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Effect of the antipsychotic drug haloperidol on arrhythmias during acute myocardial infarction in a porcine model

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ABSTRACT

Patients receiving psychiatric medication, like the antipsychotic drug haloperidol, are at an increased risk of sudden cardiac death (SCD). Haloperidol blocks the cardiac rapidly-activating delayed rectifier potassium current, thereby increasing electrical dispersion of repolarization which can potentially lead to arrhythmias. Whether these patients are also at a higher risk to develop SCD during an acute myocardial infarction (AMI) is unknown. AMI locally shortens action potential duration, which might further increase repolarization dispersion and increase the risk of arrhythmia in the presence of haloperidol compared to without. Our aim was to test whether treatment with haloperidol implies an increased risk of SCD when eventually experiencing AMI. Twenty-eight female Danish Landrace pigs were randomized into three groups: low dose haloperidol (0.1 mg/kg), high dose (1.0 mg/kg) or vehicle-control group. One hour after haloperidol/vehicle infusion, AMI was induced by balloon-occlusion of the mid-left anterior descending coronary artery and maintained for 120 min, followed by 60 min of reperfusion. VF occurred during occlusion in 7/11 pigs in the control group, 3/11 in the low dose ($p = 0.198$) and 2/6 in the high dose group ($p = 0.335$). High dose haloperidol significantly prolonged QT, and reduced heart rate, vascular resistance and blood pressure before and during AMI. Premature ventricular contractions in phase 1b during AMI were reduced with high dose haloperidol. AMI-induced arrhythmia was not aggravated in pigs with haloperidol treatment. Our results do not suggest that AMI is contributing to the excess mortality in patients treated with antipsychotic drugs seen in epidemiological studies.

1. Introduction

The incidence of sudden cardiac death (SCD) is increased dramatically in psychiatric patients compared to the background population [1]. We have previously found a four-fold increase of SCD in young patients with prior psychiatric hospitalization in a nationwide Danish study [2]. The excess mortality in psychiatric diseases are multifactorial, including environmental factors, life-style, and psychopharmacological treatment [3]. Medication is thought to be a risk factor and a quarter of all patients in the age group of 1–49 years suffering from SCD due to coronary artery disease had a positive toxicology for psychiatric medication [4]. A number of psychopharmacological drugs are known to block cardiac ion channels, in particular the delayed rectifier potassium channel hERG1, conducting I_{Kr}, thereby prolonging cardiac repolarization. This leads to a prolonged QT interval, a risk factor for torsades de pointes (TdP) tachycardia and, as a final consequence, SCD [3].

Haloperidol is a widely used first generation (typical) antipsychotic drug, blocking the D_2 dopamine receptor family. It is mainly

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used to treat schizophrenia and agitation, but is also the preferred antipsychotic compound for the treatment of delirium [5,6]. Little is known on whether or to what extent haloperidol's arrhythmic potential is modulated by potential proarrhythmic events, like acute myocardial infarction (AMI). AMI is the leading cause of SCD in the Western world [7] with more than 10% of all AMI patients developing ventricular fibrillation (VF) in the early phase (within minutes after symptom onset) [8], caused by proarrhythmic alterations of a variety of electrophysiological parameters [9]. Further, signs of AMI in the absence of symptoms were detected in greater than 40% of SCD victims that had no history of coronary artery disease [10].

We hypothesized that patients taking a first generation (typical) antipsychotic drug, like haloperidol, are at higher risk to develop VF when eventually experiencing AMI and that (silent) AMI contributes to the excess mortality seen in epidemiological studies. We expected effects on both, electrophysiological substrate and triggers. The substrate might be changed by an increase in ventricular dispersion of repolarization as AMI locally shortens action potential duration (APD) in a ventricle with globally prolonged APD due to haloperidol treatment. This could facilitate ventricular arrhythmias and consecutive VF.

Our aim was to test acute administration of a low dose of 0.1 mg/kg haloperidol (as recommended in chronic treatment) and a high dose of 1.0 mg/kg haloperidol (as often seen in treatment of acutely agitated patients) one hour before the onset of AMI in a porcine model. We aimed to assess its effect on arrhythmias including VF, changes in cardiac repolarization, and hemodynamic parameters during AMI and reperfusion. With this study we aimed to gain a deeper understanding into circumstances of SCD in psychiatric patients treated with antipsychotic drugs.

2. Material and methods

Twenty-eight female Danish Landrace pigs (mean body weight 52 kg, range 47–57 kg, mean heart weight 250 g, range 200–295 g) were randomized to a control (n = 11), a low dose (n = 11), or a high dose (n = 6) intervention group. Only female animals were included as the risk for TdP and VF during AMI is higher with female gender [11]. Fewer pigs were randomized into the high dose group as an excess mortality during AMI was expected. Randomization was done the day before the experiment using a randomization table. Persons who carried out coronary occlusion and data analysis were blinded regarding randomization results. All experiments were performed under the animal license number (2015-15-0201-00613) authorized by the Danish Animal Inspectorate in accordance with EU legislations for animal protection and care.

2.1. Procedure

The experimental procedure is depicted in Fig. 1A. Pigs were premedicated with tiletamin/zolazepam, xylazine, ketamine, butorphanol, methadone, intubated and ventilated (tidal volume 8 ml/kg, frequency 14 min^{-1}, and inspirational concentration of oxygen 0.3). Ventilation was adjusted when necessary to keep blood gas parameters at normal levels. Anesthesia was maintained

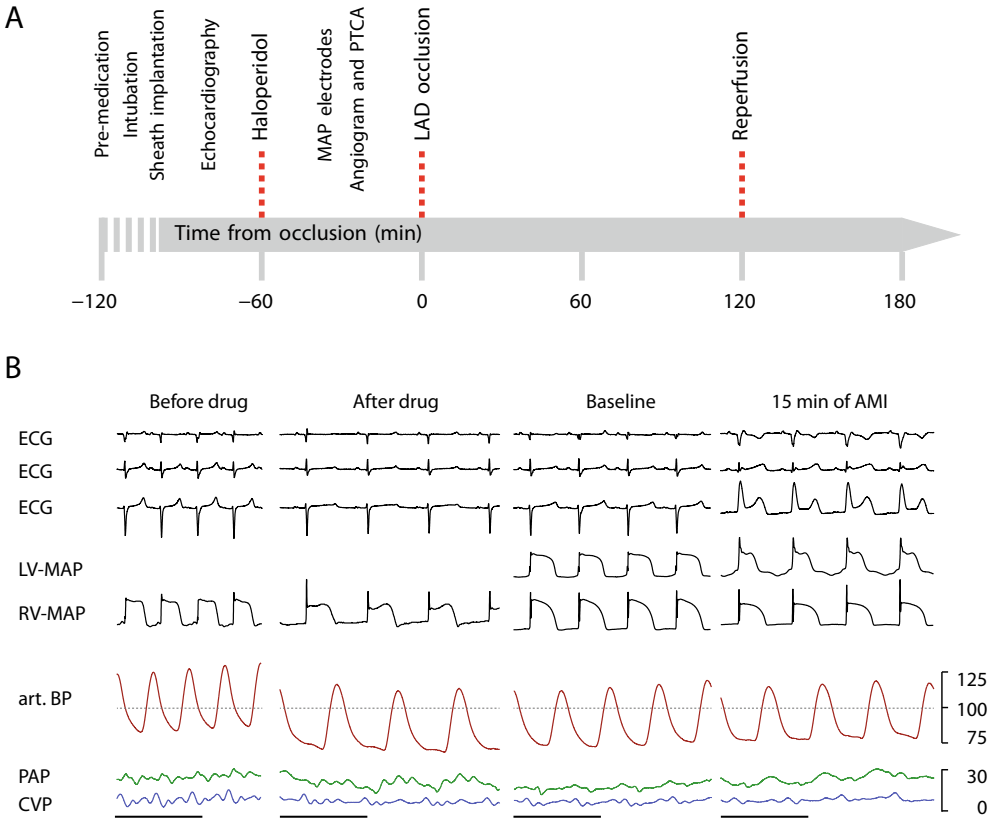

Fig. 1. *Experimental setup and representative traces.* **A**: Experimental setup. Pigs were medicated, intubated and equipped with arterial and venous sheaths. After baseline echocardiography, haloperidol (0.1 mg/kg or 1.0 mg/kg) or saline control was infused 60 min prior to acute myocardial infarction (AMI). Left anterior descending coronary artery (LAD) was kept occluded for 120 min, followed by a 60 min reperfusion phase. **B**: Representative tracings depicting electrocardiogram (ECG), left ventricular monophasic action potentials (LV-MAP), right ventricular (RV) MAP, arterial blood pressure (art. BP), pulmonary artery pressure (PAP), and central venous pressure (CVP), before and after infusion of haloperidol (1.0 mg/kg), at baseline and during occlusion. Infusion of haloperidol decreased heart rate and blood pressure and prolonged MAP and QT interval. AMI resulted in ST elevation and local MAP shortening. PTCA: percutaneous transluminal coronary angioplasty. Black bar: 1 s.

throughout the procedure with continuous intravenous propofol 12.5 mg/h/kg (Propolipid 10 mg/ml, Fresenius Kabi AB, Uppsala, Sweden) and fentanyl 5 μg/h/kg (Fentanyl-Hameln 50 μg/ml, Hameln, Germany).

A 22 gauge arterial catheter was placed in the right femoral artery (Arrow arterial catherization set, SAC-01222, Arrow International Inc., Reading, USA) to measure arterial blood pressure. A mid-side 8 cm long cut was performed on the ventral side of the neck and two venous and two arterial 8 french sheaths (Check-Flo Performer Introducer, Cook Inc., Bloomington, USA) were placed. Electrocardiogram (ECG) was recorded in x-y-z configuration during the whole experiment using three BioAmps (AD Instruments, Dunedin, New Zealand). To measure pulmonary artery pressure and cardiac output (CO) a Swan-Ganz catheter (Swan-Ganz VIP, Edwards Lifesciences, Irvine, USA) was placed into the pulmonary artery.

Haloperidol (0.1 or 1.0 mg/kg) or saline as control was given according to randomization over 10 min, 60 min before AMI was induced via the atrial lumen of the Swan Ganz catheter. After a stabilization phase of 20 min, Franz electrodes (Easy MAP, Föhr Medical Instruments GmbH, Seeheim, Germany) to record monophasic action potentials (MAP) were placed at the free wall of the right and the infarcted area (apico-septal) of the left ventricle (LV).

An angiogram was performed using a Judkin's Left 3.5, 6 French catheter (Launcher, Medtronic Inc. Minneapolis, USA), positioned into the left main coronary artery. Following that, a balloon (3.5 × 12 mm, TREK, Abbott Vascular, Santa Clara, USA) was positioned into the left anterior descending artery at its mid position (after take-off of the first diagonal branch). A baseline echocardiography and CO measurement was done and the balloon was inflated with 12 bar and occlusion was confirmed by angiogram. Occlusion was maintained for 120 min followed by 60 min of reperfusion. Pigs were euthanized at the end of the experiment by inducing VF via burst pacing (50 Hz, 3 s, 7 V output).

2.2. Electrophysiology and hemodynamics

ECG, MAP and hemodynamic (blood pressure, central venous pressure and pulmonary artery pressure) were recorded continuously at a 2 kHz sampling rate (built-in hardware filter set to 0.1–2000 Hz) using AD Instruments PowerLab 16/30 (AD Instruments, Dunedin, New Zealand). RR, PQ, QT, corrected QT ($QTc = (QT/RR)^{1/3}$), and T_{peak} dispersion intervals as well as vector magnitude of ST elevation 60 s after the J point (STVM, with $STVM=(ST_x^2 + ST_y^2 + ST_z^2)^{1/2}$) and QRS duration. Parameters were manually measured before and after drug injection, before coronary occlusion and during occlusion at time points 1, 3, 5, 10, 15, 20, 30 and every 15 min during occlusion and reperfusion.

CO was measured by means of thermodilution via the Swan Ganz catheter before and after drug injection, before occlusion, and every 15 min during reperfusion and occlusion. Along with CO, blood pressure, central venous pressure and pulmonary artery pressure were measured. Systemic vascular resistance (SVR) was calculated according to *SVR = 80 (mean arterial pressure − central venous pressure)/CO*.

PVCs were manually counted for every minute and analyzed separately for their distinct peaks of occurrence, phase 1a and 1b [9]. More than three consecutive PVCs with a heart rate greater than 100 min^{-1} were defined as non-sustained ventricular tachycardia (VT) or VT when lasting for more than 30 s.

MAP recordings were used to measure APD duration at 90% of repolarization ($MAPD_{90}$) in the infarcted and non-infarcted area. Measurements were performed before occlusion and during the first 20 min of AMI. During the procedure, no repositioning of MAP electrodes was performed to avoid induction of arrhythmias or VF. Changes from baseline ($\Delta MAPD_{90}$) and $MAPD_{90}$ dispersion between the two electrodes ($|MAPD_{90,RV} - MAPD_{90,LV}|$) were calculated.

2.3. Dominant frequency analysis

Dominant frequency (DF) of VF was determined using fast Fourier transform (FFT). Analysis was performed using MATLAB (Version R2019a, MatWorks Inc.). ECG was imported into MATLAB and a FFT was performed using a 6-second sliding window with 3 s overlap. The DF was extracted from each FFT spectrum. DF values were compared in the first 30 s of the VF episode. Spontaneous VF episodes (n = 7, 3 and 2 for control, low dose and high dose group, respectively) and the combination of spontaneous and induced VF episodes (n = 11, 11 and 6) were analyzed.

2.4. Short-term variability

Beat-to-beat variation of repolarization (BVR) measured as short-term variability (STV) according to *Thomsen et al.* [12] was performed on MAP recordings in the LV. MAP duration were automatically analyzed and manually controlled using a custom-made software in MATLAB. Thirty consecutive beats in sinus rhythm without ectopic beats were selected for analysis at baseline (−5) and upon 15 min of AMI. Additionally, in the high dose haloperidol group MAP recordings before and after drug-infusion were available and analyzed (−60 and −50, respectively). MAP duration at 80% of repolarization ($MAPD_{80}$) was used to calculate short-term variability (STV) according to

$$STV = \sum_{n=1}^{30} |MAPD_{n+1} - MAPD_n| / (30\sqrt{2})$$

2.5. Echocardiography

Image acquisition was performed using an iE33 echocardiography system (Philips Healthcare, Amsterdam, The Netherlands) equipped with a S5-1 transducer (3.5 MHz, Philips Healthcare, Amsterdam, The Netherlands). A modified apical four-chamber view was performed using a *trans*-diaphragmal approach at baseline and at 0, 7, 15, and 30 min of occlusion. Tissue Doppler imaging was used to measure average s'-wave velocity. All examinations were stored externally and transferred to the vendor-specific workstation Philips Xcelera for post-processing analyzing. LV ejection fraction (LVEF) was calculated by one experienced reader using Simpson's method of discs by manually delineating the endocardial border in end-systole and end-diastole.

2.6. Statistics

Statistical analysis was done in R (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Data are shown as mean values and standard error of the mean. Electrophysiological and hemodynamic parameters as well as echocardiographic measurements were compared using a permutation test. Comparisons were performed to assess the effect of haloperidol before AMI (t = −50 to −5) and during occlusion (t = 1 to 15 for hemodynamic parameters, t = 1 to 20 for electrophysiological parameter). Freedom from VF was compared using a two-tailed permutation test based on the Log rank test statistic and an exact Fisher test. We considered a p-value of < 0.05 as statistically significant.

3. Results

Representative traces of ECG, MAP and hemodynamic recordings are depicted in Fig. 1B.

3.1. Electrophysiology

Temporal changes of the ECG parameters are shown for low and high dose haloperidol and control group in Fig. 2. Pigs treated with haloperidol had a trend towards longer RR intervals in a dose-dependent manner before AMI (control: 684 ± 36 ms, low dose: 773 ± 71 ms, high dose: 877 ± 71 ms; low dose versus control p = 0.331, high dose versus control p = 0.052) and during the first 20 min of AMI (control: 686 ± 35 ms, low dose: 713 ± 54 ms, high dose: 784 ± 55 ms; low dose versus control p = 0.331, high dose versus control p = 0.047, Fig. 2A). QRS complexes showed a transient widening during AMI, comparable in the three groups (low dose versus control p = 0.58, high dose versus control p = 0.139, Fig. 2B). QT intervals were prolonged in the high dose group (before AMI: control: 339 ± 13 ms, low dose: 334 ± 11 ms, high dose: 382 ± 10 ms; high dose versus control p = 0.007, during AMI: control: 330 ± 15 ms, low dose: 321 ± 12 ms, high dose: 379 ± 12 ms; high dose versus control p = 0.012; Fig. 2C). Similar behavior was observed after correcting for heart rate (before AMI: control: 385 ± 11 ms, low dose: 374 ± 11 ms, high dose: 402 ± 16 ms; during AMI: control: 375 ± 15 ms, low dose: 358 ± 11 ms, high dose: 421 ± 10 ms; Fig. 2D). No QT prolongation was seen in the low dose group (low dose versus control p = 0.871 at baseline, low dose versus control p = 0.788 during AMI). T_{peak} dispersion increased with high dose haloperidol treatment (before AMI: control: 8 ± 2 ms, low dose: 7 ± 2 ms, high dose: 10 ± 3 ms; during AMI (t = 5): control: 18 ± 5 ms, low dose: 14 ± 4 ms, high dose: 58 ± 6 ms; during AMI (t = 20): control: 14 ± 5 ms, low dose: 20 ± 6 ms, high dose: 49 ± 6 ms).

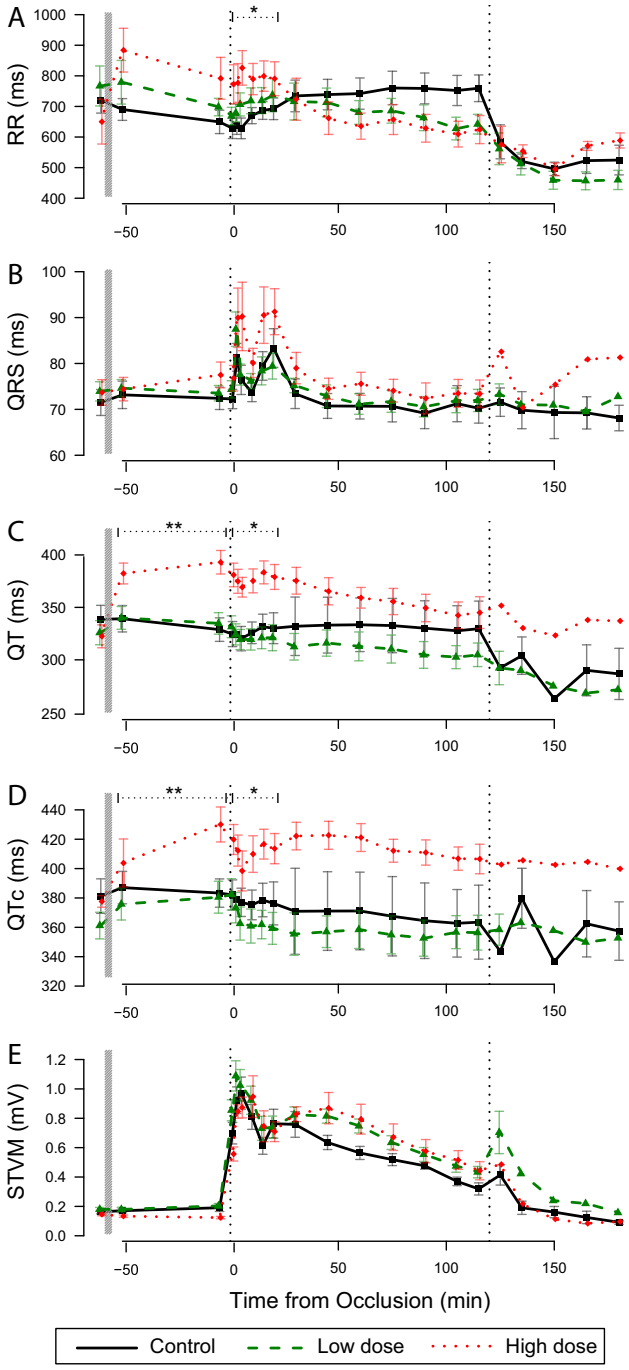

Fig. 2. *Electrocardiogram (ECG) parameters.* **A**: RR intervals with a trend towards longer RR interval for the high dose group before and during the first 20 min of AMI. **B**: Infarct related changes in QRS width were comparable in the three groups. **C** and **D**: High dose haloperidol prolonged QT with similar effects for QTc while no effect was seen with low dose haloperidol. **E**: ST elevation was comparable for all three groups during occlusion and reperfusion. Gray bar indicates treatment with low dose haloperidol, high dose haloperidol or vehicle. Significance level: high dose vs. control, * $p < 0.05$, ** $p < 0.01$.

All pigs had ST elevation after induction of AMI that occurred in three peaks, two during occlusion (approximately at 10 and 45 min after onset of AMI) and one immediately after reperfusion occurred. ST elevation, measured as STVM was not changed by low or high dose haloperidol treatment (p = 0.102 and p = 0.719, respectively, Fig. 2E).

In order to investigate effects of haloperidol on the ventricular electrophysiology we analyzed $MAPD_{90}$ and the change of $MAPD_{90}$ compared to baseline ($\Delta MAPD_{90}$) for the infarcted and non-infarcted area. $MAPD_{90}$ was prolonged at baseline in the high dose haloperidol group (high dose versus control p = 0.007, Fig. 3A). AMI caused a shortening of $MAPD_{90}$ in the infarcted area, but $\Delta MAPD_{90}$ was similar for low and high dose haloperidol and control group (low dose versus control p = 0.504, high dose versus control p = 0.465, Fig. 3B). No changes with AMI occurred in the non-infarcted area (Fig. 3A). Dispersion of $MAPD_{90}$ between RV and LV showed only a tendency towards higher dispersion in the low dose and high dose haloperidol group at baseline: 10 ± 3 ms, 17 ± 4 ms, and 15 ± 4 ms for control, low dose, and high dose group, respectively (low dose versus control p = 0.258, high dose versus control p = 0.468).

STV, a parameter predictive of TdP slightly increased with high dose haloperidol infusion from 0.7 ± 0.2 ms to 1.0 ± 0.3 ms, but returned to baseline before AMI was induced. AMI increased STV within 15 min of occlusion, similar in the three groups (baseline 0.5 ± 0.1 ms; 15 min of AMI 1.1 ± 0.5 ms, 2.1 ± 0.5 ms and 2.0 ± 1. 0 ms for control, low dose, and high dose haloperidol group, respectively; low dose versus control p = 0.226 and high dose versus control p = 0.488, Fig. 4).

3.2. Hemodynamics

Effects of haloperidol on SVR, mean arterial blood pressure, heart rate, and CO were measured at baseline and during AMI (Fig. 5). Haloperidol led to vasodilatation, measured as decreased SVR in the high dose group. A drop in SVR was observed before AMI was induced (low dose versus control p = 0.738, high dose versus control p = 0.013) and during the first 15 min of AMI (low dose versus control p = 0.125, high dose versus control p = 0.014, Fig. 5A). This resulted in a dose-dependent drop in blood pressure before AMI was induced (low dose versus control p = 0.330, high dose versus control p < 0.001) and during the first 15 min of AMI (low dose versus control p = 0.125, high dose versus control p = 0.004, Fig. 5B). CO was not affected by haloperidol treatment

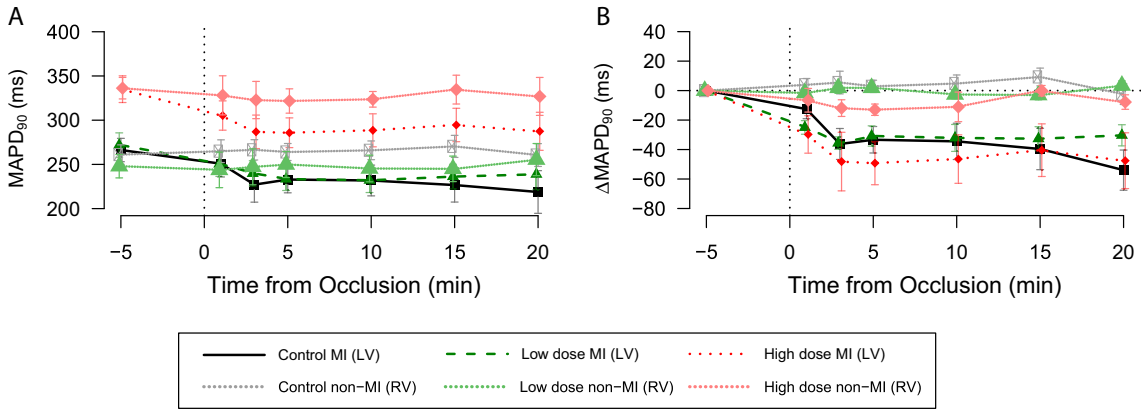

Fig. 3. *Monophasic action potentials* **A**: monophasic action potential duration at 90% of repolarization ($MAPD_{90}$) **B**: Similar change of $MAPD_{90}$ from baseline ($\Delta MAPD_{90}$) for infarcted and non-infarcted area in low and high dose, and control group.

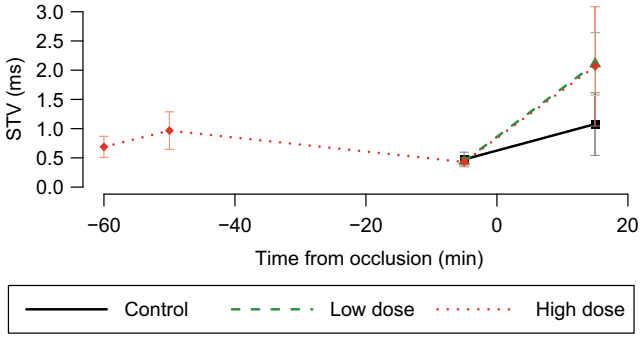

Fig. 4. *Short-term variability (STV).* Infusion with high dose haloperidol (from t = −60 to −50) increased STV. Also acute myocardial infarction increased STV, with a tendency towards increased STV with haloperidol (low dose versus control p = 0.226 and high dose versus control p = 0.488).

before AMI (low dose versus control p = 0.920, high dose versus control p = 0.368) or during AMI (low dose versus control p = 0.733, high dose versus control p = 0.662, Fig. 5D). In the high dose group, CO increased due to higher heart rate after the first 30 min of AMI and led to an increase in arterial blood pressure while SVR stayed unchanged.

3.3. Arrhythmia

Arrhythmias during AMI were assessed for control and haloperidol groups. The distribution of PVCs during myocardial infarction is shown in Fig. 6A. The mean number of PVCs per minute in phase 1a (2–15 min from occlusion; 4.3 ± 1.1, 3.2 ± 1.2, 6.7 ± 2.5; control, low dose, high dose) was neither statistically different for low dose versus control group (p = 0.492), nor for high dose versus control group (p = 0.404). PVCs in phase 1b (16–30 min from occlusion; 6.1 ± 1.2, 4.2 ± 1.1, 1.5 ± 0.7; control, low dose, high dose) were reduced with high dose haloperidol (p = 0.001), but not different for low dose and control (p = 0.26).

We did not observe non-sustained VT exceeding 10 beats or VT during coronary occlusion. Reopening of the coronary occlusion led to reperfusion arrhythmia, an idioventricular rhythm with cycle lengths of approximately 500 ms or above, in all animals covering the whole reperfusion period.

VF during AMI occurred in 27% (3/11), 33% (2/6), and 64% (7/11) of pigs in low dose, high dose and control groups, respectively (Fisher's exact test: low dose versus control p = 0.198, high dose versus control p = 0.335; Permutation test based on the Log rank test statistic: low dose versus control p = 0.197, high dose versus control p = 0.122). Overall, VF occurred in 11 out of 12 cases between 15 and 25 min after coronary occlusion was initiated (Fig. 6B). DF during spontaneous VF was significantly lower in the high dose haloperidol group (p = 0.037) compared to control while no difference was observed with low dose treatment (p = 0.668, Fig. 6C and 7A). When including animals with induced VF at the end of the experiment the high dose haloperidol group still had a lower DF (p = 0.043). No difference with low dose haloperidol treatment compared to control was observed (p = 0.450, Fig. 7B). None of the pigs had VF during the reperfusion period. Hemodynamic characteristics of the individual pigs prior to VF are given in Table 1.

Stratifying our results into pigs with and without VF revealed trends towards possible characteristics that differ between these groups (figure S1). Pigs that developed VF had a tendency towards shorter RR, and QT_{peak} intervals, longer PQ, QRS, and $T_{peak} - T_{end}$ intervals, as well as higher STVM. Hemodynamically, higher blood pressure (diastolic, mean and systolic), and SVR was seen in pigs with VF during AMI.

3.4. Echocardiography

LVEF was measured along with CO to assess impairment of cardiac function during AMI and decreased equally within the first minutes of AMI in all groups (low dose versus control p = 0.998, high dose versus control p = 0.790, Fig. 8B). Results from tissue Doppler imaging showed a decrease in average s'-wave velocity with AMI, comparable between the groups (low dose versus control p = 0.863, high dose versus control p = 0.967, Fig. 8C).

4. Discussion

The aim of this study was to investigate the effect of haloperidol on electrophysiological properties, arrhythmia, and hemodynamics during AMI. AMI alone led to changes in RR, QRS, and STVM, shortening of $MAPD_{90}$, increase in STV, drop in blood pressure and CO as well as ventricular arrhythmias. Haloperidol (1.0 mg/kg), given one hour prior to AMI prolonged RR, QT and QTc intervals and decreased mean arterial blood pressure and SVR compared to AMI alone. Further, $MAPD_{90}$ was prolonged at baseline, with similar shortening to control during AMI. Haloperidol did not result in a higher proportion of pigs developing VF during two hours of occlusion and one hour of reperfusion, but on the contrary showed a tendency towards lower VF incidence and fewer PVCs in phase 1b.

Treatment with antipsychotic drugs increase the risk of both SCD and out-of-hospital cardiac arrest in a dose dependent manner

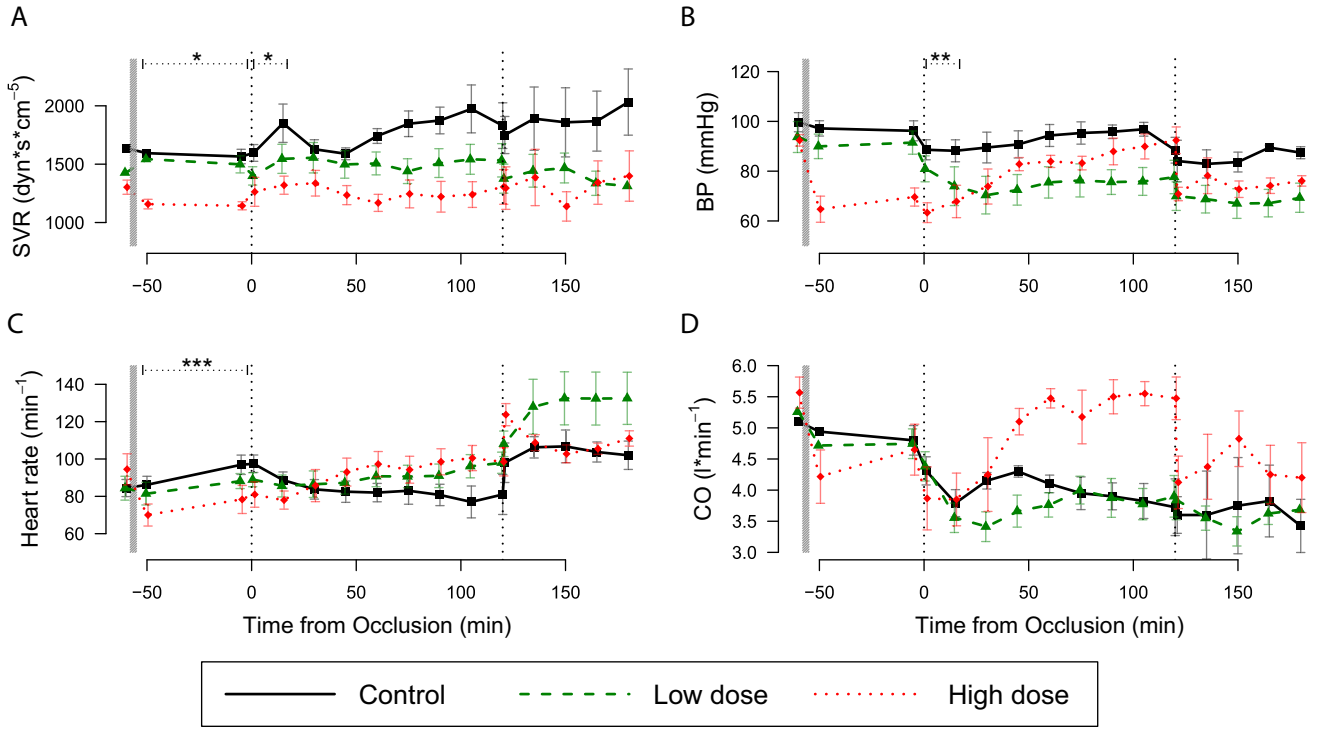

Fig. 5. *Hemodynamic parameters.* **A**: High dose haloperidol decreased systemic vascular resistance (SVR) before and during the first 15 min of coronary occlusion **B**: High dose haloperidol significantly decreased mean arterial pressure before coronary occlusion and during the first 15 min of coronary occlusion. **C**: During AMI, heart rate increased to compensate during AMI with haloperidol treatment **D**: Cardiac output. Gray bar indicates treatment with low dose haloperidol, high dose haloperidol or vehicle. Significance level: high dose vs. control *p < 0.05, **p < 0.01, ***p < 0.001.

[13,14]. Certain risk factors have been suggested to contribute to this excess mortality, like female gender, heart disease, concomitant drug and high doses [11]. We sought to investigate whether treatment with haloperidol increases the chance of experiencing ventricular arrhythmia and subsequent VF during AMI.

4.1. QT prolongation and dose dependence

High dose haloperidol treatment resulted in a prolongation of QT-intervals that started ten minutes after infusion and QT-intervals stayed prolonged following AMI. Low dose haloperidol treatment or AMI did not affect QT interval significantly. QT prolongation and increased dispersion in repolarization that eventually lead to TdP are the suspected pro-arrhythmic mechanisms underlying SCD in patients taking antipsychotic drugs. Many studies investigating those found only moderate or no QT prolongation for haloperidol [15]. Vieweg *et al.* reviewed cases of QT prolongation focusing on elderly patients taking psychotropic drugs. In many cases where psychotropic drugs led to QT prolongation, higher drug doses than recommended were used [16]. Although many patients with TdP have used haloperidol dosages of several hundred mg daily or even more than one gram daily, some cases occurred at lower doses, i.e. 9–35 mg [6]. Sugiyama *et al.* tested three different doses of haloperidol (0.03, 0.3 and 3 mg/kg, infused over 10 min) in a canine model and found effects on QT and QTc starting at doses of 0.3 mg/kg [17]. In a porcine model, Tisdale *et al.* did not detect a significant influence of haloperidol (2–3.3 mg/kg) on heart rate, QRS duration or QTc interval [18].

We have used two different haloperidol doses in our experiments. The dose of 0.1 mg/kg haloperidol, approximately 5 mg per pig, was chosen since starting doses for moderate agitation in humans are recommended to be 5 to 10 mg and this dose is known to increase risk for SCD [5,13,19]. A high dose of 1.0 mg/kg haloperidol, approximately 50 mg per pig, was used as high doses are regularly used in clinics for acute management of delirium [11,20].

4.2. Arrhythmias and AMI moderated substrate and triggers

Our study did not show higher incidence rates of VF with haloperidol compared to AMI alone. On the contrary, a tendency towards fewer animals with VF was seen with haloperidol treatment: Only 27% (3/11) of the pigs treated with low dose haloperidol and 33% (2/6) treated with high dose haloperidol compared to 64% (7/11) in the control group, experienced VF. While no studies in large animal models with ischemia and haloperidol exist, Davis and Bigger reported the effects of thioridazine, another antipsychotic drug and a potent hERG channel blocker, on VF during AMI in dogs. Although thioridazine reduced heart rate and decreased excitability in the ventricle without altering VF threshold, an increased number of dogs experienced VF during AMI compared to control [21]. In the context of haloperidol, Tisdal *et al.* found that altering VF threshold in pigs after intravenous haloperidol (2–3.3 mg/kg) treatment, was increased 15 min after infusion, making an induction of VF more difficult [18]. In humans, Park *et al.* reported an increased risk of in-hospital death in AMI patients with acute delirium when treated with haloperidol compared to atypical antipsychotic drugs [22]. However, treatment in this cohort study was started after AMI and patients with haloperidol treatment before AMI were excluded in the analysis. This limits comparison with our data as electrophysiological properties change considerably within the first days of AMI [9].

Arrhythmia can arise if a certain trigger hits an arrhythmogenic substrate. AMI on the one side, can induce such proarrhythmic conditions by local shortening of APD, slowing of conduction, triggering of PVCs, increased sympathetic tone, and increased disper-

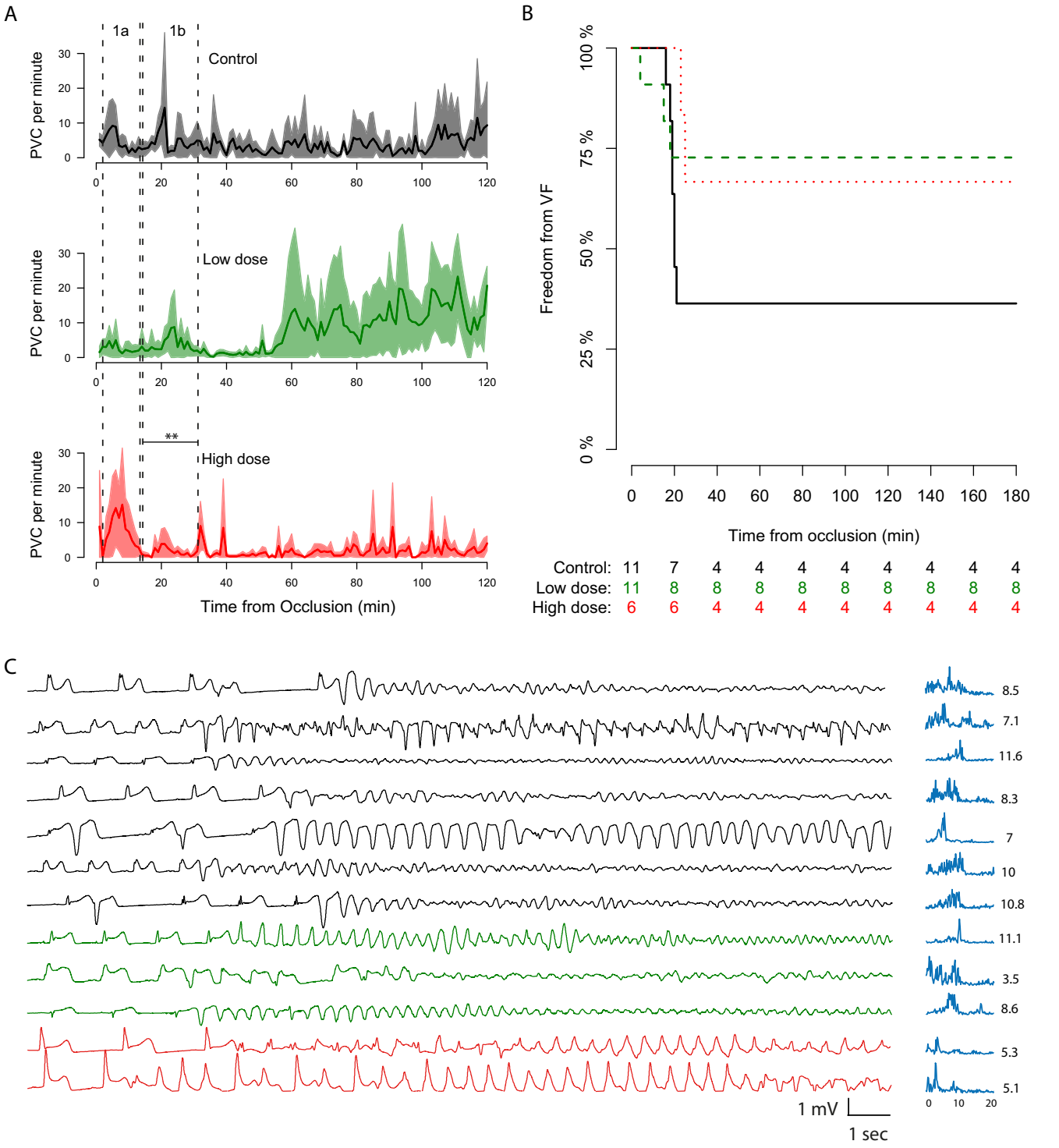

Fig. 6. *Arrhythmia*. **A**: Distribution of premature ventricular contractions (PVCs) during coronary occlusion (solid lines indicate mean, shaded areas standard error of the mean). No differences between low dose, high dose and control were observed during phase 1a (2–15 min from occlusion). High dose haloperidol resulted in fewer PVCs in phase 1b (16–30 min from occlusion). **B**: Similar incidence rates of ventricular fibrillation (VF) in low dose, high dose and control group. **C**: ECG traces of spontaneous VF during occlusion and frequency spectrum (in Hz) with dominant frequency of the depicted VF episode. Significance level: $^{**}p < 0.01$.

sion in activation and repolarization [9]. In cardiomyocytes, ischemia leads to an increase in outward potassium currents, a decrease in sodium current and a depolarized resting membrane potential [23].

Antipsychotic drugs on the other side, are likely to induce TdP tachycardia when a high dispersion of repolarization is present [24]. Simultaneously firing multiple foci generating early after depolarizations are believed to underlie the generation of TdP. Mechanisms underlying subsequent beats is thought to be reentry in a ventricle with high inhomogeneity of refractoriness [25]. In patients, episodes of TdP are often described to happen in situations of physical or emotional stress and are enhanced by beta-adrenergic agonists [26]. Although not typically seen with ischemia or AMI, short runs of TdP-like ventricular tachycardia

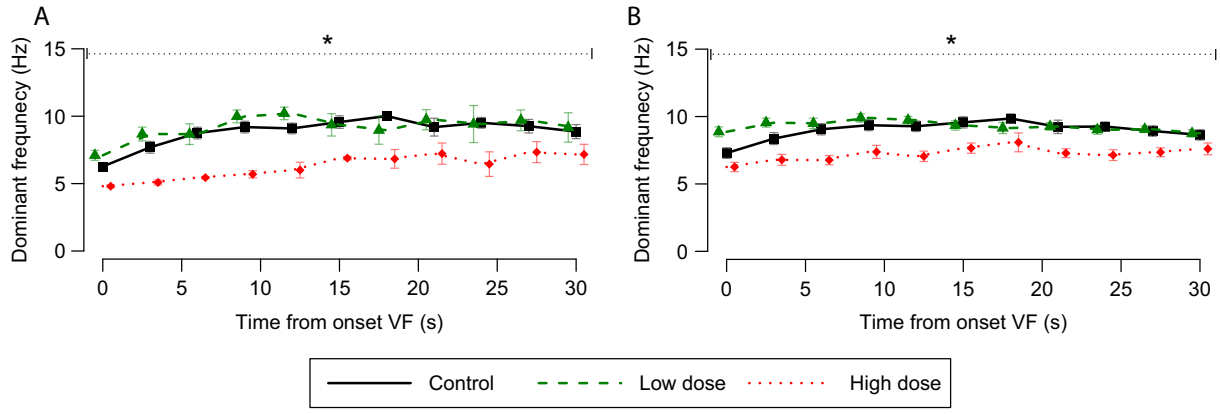

Fig. 7. *Dominant frequency* in spontaneous occurring ventricular fibrillation (VF) was lower with high dose haloperidol compared to control (A), and in spontaneous and induced VF combined (B). *, $p < 0.05$.

Table 1
Characteristics of ventricular fibrillation.

	Prior to VF			
	HR (min^{-1})	BP (mmHg)	Lactate (mmol/l)	Time to VF (min)
Control	71	116/79 (91)	1.1	18
	110	85/48 (60)	1.8	20
	106	123/83 (96)	0.6	20
	78	95/56 (69)	0.9	19
	120	119/78 (92)	1.9	21
	113	130/90 (103)	1.6	19
	95	111/74 (86)	0.8	16
	99 ± 6.5	111/73(85) ± 6/5(5)	1.2 ± 0.2	19 ± 0.6
Haloperidol 0.1 mg/kg	98	111/75 (87)	1.9	15
	90	104/71 (82)	0.8	4
	81	120/79 (93)	0.7	18
	89 ± 4.0	112/75 (87) ± 4/2(3)	1.1 ± 0.3	12 ± 3.4
Haloperidol 1.0 mg/kg	62	95/45 (62)	1.2	25
	80	88/47 (61)	1.9	23
	71 ± 6	91/46(62) ± 2/1(1)	1.6 ± 0.2	24 ± 0.7

HR: Heart rate, BP: Arterial blood pressure (systolic/diastolic (mean)), VF: ventricular fibrillation.

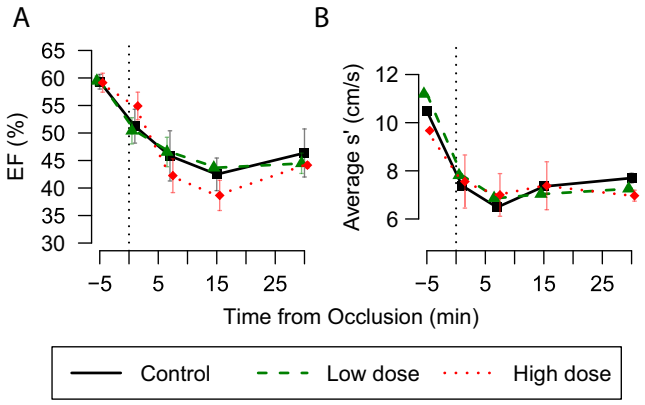

Fig. 8. *Echocardiography*. **A**: Similar ejection fraction (EF) and (**B**) average s'-wave velocity measured during AMI in the control and haloperidol group, respectively.

that rapidly degenerated into VF have been described in canine models [25].

In our experiments, high dose haloperidol prolonged $MAPD_{90}$ compared to control. The AMI induced $MAPD_{90}$ shortening in the infarcted area was comparable in low dose, high dose and control group. However, experiments on explanted papillary muscles from guinea pigs suggest that ischemia induced shortening of APD can be partially prevented with haloperidol [27]. We observed a trend towards higher RV-LV dispersion in repolarization with haloperidol before AMI was induced, as previously described in Langendorff perfused rat hearts, where haloperidol increased local dispersion of repolarization [28], that resolved during AMI. Thomsen *et al.* suggested that BVR, a measure of temporal dispersion of repolarization, might be of even greater importance in predicting TdP than QT prolongation [12,29]. In our study, BVR (measured as STV) increased slightly immediately after high dose haloperidol was administered. However, STV was not different between the groups before AMI induction or upon AMI, although AMI itself increased STV.

PVCs during AMI occur in distinct phases with an early (1a) and a later phase (1b) that can be identified within the first 30 min [9]. As we found VF to arise exclusively in the first 30 min in the porcine AMI model, we focused on phase 1a and 1b arrhythmias. No differences in PVCs with haloperidol in phase 1a could be observed, while PVCs in phase 1b were reduced in the high dose group. Arrhythmias in phase 1b are linked to catecholamine levels in the infarcted area and blockage of α_1-adrenergic receptor reduced ventricular arrhythmias [30]. Haloperidol has antagonistic α_1-adrenergic receptor properties that could potentially explain the trend towards antiarrhythmic effects observed. Mow *et al.* reported anti-arrhythmic effects of antipsychotic drugs that depend on their potency of α1-adrenergic receptor affinities [31].

Besides the substrate and triggers, VF itself was changed with haloperidol treatment. The dominant frequency of VF was reduced with high dose haloperidol, suggesting slowing in ventricular repolarization and/or conduction.

4.3. Hemodynamic effects

We observed a dose-dependent reduction in arterial blood pressure after haloperidol infusion that was further aggravated during AMI in the high dose group. As CO and EF was comparable between all three groups, the decrease in blood pressure was due to decreased SVR. The α_1-adrenergic receptor antagonistic effects of haloperidol resulted in blood pressure drop as previously described [17,18]. Hence, it can be speculated that the reduction in cardiac afterload with haloperidol can reduce the work and oxygen consumption of the infarcted heart and thereby have anti-arrhythmic properties.

4.4. Limitations

All experiments were carried out in general anesthesia which can have substantial effects on the autonomic system. Our study investigated a single treatment with haloperidol administered an hour before AMI. Effects of long-term drug intake or polypharmacy was not studied. Long-term treatment could potentially alter ion-channel expression to compensate for chronic hERG blockage or weaken effects on SVR and blood pressure. We solely investigated haloperidol in the setting of AMI, while treatment with the drug during the days following AMI, when electrophysiology is different or heart failure might be present, was not studied.

Changes in the electrophysiological parameters can differ greatly between different regions of the heart. In our study, we only used two MAP electrodes to measure changes in APD with haloperidol and during AMI. Whole-heart mapping techniques could provide further insights into electrical dispersion.

Plasma or tissue levels of haloperidol concentration were not measured during the experiments. We did not measure infarct size directly in our experiments but only used indirect markers, like STVM. However, to ensure an equally distributed infarct size the occlusion was performed blinded in regard to treatment group.

Experiments were performed in a porcine model of acute ischemia. This model is well established in our group and widely used in ischemia research, although with differences in the conduction system compared to humans [23]. Furthermore the use of dogs is fairly restricted at our research institution. Research on TdP has predominantly been carried out in guinea pigs, rabbits and dogs, while porcine models have been used rarely, making comparison to other studies more difficult [25,32].

5. Conclusion

Haloperidol, administered before AMI, did not lead to a higher incidence of VF in our porcine model. With regard to hemodynamic parameters, we observed a reduced SVR leading to a reduction in blood pressure with haloperidol treatment. Although high dose haloperidol treatment led to prolonged QT intervals, no TdP was induced by PVCs. Further, we saw a significant reduction in number of PVCs in phase 1b.

We could not identify an increased risk of VF and subsequent SCD during AMI in pigs treated with the antipsychotic drug haloperidol. Haloperidol's α_1-adrenergic receptor blocking effect with subsequent reduced cardiac afterload might counterbalance the potential arrhythmic effects of hERG channel blockage in this setting. It could be argued that this blockage in combination with a mild QT prolongation is protective of VF in the early phase of AMI. Of course this needs further pre-clinical testing. Our study does not suggest that AMI might contribute to the excess mortality in patients treated with antipsychotic drugs as seen in epidemiological studies. However, further studies, including long-term haloperidol treatment before AMI is induced and haloperidol treatment during the days following AMI, are needed.

CRediT authorship contribution statement

Stefan M. Sattler: Conceptualization, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Anniek F. Lubberding:** Conceptualization, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Charlotte B. Kristensen:** Investigation, Methodology, Writing - review & editing. **Rasmus Møgelvang:** Methodology, Writing - review & editing. **Paul Blanche:** Software, Methodology, Writing - review & editing. **Anders Fink-Jensen:** Funding acquisition, Writing - review & editing. **Thomas Engstrøm:** Project administration, Writing - review & editing. **Stefan Kääb:** Project administration, Writing - review & editing. **Thomas Jespersen:** Project administration, Conceptualization, Funding acquisition, Writing - review & editing. **Jacob Tfelt-Hansen:** Project administration, Conceptualization, Funding acquisition, Writing - review & editing.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100455.

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