Effects of deep sedation on cardiac electrophysiology in patients undergoing radiofrequency ablation of supraventricular tachycardia: impact of propofol and ketamine

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Aims
Propofol is commonly used as an anaesthetic during catheter ablation. Bradycardia and termination of supraventricular tachycardia (SVT) under propofol are reported. Ketamine is used for cardiac catheterization procedures and increases heart rate and blood pressure. Our study aimed to determine the effects of propofol and ketamine on atrial electrophysiology.

Methods and results
Thirty-one patients undergoing electrophysiological study prior to SVT ablation were enrolled. Patients received a combination of propofol/midazolam (n = 10), ketamine/midazolam (n = 9), or midazolam alone (n = 12). Electrophysiological study was performed before and after administration of the anaesthetic agents. Blood pressure, corrected sinus node recovery time, Wenckebach cycle length, and atrial conduction time were measured. We found a significant increase in heart rate, systolic, and diastolic blood pressure and a significant shortening of atrial conduction time after administration of ketamine compared with propofol and the control. Results for ketamine, propofol and the control, respectively: mean (SD) change in heart rate was 12.4 (8.3), −1.4 (8), and 1 (7.5) b.p.m. (P = 0.002); mean (SD) change in systolic blood pressure was 19.2 (8.1), −22 (9), and 0.1 (5.7) mmHg (P < 0.001); mean (SD) change in diastolic blood pressure was 6.6 (9.7), −7.8 (2.9), and 2.3 (4.5) mmHg (P = 0.001); and mean (SD) change in atrial conduction time was −13.7 (16.4), 4.5 (11.1), and −0.3 (3.8) ms (P = 0.008). No significant affection of sinus node or antroventricular node function was seen.

Conclusion
Our results show stimulatory effects of ketamine on heart rate, atrial conduction, and blood pressure. Ketamine, therefore, may be beneficial in patients with pre-existing hypotension and bradycardia.

Keywords
Ablation • Sedation • Propofol • Ketamine • Supraventricular tachycardia • Atrial conduction

Introduction
Catheter ablation is a standard treatment of cardiac arrhythmias with an increasing number of procedures worldwide.1–3 However, the ablation procedure may be painful and of long duration.4,5 Patient movements in reaction to pain and random movements during long procedures reduce catheter stability and increase probability of complications due to catheter dislocation during delivery of radiofrequency energy. Therefore, anaesthesia is widely used during catheter ablation of cardiac arrhythmias to provide analgesia, patient comfort, and immobilization.6–8

Propofol is an anaesthetic well established for the use in adults and has been shown to be safe and effective during catheter ablation in various settings.7,9–11 However, there is evidence for effects of propofol on haemodynamics and on cardiac electrophysiology, that could limit the use of propofol during ablation procedures: hypotension6,10 is seen after propofol administration as well as hypoxemia12 and bradyarrhythmia13,14. Furthermore, prolonged...

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atrial and atrioventricular conduction have been reported. Suppression and non-inducibility of supraventricular tachycardia (SVT) during propofol anaesthesia are described in the literature. The latter is most important for the use of propofol during ablation procedures, because induction of arrhythmia during the procedure and/or re-inducibility after ablation are crucial for the diagnosis and catheter mapping of arrhythmia and for control of success after ablation. Hence, diagnosis, ablation, and control of success are limited if the anaesthetic has antiarrhythmic properties and hinder the induction of tachycardia.

The underlying mechanism for the suppressive influence of propofol on SVT could be an inhibitory effect of propofol on cardiac sodium channels. In addition, propofol blocked slow delayed rectifier K⁺ current and transient outward K⁺ current, and induced fatal polymorphic ventricular tachycardia in a rabbit model of long-QT. Recently, our group published a study on propofol deep sedation during catheter ablation of atrial fibrillation. Moderate hypotension was observed, but no patient was haemodynamically unstable and no ventricular arrhythmia was observed. However, the study population was relatively healthy. The effects of propofol on haemodynamics and respiration may be more problematic in patients with severe co-morbidities and of older age. Taken together, propofol may not be eligible for all patients undergoing catheter ablation because of its electrophysiological and haemodynamic effects.

The anaesthetic ketamine could be a promising alternative for patients who are at risk for haemodynamic instability and for ablation procedures, where induction of the arrhythmia is especially crucial – such as mapping and ablation of atrial tachycardia. It is long known that ketamine has stimulatory effects on the sympathetic nervous system and increases heart rate and blood pressure. Studies in haemodynamically compromised or elderly patients showed beneficial cardiovascular effects. Furthermore, experimental studies revealed a shortening of action potential duration of human atrial myocytes under clinically relevant concentrations of ketamine, a shortening of atrial wavelength and—compared to propofol and thiopental—only minimal effect on atrioventricular nodal conduction. In contrast to propofol and other anaesthetics, no reports on the suppression of cardiac arrhythmias under ketamine are available. Actually, it has been reported that ketamine was used to induce the target arrhythmia after other agents had failed. Although the effects of propofol and ketamine on cardiac repolarization in normal hearts and experimental long-QT syndrome remain controversial, no prolongation of QT interval by ketamine was seen in a recent study in wild-type rabbits and rabbits with long-QT.

The procedural use of ketamine for emergency and orthopaedic procedures in adults and children is well documented and considerably safe. Recent studies report the use of ketamine in cardiac catheterization in children, but data on ketamine administration during ablation procedures and on the use of ketamine during cardiac procedures in adults are still missing. The effect of ketamine on atrial conduction and inducibility of cardiac arrhythmias has not been evaluated yet.

The purpose of our study was to evaluate the effects of propofol and ketamine on atrial electrophysiology and induction of arrhythmias in patients undergoing catheter ablation of SVT.

**Methods**

Thirty-one consecutive patients (mean age 53 years, range 19–86; 45.2% men) presenting to our centre for ablation of SVT were enrolled. Resting electrocardiogram (ECG), transthoracal or transesophageal echocardiography, physical examination, and standard blood test were performed prior to electrophysiological study (EPS). Patients’ clinical characteristics are listed in Table 1.

Deep sedation was achieved with either a combination of propofol and midazolam (n = 10) or a combination of ketamine and midazolam (n = 9). Patients who received midazolam alone because of good tolerance of the procedure or because of very short duration of the procedure were used as the control group (n = 12). In each group, EPS was carried out before and after administration of propofol/midazolam, ketamine/midazolam, or midazolam.

Exclusion criteria for the study were severe liver or kidney dysfunction, severe heart failure (Class: New York Heart Association III and IV), asthma, relevant psychiatric or neurological disorder at the time of admittance, history of adverse reaction to propofol and soy allergy, history of psychosis, or other adverse reaction to ketamine. All patients gave informed consent. The study complies with the Declaration of Helsinki and was approved by the ethical committee of the Charité Universitätsmedizin Berlin.

**Electrophysiological study**

After obtaining venous access using bilateral femoral veins a catheter was positioned in the right atrial appendage (high right atrium, HRA).

**Table 1 Clinical characteristics of patients enrolled in the study**

<table>
<thead>
<tr>
<th></th>
<th>Propofol (n = 10)</th>
<th>Ketamine (n = 9)</th>
<th>Control (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>52 (16)</td>
<td>57 (21)</td>
<td>52 (16)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (60%)</td>
<td>3 (33%)</td>
<td>5 (41%)</td>
</tr>
<tr>
<td>LV-EF (SD)</td>
<td>59% (4.5)</td>
<td>57% (5)</td>
<td>55.4% (11)</td>
</tr>
<tr>
<td>Concomitant disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>5 (50%)</td>
<td>6 (66%)</td>
<td>5 (41%)</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>CAD</td>
<td>2 (20%)</td>
<td>0</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>0</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean dose in mg (SD)</td>
<td>86.7 (38.2)</td>
<td>23.6 (11.5)</td>
<td>–</td>
</tr>
<tr>
<td>Mean midazolam dose in mg (SD)</td>
<td>5.3 (0.4)</td>
<td>8.2 (3.8)</td>
<td>5.7 (1.7)</td>
</tr>
</tbody>
</table>

LV-EF, left ventricular ejection fraction; CAD, coronary artery disease.
Effects of deep sedation on cardiac electrophysiology in patients undergoing radiofrequency ablation

Table 2 Change of parameters: difference between baseline EP study and EP study after administration of popofol or ketamine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Propofol (n = 10)</th>
<th>Ketamine (n = 9)</th>
<th>Control (n = 12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHeart rate (b.p.m.) (SD)</td>
<td>-1.4 (8)</td>
<td>12.4 (8.3)</td>
<td>1 (7.5)</td>
<td>0.002^*</td>
</tr>
<tr>
<td>ΔCycle length (ms) (SD)</td>
<td>242 (99.5)</td>
<td>-122.1 (119.4)</td>
<td>-5.2 (48.1)</td>
<td>0.004^*</td>
</tr>
<tr>
<td>ΔP wave (ms) (SD)</td>
<td>8.3 (17.1)</td>
<td>-10.6 (19.9)</td>
<td>-0.3 (2.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>ΔPOQ (ms) (SD)</td>
<td>9 (13.9)</td>
<td>-11.1 (17)</td>
<td>-1.3 (5.8)</td>
<td>0.009^*</td>
</tr>
<tr>
<td>ΔQRS (ms) (SD)</td>
<td>0.2 (8.2)</td>
<td>2.3 (7.8)</td>
<td>0.7 (3.6)</td>
<td>0.783</td>
</tr>
<tr>
<td>ΔQT (ms) (SD)</td>
<td>-4.1 (2.19)</td>
<td>2.3 (29.2)</td>
<td>4.2 (10.8)</td>
<td>0.675</td>
</tr>
<tr>
<td>ΔcSNRT (ms) (SD)</td>
<td>40.1 (93.9)</td>
<td>-64.5 (119.8)</td>
<td>-15 (154.1)</td>
<td>0.253</td>
</tr>
<tr>
<td>ΔWBCL (ms) (SD)</td>
<td>-10 (48)</td>
<td>-56.5 (67.9)</td>
<td>-5 (9.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>ΔERPAVN (ms) (SD)</td>
<td>5 (33.4)</td>
<td>-4.4 (13.3)</td>
<td>3.3 (6.5)</td>
<td>0.576</td>
</tr>
<tr>
<td>ΔERPA (ms) (SD)</td>
<td>30 (26.9)</td>
<td>1.2 (8.3)</td>
<td>0.9 (5.3)</td>
<td>0.001^*</td>
</tr>
<tr>
<td>ΔAtrial conduction (ms) (SD)</td>
<td>4.5 (11.1)</td>
<td>-13.7 (16.4)</td>
<td>-0.3 (3.8)</td>
<td>0.008^*</td>
</tr>
<tr>
<td>ΔSignal duration 1 (ms) (SD)</td>
<td>0 (13.8)</td>
<td>-6 (12.3)</td>
<td>0 (2.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>ΔSignal duration 2 (ms) (SD)</td>
<td>11.1 (12.1)</td>
<td>-25.5 (33.2)</td>
<td>0.4 (1.1)</td>
<td>0.012^*</td>
</tr>
<tr>
<td>ΔBP systolic (mmHg) (SD)</td>
<td>-22 (9)</td>
<td>19.2 (8.1)</td>
<td>0.1 (5.7)</td>
<td>&lt;0.001^*</td>
</tr>
<tr>
<td>ΔBP diastolic (mmHg) (SD)</td>
<td>-7.8 (2.9)</td>
<td>6.6 (9.7)</td>
<td>2.3 (4.5)</td>
<td>0.001^*</td>
</tr>
</tbody>
</table>

Signal duration 1: duration of the signal on proximal CS with extrastimulus 350 ms. Signal duration 2: duration of the signal on proximal CS with extrastimulus 10 ms above ERPA. cSNRT, corrected sinus node recovery time; WBCL, Wenckebach cycle length; ERPAVN, atrioventricular node effective refractory period; ERPA, atrial effective refractory period; SD, standard deviation.

^*Statistically significant.

and the coronary sinus (CS) under fluoroscopic guidance. Additional diagnostic catheters were used if required for further diagnosis in the individual patient. Surface ECG and intracardiac recordings were displayed and recorded on a standard multichannel recording system (Siemens AXIOM® Sensix XP, Siemens Medical Solutions), a standard electrostimulator (Biotronik UHS 20® Universal heart Stimulator, Biotronik) was used for stimulation.

Heart rate, cycle length, and duration P-wave, PQ interval, QRS, and QT interval were obtained. Atrial overdrive pacing and incremental atrial pacing were used to determine corrected sinus node recovery time and Wenckebach cycle length (VBCL), respectively. Extrastimulus testing at basic cycle length 500 ms from HRA was performed to determine effective refractory period of atrium (ERPA), and fast pathway of atrioventricular node (ERPAVN). During extrastimulus testing, duration of the signal on proximal CS (CS signal between electrodes 9/10) was measured at extrastimulus 350 and 10 ms above ERPA. Atrial conduction time was measured as time from signal onset on HRA to signal onset on proximal CS (CS 9/10) at overdrive stimulation with cycle length 500 ms from HRA. In addition, programmed stimulation with extrastimulus was performed with 600 S2, 500 S2, and 400 S2 in every group before and after administration of propofol/midazolam, ketamine/midazolam, or midazolam alone, respectively. Number, type, and mechanism of induction (spontaneous or in response to stimulation) of all arrhythmias was documented. Arrhythmia was classified ‘unspecific’ if it was any other arrhythmia than the target arrhythmia that was eventually ablated. Table 2 gives and overview of all electrophysiological measures that were obtained. The stimulation protocol was performed at baseline and repeated after administration of propofol/midazolam, ketamine/midazolam, or midazolam alone.

All measures were obtained before any ablation procedure and before application of other agents affecting cardiac conduction such as orciprenalin or adenosine. Each procedure was prepared and performed by two physicians (electrophysiologist and electrophysiology fellow) and two qualified nurses. Offline analysis of parameters was done without knowledge of type of anesthetic.

Drug administration and monitoring

Patients who were treated with propofol received 0.5–1 mg/kg intravenous propofol in combination with 0.03 mg/kg intravenous midazolam to save absolute propofol dose. Additional boli of 0.5 mg/kg were given as needed every 3 min to maintain deep sedation.

Patients who were treated with ketamine received 0.5 mg/kg intravenous ketamine in combination with 0.03 mg/kg intravenous midazolam to prevent recovery agitation as previously described. Additional boli of 0.5 mg/kg were given as needed every 3 min to maintain deep sedation.

Patients who were treated with midazolam alone received 0.05 mg/kg intravenous midazolam. Additional boli of 0.05 mg/kg were given as needed to achieve minimal to moderate sedation.

In deep sedated patients guedel airway was applied. In every patient oxygen was delivered via nasal cannula (2–8 L/min) throughout the procedure with a target SaO2 of >95%. SaO2, ECG, and blood pressure were monitored continuously throughout the entire procedure. Respiratory depression was defined as oxygen saturation <90%. Severe hypotension was defined as a decrease in systolic blood pressure of >40% from baseline or a systolic blood pressure of <80 mmHg. Bradycardia was defined as a heart rate <50 b.p.m. These criteria were considered present if they occurred any time during the procedure, regardless of their duration. All patients were spontaneously breathing throughout the procedure, no patient was intubated.

Statistical analysis

Delta values of all parameters were calculated to quantify the change after drug administration. Analysis of variance was used to determine
group differences with type of anaesthetic agent as group variable and electrophysiological and blood pressure delta values as dependent variables. All analyses were performed using SPSS software version 20.0 (SPSS Inc.). Data are presented as mean ± standard deviation (SD). A P value < 0.05 was considered statistically significant.

Results

A total of 31 Patients were analysed. Patients in the propofol group received a mean dosage of 86.7 mg propofol and 5.3 mg midazolam. Patients in the ketamine group received a mean dosage of 23.6 mg ketamine and 8.2 mg midazolam. Patients in the control group received a mean dosage of 5.7 mg midazolam. Delta values of electrophysiological data and blood pressure are depicted in Table 2 and Figure 1. No sedation related or procedural complications occurred during EPS.

After administration of ketamine/midazolam an increase in heart rate and blood pressure and a shortening of cycle length, PQ interval, atrial effective refractory period, atrial conduction time, and signal duration on proximal CS at extrastimulus 10 ms above ERPA was detected, while after administration of propofol/midazolam a decrease and elongation of those parameters was seen (Table 2, Figure 1). Analysis of variance of delta values revealed significant group differences in systolic and diastolic blood pressure, heart rate, cycle length, PQ interval, atrial effective refractory period, atrial conduction time, and signal duration on proximal CS at extrastimulus 10 ms above ERPA. No significant differences in WBCL and ERPAVN were detected (Table 2).

Supraventricular tachycardia induction rates before and after administration of anaesthetic agent did not differ significantly between the groups. No case of non-inducibility of arrhythmia after administrations of anaesthetic medication occurred (Table 3).

Discussion

We found a statistically significant shortening of atrial conduction time, shorter signal duration of extrastimulus response, increased heart rate, and increased systolic and diastolic blood pressure after administration of ketamine/midazolam compared with propofol/midazolam or midazolam alone. No affection of AV-node or sinus node function was seen under any of the anaesthetic drugs. The latter is consistent with previous data.9,36,37

The shortening of atrial conduction time and the increase in heart rate and blood pressure under ketamine are most likely...
due to stimulation of the sympathetic nervous system. Notably, our results are in line with the previously reported effects of ketamine on isolated human atrial myocytes and isolated guinea pig hearts.27,28 A stimulatory effect of ketamine on atrial conduction could on one hand promote inducibility and maintenance of supraventricular arrhythmias. This could increase success rates of ablation procedures by improving mapping capabilities and sensitivity of electrophysiological testing after ablation.38 In addition, in patients with suspected or documented SVT, sinus bradycardia can be present.39 An anaesthetic with stimulatory effects on heart rate would be of advantage during EPS and ablation procedures in patients with sinus bradycardia.

On the other hand, stimulatory effects on cardiac tissue may also promote induction of unspecific arrhythmias without clinical significance. We tested how many and which arrhythmias were induced during standard EPS before and after the administration of anaesthetic drugs. The induction rates of SVT were not significantly different between the groups. No case of non-inducibility of the target arrhythmia after administration of the anaesthetic agent was detected in any of the experimental groups. No unspecific arrhythmia occurred. In a small number of patients in each group no arrhythmia was induced with the initial stimulation protocol. In those patients, induction protocol was escalated during the EPS in order to induce arrhythmia (e.g. burst stimulation and pharmacological induction with orciprenaline).38 The additional stimulation protocol and drug administration was not analysed for reasons of comparability in our relatively small experimental groups. In summary, ketamine and propofol had similar effects on the inducibility of SVT in adults undergoing EPS before SVT ablation.

Blood pressure and heart rate were higher under ketamine and lower under propofol. This was expected and is consistent with previous data.7,25 No case of haemodynamic instability or oxygen desaturation was seen, no sedation-related complications occurred. For the elective electrophysiological procedures of short duration in our study collective both sedation regimens were comparably safe. Because of the stimulatory effects on blood pressure, heart rate, and atrial conduction, ketamine may be of advantage in patients with pre-existing hypotension or bradycardia or in patients who are at risk to develop hypotension under propofol sedation.

**Limitations**

There are limitations of the study that should be acknowledged. The groups were relatively small, which in particular limits drawing conclusions from the number of arrhythmia inductions before and under anaesthesia, since non-inducibility of a previously documented SVT in the electrophysiology laboratory in general is relatively rare.38,40 Further studies in a larger study collective are needed to evaluate if non-inducibility of SVT is influenced by the sedation regimen.

**Conclusion**

We here present the first data that ketamine is feasible and effective for sedation during ablation of SVT in adults. Our results show that ketamine, in contrast to propofol, shortens atrial conduction time without significant effects on AV-nodal function. Therefore, ketamine may be beneficial in patients with pre-existing hypotension or known episodes of bradycardia and can be considered in patients at risk for haemodynamic instability.

**Conflict of interest:** none declared.

**References**