Propofol sedation administered by cardiologists without assisted ventilation for long cardiac interventions: an assessment of 1000 consecutive patients undergoing atrial fibrillation ablation

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Aims
Patients can expect a cure from atrial fibrillation (AF) with ablation. Procedural safety and success depend on patient comfort, compliance, and immobility. This is difficult to achieve with benzodiazepine and opiate boluses that are the mainstay of current practice. We sought to determine the safety and efficacy of propofol infusion sedation administered to patients without assisted ventilation for AF ablation.

Methods and results
Procedural data from 1000 consecutive patients undergoing AF ablation were analysed. Sedation with 2% propofol was used in all procedures without assisted ventilation and was administered, monitored, and controlled by electrophysiologists. Primary outcome measures were adverse sedative effects including (i) respiratory depression (SpO2 < 90% for > 20 s) and (ii) persistent hypotension [systolic blood pressure (SBP) < 90 mmHg at minimum sedation level]. Secondary endpoints included full recovery within 60 min and procedural complications. Of 1000 ablations, 506 ablations were performed for persistent and 494 for paroxysmal AF. Average patient age was 60.1 ± 11.3 years (72.3% male). Propofol was commenced in all patients at a mean infusion rate of 18.5 ± 4.8 mL/h with a mean baseline SBP of 140.3 ± 19.9 mmHg. Mean procedure time was 148.7 ± 57.7 min. Adverse sedative effects necessitating cessation of propofol and switch to midazolam bolus sedation occurred in 15.6% of patients (13.6% due to persistent hypotension, 1.9% due to respiratory depression, and 0.1% due to hyper-salivation). Patients who had persistent hypotension were older (62.9 ± 11.2 vs. 60.0 ± 11.4 years, P = 0.011) and more likely to be female (39.5 vs. 23.7%, P < 0.001) than those who tolerated propofol. Patient age correlated to maximum blood pressure drop with propofol (R² = 0.101, P < 0.001) and inversely correlated to mean propofol infusion rate (R² = 0.066, P < 0.001). No procedures were abandoned due to adverse effects of sedation. All patients recovered within 60 min. Serious procedural complications, unrelated to sedation, occurred in 0.5%, all of whom had pericardial tamponade successfully treated with percutaneous pericardiocentesis.

Conclusions
Sedation with 2% propofol infusion administered by cardiologists without assisted ventilation is safe, effective, and practical for use in AF ablation without serious or residual complications. In this setting, persistent hypotension is the most common acute adverse effect requiring cessation of propofol in ~14%.

Keywords
Atrial fibrillation ablation • Propofol sedation • Safety
Introduction

Catheter ablation has come to the fore in the treatment of atrial fibrillation (AF). Although the expectation of cure is excellent, the procedure is often long and uncomfortable for patients who must remain recumbent and motionless, often for hours. When the cardiac chambers are instrumented with catheters, sheaths, and needles, it is imperative that the patient remains still lest risk of serious complication or procedural failure. This is only possible if patients are made comfortable with appropriate sedation and analgesia and is attempted in most centres in the USA and Europe with benzodiazepines and opiates used in a repeated bolus fashion. While this may suffice for short procedures, it is very often hopelessly inadequate for procedures lasting 90 min or more. The inevitable waxing and waning levels of sedation cause patients to move when under-sedated due to discomfort and when over-sedated due to delirium. A safe and effective alternative, short of the added risk of general anaesthesia with mechanical ventilation, is sorely needed.

In intensive care, propofol has been shown to have a better and more predictable clinical response compared with benzodiazepines and is more cost effective with short-term use. Recovery time and risk of respiratory depression is significantly lower with propofol compared with benzodiazepines. Consequently, propofol infusion with assisted spontaneous ventilation has been widely preferred for short-term procedural sedation, particularly when endotracheal intubation is impractical. In this study, we assess the safety and efficacy of propofol infusion for sedation for AF ablation administered, monitored, and controlled entirely by the operating cardiologist and without intubation and assisted ventilation.

Methods

The study was conducted at the University of Eppendorf Heart Centre, Hamburg, Germany where all AF ablation procedures are performed under sedation with a propofol infusion and analgesia with fentanyl boluses. Propofol was administered and monitored by catheter laboratory nurses, under the direct supervision and instruction of the operating electrophysiologist. The electrophysiological team consisted of two laboratory nurses, the operating electrophysiologist, and an electrophysiology fellow. All medical staff were trained in advanced life support. An on-call anaesthetist is available from within the hospital if required.

Patient assessment and inclusion

All patients were pre-assessed in the outpatient department prior to scheduling and consenting for AF ablation. All patients who were considered eligible for AF ablation were considered eligible for inclusion in the study and hence there were no exclusion criteria for enrolment. Informed written consent was obtained from all patients.

Sedation protocol and monitoring

Patients were positioned fully recumbent on the catheter laboratory table. Induction of sedation was administered with a bolus of 2–5 mL of 2% propofol and maintained with an infusion starting at 15 mL/h. The infusion rate was titrated to clinical response. Adequate sedation was considered to have been achieved upon cessation of body movements, failure to respond to verbal commands. If sedation was not adequate, additional 2 mL boluses of 2% propofol were administered and the infusion rate was increased by 2–5 mL/h. Oxygen was administered via a face mask starting at 5 L/min. Peripheral oxygen saturation, heart rate, and blood pressure (BP) were monitored continuously. For paroxysmal AF ablation, BP was monitored non-invasively with a brachial cuff at 3 min intervals. In persistent AF ablation, femoral arterial access is routinely acquired in which case continuous arterial pressure monitoring was used. All measurements were documented on a flowchart every 5 min with repeated clinical assessment of level of sedation and respiratory effort using visual inspection and palpation. Observations were recorded every 5 min with meticulous documentation of oxygen saturation. Trough oxygen saturation alarms were set to 90%. Boluses of fentanyl 0.05 mg intravenous were administered prior to application of radiofrequency and whenever the sedated patients were assessed to be displaying pain responses such as grimacing or body movements.

Access, cardiac instrumentation, and procedural details

Our procedure for AF ablation in both paroxysmal and persistent forms has been previously described in detail. Briefly, all patients were fasted for at least 8 h prior to ablation and underwent transoesophageal echocardiography to exclude left atrial thrombus prior to the procedure. Access was acquired via bilateral femoral venous cannulation. Left femoral arterial access was also acquired for persistent AF ablation for monitoring purposes. A steerable decapolar catheter and a fixed quadripolar catheter (both Inquiry, IBI, Irvine Biomedical Inc.) were positioned via left femoral venous access in the coronary sinus (CS) and right atrium (RA) appendage, respectively. Through right femoral venous access, a circular decapolar catheter (Lasso, Biosense-Webster, Diamond Bar, CA, USA) was used to map the pulmonary veins (PVs) and a 3.5 mm irrigated-tip ablation roving catheter (Thermocoool, Biosense-Webster) was used for mapping and ablation. The left atrium (LA) was instrumented with the Lasso and ablation catheter through a single transseptal puncture via long sheaths (SL0 Diag, St Jude Medical, St Paul, MN, USA) to enhance stability. The SL0 sheaths were continuously irrigated with heparinized saline. A single bolus of 50 IU/kg of heparin was administered after transseptal puncture. Thereafter, additional boluses of heparin were given to maintain an activated clotting time of 250–300 s.

If patients were in sinus rhythm at the beginning of the procedure, AF was induced with rapid atrial pacing. As the first step of ablation, the PVs were electrically isolated. If AF persisted despite complete PV isolation, complex-fractionated atrial electrograms as well as areas displaying specific local activation characteristics presumably involved in the arrhythmogenic process (activation gradients, centrifugal activation, and localized rapid activity) were targeted for ablation. These were targeted sequentially in the LA, CS, and RA. The desired endpoint was termination of AF. If AF terminated to one or more atrial tachycardias, these were also targeted with the aim of achieving sinus rhythm through ablation.

Data analysis and study endpoints

Procedural documentation of all AF ablations between June 2008 and September 2009 were analysed in detail. Baseline clinical details including basic patient demography, starting BP and oxygen saturations were recorded. Procedural details of interest were total procedure time (induction of sedation to sheath removal) and fluoroscopy time. Sedative and analgesia doses including starting and mean propofol infusion rates and cumulative fentanyl dose was recorded. In the event of
cessation of propofol, the cumulative midazolam dose was also documented. Trough levels of BP and oxygen saturation were also recorded.

The primary outcome measures were (i) adverse sedative effects requiring cessation of propofol and (ii) oxygen desaturation (defined as SpO₂ < 90% for >20 s) or need for assisted ventilation in any form (including chin lift, bag, and mask ventilation or intubation). Secondary endpoints included full recovery within 30 min, procedural completion, and presence of any other complications.

**Statistical analysis**

Data are expressed as the mean value ± SD. Continuous measures were compared using the Student’s t-test and non-continuous variables using χ² test to a 0.05 level of significance.

**Results**

**Patients and baseline physiology**

One thousand consecutive AF ablations were included for analysis. Of these, 494 were performed for paroxysmal and 506 for persistent AF. Average age of patients was 60.1 ± 11.3 years and 72.3% were male. Prior to sedation, mean systolic blood pressure (SBP) was 140.3 ± 19.9 mmHg and mean oxygen saturation was 97.9 ± 3.3%. All patients were unselected and represented a typical referral cohort for AF ablation. No patients were excluded and none were pre-assessed to require intubation and general anaesthetic.

**Procedural data and endpoints**

In this unselected study cohort, the procedures included a mixture of ablation for paroxysmal AF and persistent AF as well as de novo (63%) and repeat (37%) procedures. Thus, even though procedural techniques were standardized, procedural endpoints differed. Pulmonary vein isolation alone was all that was required and was achieved in 524 patients. Pulmonary vein isolation with further atrial and CS defragmentation to the point of AF termination was achieved in a further 333 patients, while 143 failed to terminate through ablation and required cardioversion. Mean procedure time was 148.7 ± 57.7 min. No procedures were abandoned prematurely and failure to reach the endpoint of AF termination was never a result of an intra-procedural complication or an adverse effect of sedation.

**Sedation and analgesia**

All 1000 patients had induction of sedation with a bolus of 2.2 ± 0.9 mL of 2% propofol followed by a continuous infusion starting at 15 mL/h which was then titrated according to response. The peak and mean propofol infusion rates for the entire cohort were 20.9 ± 4.1 and 18.5 ± 4.8 mL/h, respectively. Fentanyl was used for analgesia in 99% of patients and was administered in repeated boluses as required. The mean cumulative fentanyl dose was 0.15 ± 0.09 mg. This combination regimen resulted in a mean intra-procedural decrease in SBP by 46.1 ± 22.9 mmHg (from 140.3 ± 19.9 to 94.2 ± 15.3 mmHg, P < 0.001) and a mean fall in oxygen saturation by 2.3 ± 4.3% (from 97.9 ± 3.3 to 95.5 ± 3.6%, P < 0.001).

**Adverse effects of sedation**

Adverse effects of sedation led to cessation of propofol and to a change to midazolam boluses in 15.6% of cases. This was specifically due to persistent hypotension in 13.6%, respiratory depression in 1.9% and hypersalivation in 0.1% of cases.

Persistent hypotension, defined as failure to maintain a SBP > 90 mmHg at a propofol infusion rate required to achieve adequate sedation, occurred in 136 patients. The mean drop in SBP in this group was significantly greater than those who tolerated propofol (62.7 ± 23.3 vs. 43.9 ± 21.8 mmHg, P < 0.001). Blood pressure recovered in all patients after cessation of propofol. Patients who did not tolerate propofol due to persistent hypotension were older (62.9 ± 11.2 vs. 60.0 ± 11.4 years, P = 0.011) and there was a greater prevalence of female patients among this group (39.5 vs. 23.7%, P < 0.001) compared with those who tolerated propofol.

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*P values for comparison of patients who tolerated propofol vs. those who had persistent hypotension. Comparison of continuous data with t-test and non-continuous data with χ² test.
tolerated propofol (see Table 1). However, neither age nor gender emerged as independent predictors of propofol-induced hypotension.

This observation is also reflected in a significant though weak correlation between age and maximum drop in BP ($R^2 = 0.101$, $P < 0.001$) and inverse correlation between age and mean tolerated propofol infusion rate within the entire cohort (see Figure 1). The lower doses of propofol tolerated by patients with persistent hypotension resulted in a compensatory increase in fentanyl dose ($0.22 \pm 0.1$ vs. $0.13 \pm 0.07$ mg, $P < 0.001$) and procedure time ($157.8 \pm 57.9$ vs. $146 \pm 56.9$ min, $P = 0.038$) compared with patients who tolerated propofol (see Table 1).

Nineteen patients experienced respiratory depression resulting in sustained oxygen saturation of <90%. All but one recovered with cessation of propofol alone. One patient required 4 min of manual bag-and-mask ventilation before resumption of spontaneous breathing. On no occasion was endotracheal intubation, invasive mechanical ventilation, or the attendance of an anaesthetist required. One patient developed profuse hypersalivation upon commencement of propofol. This rare adverse effect resolved after switching to midazolam.

Recovery
After all procedures, patients were observed in a recovery unit for 60 min before returning to the ward. All patients were reviewed by a physician after 30 min. Full recovery of psychomotor and cognitive function was observed in all patients after 60 min.

All patients were routinely observed on the main ward after ablation for at least 1 day prior to discharge. In this cohort of 1000 patients, only one developed a post-procedural pneumonia and was treated with oral antibiotics. This patient made an uneventful recovery and was discharged after 4 days.

Complications
Serious procedural complications occurred in 0.5% of patients, all of whom had pericardial tamponade after the procedure and were all successfully treated with percutaneous pericardiocentesis. This recognized complication of AF ablation was not related to the sedation regimen or the transseptal puncture.

Discussion
Main findings
In a cohort of 1000 unselected, consecutive patients, deep sedation without assisted ventilation using a continuous infusion of 2% propofol is safe and effective for prolonged cardiac interventions such as AF ablation. The present study is the first to demonstrate that propofol sedation with fentanyl analgesia can be safely administered and monitored by cardiologists without assisted ventilation or an anaesthetist in immediate attendance. The effects of propofol were predictable and resulted in excellent levels of sedation and patient compliance. Only 1 patient of the 1000 studied required 4 min of mechanical bag and mask ventilation before resumption of spontaneous ventilation. There were no serious or long-term complications as a result of propofol sedation.

During short electrophysiological procedures, such as ablation of common supraventricular tachycardias (typically 30–40 min), patients can cope with lying still and sedation with benzodiazepine boluses will suffice. When administered in repeated bolus fashion over longer periods, the disadvantage of the benzodiazepine dose–response relationship becomes apparent with waxing and waning levels of arousal jeopardizing procedural safety and success. Thus, for longer procedures such as AF ablation, an appropriate and maintained level of sedation is best achieved through a continuous infusion. In this regard, propofol offers significant advantages over benzodiazepines including more rapid induction, minimal adverse effects, better acute intra-procedural control of sedation level, and more rapid recovery of psychomotor and cognitive function.

Since its introduction, propofol has been used as a procedural sedative in several settings but most notably during endoscopy or dental procedures, when endotracheal intubation is impractical.
Although, many studies also report excellent intra-procedural safety, minimal adverse event, and rapid recovery from sedation, all used propofol in bolus or repeated bolus fashion. This was primarily because procedures were much shorter than those of the present study. This study reports, for the first time, the excellent safety profile of propofol administered through continuous infusions, without assisted ventilation and exclusively by cardiologists during invasive cardiac procedures. It is also important to note the broad inclusion criteria of our study cohort. Patients who were eligible for AF ablation were included and thus represent a typical population encountered in clinical practice with a broad range of age and comorbidity who, as a population, tolerate propofol very well.

Of the 1000 patients included 74.4% were able to tolerate propofol throughout the procedure, while 15.6% suffered adverse effects requiring switch to midazolam boluses. Of these, remarkably few patients suffered respiratory depression while most (13.6%) experienced persistent hypotension. Patients with persistent hypotension were older and more likely to be female compared with those who tolerated propofol. The pharmacology of propofol and the physiology behind the most common adverse effects has been extensively reviewed and is only briefly outlined here.

**Pharmacokinetics and pharmacodynamics**

Intravenously administered propofol has very rapid tissue distribution and rapid metabolic clearance from the circulation. Its highly lipophilic properties allow for rapid breach of the blood–brain barrier after which the drug is rapidly redistributed, thus accounting for its quick onset of action (typically 30–40 s, or one arm to brain circulation time) and short duration of action. During continuous infusions, as used in this study, the rate of redistribution from tissues decreases with time as plasma and tissue levels equilibrate. This slowing of tissue return accounts for the elimination half-life of 3–12 h. Hepatic metabolism is the predominant mode of clearance where propofol is metabolized into four inactive metabolites which are renally excreted. Despite this, hepatic cirrhosis and renal function have no significant effect on propofol pharmacokinetics. It is reported that with increasing age lower induction and maintenance doses are required. This was also observed in the current study with an inverse correlation between age and mean propofol dose.

The central actions of propofol are exerted via the alpha subunit of the gamma aminobutyric acid neural receptor. Hypotension is a major cardiovascular side effect as was clearly observed in this study. This effect is primarily due to a reduction in systemic vascular resistance, though a reduced inotropic effect is also observed. In the current study, transthoracic echocardiography was often performed during procedures, particularly if BP decreased. Although not routinely assessed or quantified, mild global depression of LV function was frequently observed and promptly recovered upon cessation of propofol. We suspect that like most cohorts of patients undergoing AF ablation in high-volume large centres, a significant minority would have some degree of baseline LV impairment. However, in this study all patients who were considered eligible for AF ablation were commenced on propofol first, and impaired LV function was not a barrier to its initial use. In general, propofol is tolerated well haemodynamically and is frequently used during cardiac surgery and recovery.

This study was designed to report on the safety profile of propofol administered by cardiologists in the unventilated patient. The infusion regimen was titrated manually based on clinical assessment of level of sedation. Current automated propofol delivery systems make use of computerized syringes which alter infusion rates based on patient parameters such as age and weight as well as anticipated procedure time. This so-called ‘target controlled infusion’ systems allow for a more tailored infusion rate to account for the time-dependent fluctuations in propofol redistribution mentioned above. It is plausible that had such a system been employed, a lower rate of side effects may have been observed and fewer patients may have required cessation of propofol in favour of midazolam. Nevertheless, despite a conversion rate of 15.6%, manually adjusted propofol infusions were safe and extremely effective.

**Limitations**

The study was observational by design and patients were not randomized against a comparison group with alternative form of sedation. However, we believe that our results from one thousand patients have clearly shown that the use of propofol in this setting is safe and feasible and has opened the way for a comparison study with a randomized controlled design. Our procedures were limited to AF ablation and therefore we cannot assume how patients would tolerate propofol during other long cardiac interventions.

**Conclusions**

Sedation with 2% propofol infusion administered by cardiologists without assisted ventilation is safe, effective, and practical for use in AF ablation without long-lasting or serious complications. In this setting, persistent hypotension is the most common acute adverse effect requiring cessation of propofol in ~14%. These patients were older and more likely to be female. Propofol may offer a safer, more predictable alternative to repeated boluses of midazolam for sedation during AF ablation and may be extended to other long cardiac interventions.

**Conflict of interest:** none declared.

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**References**