propofol infusion and (C) after addition of remifentanyl in the same animal. (B) and (D) represent enlarged intracardiac recordings from one beat at the distal His bundle electrogram to illustrate the increase in AH interval after addition of remifentanyl.

Table 3 Electrophysiological and electrocardiographic parameters of the His-Purkinje and right ventricle. All values in milliseconds except otherwise indicated. Study group ($n=18$). HV, His-ventricular interval; RVERP, right ventricular effective refractory period at a BCL of 400 and 600 ms

	Propofol	Propofol+remifentanil	Mean % difference	P-value
His-Purkinje function				
HV during SR	30 (8)	31 (9)	6 (29)	0.64
Ventricular function				
Ventricular threshold (mA)	0.6 (0.3)	0.6 (0.5)	0	0.43
RVERP-400	224 (33)	234 (24)	6 (11)	0.09
RVERP-600	255 (38)	285 (36)	12 (12)	0.004
QTc interval	0.46 (0.09)	0.44 (0.05)	-2 (11)	0.3
Paced QT-400	314 (23)	311 (22)	-0.6 (5.8)	0.58
Paced QT-600	349 (31)	354 (35)	1 (4.9)	0.33
Paced QRS duration	65 (10)	66 (12)	0.7 (10)	0.7

Table 4 Haemodynamic data, arterial blood gases, and electrolytes. Reference group ($n=7$). Values are mean (SD), measured at the end of sevoflurane and sevoflurane+remifentanil electrophysiological evaluation. $n=18$. DAP, diastolic arterial pressure; HR, heart rate; SAP, systolic arterial pressure

	Sevoflurane	Sevoflurane+remifentanil	P-value
SAP (mm Hg)	105 (13)	99 (18)	0.1
DAP (mm Hg)	73 (18)	53 (20)	0.09
HR (beats min^{-1})	78 (10)	71 (23)	0.02
pH	7.49 (0.01)	7.49 (0.03)	0.7
P_{aO_2} (mm Hg)	491 (46)	519 (63)	0.1
P_{aCO_2} (mm Hg)	38 (3)	36 (5)	0.07
HCO_3^- (mmol litre^{-1})	30 (3)	29 (2)	0.07
BE (mmol litre^{-1})	6 (3)	6 (2)	0.6
Sa_{O_2} (%)	100	100	1
Na^+ (mmol litre^{-1})	137 (1.4)	137 (1.7)	0.8
K^+ (mmol litre^{-1})	3.6 (0.2)	3.7 (0.3)	0.1
Ca^{2+} (mmol litre^{-1})	1.36 (0.07)	1.34 (0.06)	0.6

thus excluding a synergistic effect of propofol and remifentanil as an explanation for the observed effects.

Sinus node and AV nodal function

Few studies have attempted to investigate actions of remifentanil in the electrophysiology of the conduction system in a systematic way. Fattorini and colleagues⁸ performed a transoesophageal electrophysiological study in 40 young patients comparing the effect of remifentanil associated with propofol and vecuronium bromide to the previous awake state. They observed a significant increase in SCL, and CSRT after the anaesthetic combination. Our results are in agreement with this study and overcome some of their limitations. First, they compared the effects of remifentanil with the previous awake state, and suppression of anxiety after anaesthesia may cause a withdrawal of sympathetic output that influences sinus node function parameters. In our study, the comparison was performed with stable propofol anaesthesia that was maintained while remifentanil was administered. Secondly, transoesophageal pacing measurements were used in Fattorini's study, compared with intracardiac electrophysiological measurements in the current study. It is well known that SACT

measurements require right atrial pacing and transoesophageal pacing paces the left atrium. Thirdly, we observed similar findings in a reference group in which sevoflurane was used instead of propofol, excluding a unique synergistic effect of propofol and remifentanil as an explanation for the electrophysiological changes.

Thus, our study shows more consistently that remifentanil itself, rather than a combination of anaesthetic agents plus sedation, produces a significant depression of sinus node automaticity. It also shows that all sinus node electrophysiological properties, including sinoatrial conduction, are depressed by remifentanil. The 136% increase in CSNRT that we observed was higher than the 24% observed by Fattorini and colleagues, and could reflect the higher remifentanil maintenance dose used in our study.

Fattorini and colleagues⁸ observed that, after remifentanil, 1:1 AV conduction was lost (the so-called Wenckebach phenomenon) at an atrial pacing rate <140 beats min^{-1} in 17.5% of patients (in the baseline, the Wenckebach phenomenon occurred at a rate >140 beats min^{-1} in all). On the basis of this, and the fact that in healthy hearts pacing-related AV block usually occurs in the AV node, they suggested a general depressant effect of remifentanil on the AV nodal conduction. In our study, with direct intracardiac atrial and His bundle recordings, we could precisely determine the site of slow conduction, block, or both. We observed that remifentanil significantly depressed AV nodal conduction at all rates. It also tended to prolong AV nodal refractoriness.

These electrophysiological findings are consistent with previous clinical observations, in the form of case reports or small series, which found a decrease in heart rate, bradyarrhythmias, and asystole, after application of remifentanil, in adult and also in paediatric patients.^{3-7 14-18} In the clinical scenario, the strong responses seen with remifentanil in heart rate are generally related with its use as bolus doses and in patients susceptible to bradycardia because of concomitant therapy with beta and calcium blockers, or undergoing procedures with strong vagal stimulation.⁵⁻⁷ In contrast, other investigators report on the use of similar doses of remifentanil in patients undergoing coronary artery bypass graft surgery without bradycardic events.¹⁹⁻²¹

Table 5 Electrophysiological parameters of the sinus node, right atrium, and atrioventricular node. All values in milliseconds except otherwise indicated. Reference group ($n=7$). SCL, sinus cycle length; AH, atrio-Hisian interval; SACT, sinoatrial conduction time; CSNRT, corrected sinus node recovery time; RAERP, right atrial effective refractory period at long cycle length; AVNERP, atrioventricular nodal effective refractory period; WCL, Wenckebach cycle length

	Sevoflurane	Sevoflurane+remifentanyl	Mean % difference	P-value
Sinus node function				
SCL	690 (128)	849 (176)	23 (13)	0.018
SACT	39 (9)	61 (28)	55 (55)	0.018
SNRT	970 (320)	2046 (2218)	82 (122)	0.04
CSNRT	222 (177)	1124 (1854)	225 (294)	0.018
Atrioventricular nodal function				
AH during SR	58 (13)	74 (22)	27 (28)	0.1
WCL	291 (38)	353 (39)	21 (11)	0.017
AVNERP-400	273 (12)	327 (69)	16 (18)	0.06
AVNERP-600	313 (40)	325 (95)	12 (10)	0.06
Atrial function				
Atrial threshold (mA)	0.56 (0.49)	0.5 (0.38)	—	0.5
RAERP-600	146 (18)	162 (45)	9 (18)	0.2

The effects of remifentanyl in the autonomic system are controversial. Tirel and colleagues²² studied heart rate variability in children receiving remifentanyl and sevoflurane as anaesthetic agents, with and without atropine pre-treatment, and showed that lengthening of the RR interval was not always correlated to an activation of the parasympathetic autonomic nervous system. Furthermore, in a subpopulation of children, a decrease in heart rate with remifentanyl was observed, without an increase in parasympathetic activation. These investigators suggest a direct negative chronotropic effect of this opioid. In a study performed in intact and denervated rabbits, remifentanyl produced an intense, though brief, negative chronotropic effect in the intact animal, which suggested that remifentanyl exerts a central vagotonic action that is counteracted by an increase in sympathetic activity. In denervated rabbits, a decrease in heart rate was also observed, but it was gradual, suggesting a peripheral action that depresses the cardiovascular system.²³ However, the reversal of effects by atropine observed by Fattorini and colleagues⁸ suggests that the effects are mediated by the parasympathetic autonomic system. Furthermore, the concomitant neurally mediated changes in autonomic nervous system tone of propofol could support the cardiac effect observed with remifentanyl.²⁴ Our study does not offer information in this respect since we did not attempt to manipulate the autonomic nervous system.

Atrial, ventricular, and His-Purkinje electrophysiological function

Infranodal conduction or HV interval remained, overall, unaffected during remifentanyl. The one animal that experienced significant changes in the HV conduction and refractoriness may indicate possible effects in susceptible subjects. Information from other studies as to the effects of remifentanyl on the His-Purkinje system is lacking.

The atrial ERP was not modified by remifentanyl, but ventricular refractoriness was significantly prolonged. However, the increase in ventricular refractoriness was not reflected in the QT interval and was not associated with an increase

in the QRS duration at any pacing rate, probably related to its limited magnitude. We are not aware of previous studies describing effects of remifentanyl on ventricular refractoriness, and its mechanism would require further elucidation.

Limitations

Our study has several limitations. First, the effect of remifentanyl on the electrophysiological properties of the heart was measured in animals already under anaesthesia with propofol and that have previously received ketamine. The duration of the clinical effects of ketamine, in the 10–20 min range, is unlikely to influence the results.²⁵ We did not measure propofol plasma concentrations, so we cannot exclude that they increased during the study. However, it has been shown that, during a constant propofol rate infusion, the rate of increase in plasma drug concentration becomes gradually slower with time, and that the steady-state concentration was approached at 120 min.²⁶ This information supports our assumption that the changes in the propofol plasma concentration between the ‘propofol electrophysiological evaluation’ and the ‘remifentanyl electrophysiological evaluation’, both after more than 90 min after the initiation of propofol, are likely to be minor. The effects of propofol on the conduction system are controversial, and some reports in animal and humans have shown no significant effects on the cardiac conduction system, whereas others showed a prolonged sinus node recovery time and a depression in the His-Purkinje system in pigs.^{27–29} However, we observed similar results in the reference group when sevoflurane was used as a substitute for propofol, thus excluding a synergistic effect between propofol and remifentanyl. Moreover, in clinical practice, remifentanyl needs to be supplemented with other anaesthetics because remifentanyl, even in extremely high doses, cannot induce complete loss of consciousness. Therefore, the present results could be more relevant to the clinical context.

Secondly, the doses of remifentanyl that we used are similar to those typically used in humans, but we cannot

exclude pharmacological differences between humans and swine. However, in a porcine model that evaluated the pharmacokinetics and pharmacodynamics of remifentanyl under haemorrhagic shock, remifentanyl blood levels required for 50% of maximal effect on the spectral edge frequency (EC_{50}) were remarkably similar to those reported for humans (pigs: 24 ng ml^{-1} vs humans: 19.5 ng ml^{-1}).³⁰

Thirdly, in the absence of concomitant autonomic blockade, we could not determine if the effects of remifentanyl on electrophysiological parameters are direct or autonomically mediated. Fourthly, we had a difference in CO_2 and in pH in blood gas analyses performed during both electrophysiological studies; however, the difference in CO_2 levels (4 mm Hg) and in pH (0.04 unit) between both protocols is minimal, and probably without clinical relevance. Finally, as with all animal studies, a species-related effect is always a consideration in any possible extrapolation to humans.

In summary, we found that remifentanyl significantly depressed the sinus node and the AV node in presumably healthy and anaesthetized animals, at doses similar to those typically used clinically. If these results were confirmed in humans, they should be taken into consideration for the choice of anaesthetic agents.

References

- Egan TD. Remifentanyl pharmacokinetics and pharmacodynamics: a preliminary appraisal. *Clin Pharmacokinet* 1995; **29**: 80–94
- Hogue CW, Jr, Bowdle TA, O'Leary C, et al. A multicenter evaluation of total intravenous anesthesia with remifentanyl and propofol for elective inpatient surgery. *Anesth Analg* 1996; **83**: 279–85
- Elliot P, O'Hare R, Bill KM, Phillips AS, Gibson FM, Mirakhur RK. Severe cardiovascular depression with remifentanyl. *Anesth Analg* 2000; **91**: 58–61
- Kazmaier S, Hanekop GG, Buhre W, et al. Myocardial consequences of remifentanyl in patients with coronary artery disease. *Br J Anaesth* 2000; **84**: 578–83
- DeSouza G, Lewis MC, TerRiet MF. Severe bradycardia after remifentanyl. *Anesthesiology* 1997; **87**: 1019–20
- Reid JE, Mirakhur RK. Bradycardia after administration of remifentanyl. *Br J Anaesth* 2000; **84**: 422–3
- Wang JY, Winship SM, Thomas SD, Gin T, Russell GN. Induction of anaesthesia in patients with coronary artery disease: a comparison between sevoflurane–remifentanyl and fentanyl–etomidate. *Anaesth Intensive Care* 1999; **27**: 363–8
- Fattorini F, Romano R, Ciccaglioni A, et al. Effects of remifentanyl on human electrical system. A transesophageal pacing electrophysiological study. *Minerva Anestesiologica* 2003; **69**: 673–7, 677–9
- Holmstrom A, Akeson J. Cerebral blood flow at 0.5 and 1.0 minimal alveolar concentrations of desflurane or sevoflurane compared with isoflurane in normoventilated pigs. *J Neurosurg Anesthesiol* 2003; **15**: 90–7
- Boschert K, Flecknell PA, Fosse RT, et al. Ketamine and its use in the pigs. *Lab Anim* 1996; **30**: 209–19
- Cockshott ID, Douglas EJ, Plummer GF, Simons PJ. The pharmacokinetics of propofol in laboratory animals. *Xenobiotica* 1992; **22**: 369–75
- Martín-Cancho MF, Carrasco-Jiménez MS, Lima JR, Ezquerro LJ, Crisóstomo V, Usón-Gargallo J. Assessment of the relationship of bispectral index values, hemodynamic changes, and recovery times associated with sevoflurane or propofol anesthesia in pigs. *Am J Vet Res* 2004; **65**: 409–16
- Narula OS, Shantha N, Vasquez M, Towne WD, Linhart JW. A new method for measurement for sinoatrial conduction time. *Circulation* 1978; **58**: 706–14
- Wee LH, Moriarty A, Cranston A, Bagshaw O. Remifentanyl infusion for major abdominal surgery in small infants. *Paediatr Anaesth* 1999; **9**: 415–8
- Chanavaz C, Tirel O, Wodey E, et al. Haemodynamic effects of remifentanyl in children with and without intravenous atropine. An echocardiographic study. *Br J Anaesth* 2005; **94**: 74–9
- Wang J, Winship S, Russell G. Induction of anaesthesia with sevoflurane and low-dose remifentanyl: asystole following laryngoscopy. *Br J Anaesth* 1998; **81**: 994–5
- Weale NK, Rogers CA, Cooper R, Nolan J, Wolf AR. Effect of remifentanyl infusion rate on stress response to the pre-bypass phase of paediatric cardiac surgery. *Br J Anaesth* 2004; **92**: 187–94
- Reyntjens K, Foubert L, De Wolf D, Vanlerberghe G, Mortier E. Glycopyrrolate during sevoflurane–remifentanyl-based anaesthesia for cardiac catheterization of children with congenital heart disease. *Br J Anaesth* 2005; **95**: 680–4
- Geisler FE, de Lange S, Royston D, et al. Efficacy and safety of remifentanyl in coronary artery bypass graft surgery: a randomized, double-blind dose comparison study. *J Cardiothorac Vasc Anesth* 2003; **17**: 60–88
- Howie MB, Michelsen LG, Hug CC, Jr, et al. Comparison of three remifentanyl dose-finding regimens for coronary artery surgery. *J Cardiothorac Vasc Anesth* 2003; **17**: 51–9
- Steinlechner B, Dworschak M, Birkenberg B, et al. Low-dose remifentanyl to suppress haemodynamic responses to noxious stimuli in cardiac surgery: a dose-finding study. *Br J Anaesth* 2007; **98**: 598–603
- Tirel O, Chanavaz C, Bansard JY, et al. Effect of remifentanyl with and without atropine on heart rate variability and RR interval in children. *Anaesthesia* 2005; **60**: 982–9
- Shinohara K, Aono H, Unruh GK, Kindscher JD, Goto H. Suppressive effects of remifentanyl on hemodynamics in barodenervated rabbits. *Can J Anaesth* 2000; **47**: 361–6
- Sato M, Tanaka M, Umehara S, Nishikawa T. Baroreflex control of heart rate during and after propofol infusion in humans. *Br J Anaesth* 2005; **94**: 577–81
- Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. *Anesth Analg* 1998; **87**: 1186–93
- Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg* 1987; **67**: 1256–63
- Ikeno S, Akazawa S, Shimizu R, et al. Propofol does not affect the canine cardiac conduction system under autonomic blockade. *Can J Anaesth* 1999; **46**: 148–53
- Warpechowski P, Lima GG, Medeiros CM, et al. Randomized study of propofol effect on electrophysiological properties of the atrioventricular node in patients with nodal reentrant tachycardia. *Pacing Clin Electrophysiol* 2006; **29**: 1375–82
- Pires LA, Huang SK, Wagshal AB, Kulkarni RS. Electrophysiological effects of propofol on the normal cardiac conduction system. *Cardiology* 1996; **87**: 319–24
- Johnson KB, Kern SE, Hamber EA, McJames SV, Kohnstamm KM, Egan TD. Influence of hemorrhagic shock on remifentanyl. A pharmacokinetic and pharmacodynamic analysis. *Anesthesiology* 2001; **94**: 322–32