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RESEARCH ARTICLE | *Translational Physiology*

Comparison of hemodynamics, cardiac electrophysiology, and ventricular arrhythmia in an open- and a closed-chest porcine model of acute myocardial infarction

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Lubberding AF, Sattler SM, Flethøj M, Tfelt-Hansen J, Jespersen T. Comparison of hemodynamics, cardiac electrophysiology, and ventricular arrhythmia in an open- and a closed-chest porcine model of acute myocardial infarction. *Am J Physiol Heart Circ Physiol* 318: H391–H400, 2020. First published January 10, 2020; doi:10.1152/ajpheart.00406.2019.—Ventricular fibrillation (VF) during acute myocardial infarction (AMI) is an important contributor to sudden cardiac death. Large animal models are widely used to study AMI-induced arrhythmia, but the mode of AMI induction ranges from thoracotomy and surgical ligation of a coronary vessel (open chest) to minimally invasive techniques, including balloon occlusion (closed chest). How the choice of induction affects arrhythmia development is unclear. The aim of this study was to compare an open-chest and a closed-chest model with regard to hemodynamics, electrophysiology, and arrhythmia development. Forty-two female Danish Landrace pigs (20 open chest, 22 closed chest) were anesthetized, and occlusion of the mid-left anterior descending coronary artery was performed for 60 min. Opening the chest reduced blood pressure and cardiac output (Δ −22 mmHg, Δ −1.5 L/min from baseline, both $P < 0.001$ intragroup). Heart rate decreased with opening of the chest but increased with balloon placement ($P < 0.001$). AMI-induced ST elevation was lower in the open-chest group ($P < 0.001$). Premature ventricular contractions occurred in two distinct phases (0–15 and 15–40 min), the latter of which was delayed in the open-chest group ($P = 0.005$). VF occurred in 7 out of 20 and 12 out of 22 pigs in the open-chest and closed-chest groups, respectively ($P = 0.337$), with longer time-to-VF in the open-chest group (23.4 ± 1.2 min in open chest and 17.8 ± 1.4 min in closed chest; $P = 0.007$). In summary, opening the chest altered hemodynamic parameters and delayed the onset of ventricular arrhythmias. Hence, in the search for mechanisms and novel treatments of AMI-induced arrhythmia, caution should be taken when choosing between or comparing the results from these two models.

NEW & NOTEWORTHY We demonstrated pronounced differences in hemodynamic parameters and time course of ventricular arrhythmias in regard to mode of infarct induction. Inducing myocardial infarction by thoracotomy and subsequent ligation decreased blood pressure and cardiac output and delayed the onset of ventricular arrhythmia, whereas balloon occlusion resulted in higher heart rates during infarct.

acute myocardial infarction; animal model; arrhythmia; closed chest; open chest; ventricular fibrillation

INTRODUCTION

Acute myocardial infarction (AMI) is complicated by ventricular fibrillation (VF) in ~10% of all cases, making it a major cause of sudden cardiac death (SCD) in the Western world (12). This emphasizes the need for a better understanding of the pathophysiological processes involved in AMI-induced arrhythmia, new treatment strategies, and the development of improved risk prediction models.

Large animal models provide a key step in the translation of basic and preclinical research to the human setting (23). However, given the large variety of AMI models (including strain, sex, used anesthetics, and mode and site of occlusion), results are difficult to compare and consequently difficult to translate to the human setting. Despite the wide range of variations in AMI models, infarct induction is either performed on an open or a closed chest. The former requires thoracotomy to visualize and isolate a coronary artery for ligation. An open chest can also be necessary to obtain direct access to the heart to perform various procedures, including myocardial injections, microdialysis, and epicardial electrode placement. Thoracotomy is known to alter thoracic pressure and cardiac filling (19) and was recently shown to result in reduced infarct size and improve left ventricular function during follow up (31). With the introduction of catheter-based techniques more than 30 yr ago, a minimally invasive approach became available (10, 20, 25).

Despite the wide usage of both models seemingly interchangeably within the field, no study has compared the arrhythmic development during the early phase of AMI in these two models in the absence of antiarrhythmic drugs. Ventricular arrhythmia development during AMI is caused by a variety of concomitant variables, including ion concentration imbalance and low ATP, heterogeneity in repolarization and conduction, as well as mechanical factors such as left ventricular wall stretching (3). We can anticipate that these variables may be different in an open-chest configuration compared with a closed-chest configuration. For example, changes in thoracic pressure and a concomitant decrease in mean arterial pressure (31) may induce changes in left ventricular pressure and

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myocardial stretch, but they may also reduce workload and oxygen demand and relieve the myocardium. The combination of these changes may impact arrhythmogenesis in the early phase of AMI. Awareness of these differences is crucial for choosing and interpreting data when studying AMI-induced arrhythmia, but to our knowledge, no direct comparison exists.

Therefore, the aim of the present study was to compare an open- and a closed-chest AMI model with regard to hemodynamics, electrophysiology, and arrhythmia development. We hypothesized that opening the chest and pericardium would influence hemodynamics as well as the incidence and time course of arrhythmias, including premature ventricular contractions (PVC), ventricular tachycardia (VT), and VF during the early phase of AMI.

METHODS

From January 2016 to October 2017, experiments on 94 female Danish Landrace pigs (~15 wk old and weighing 50 kg) were performed by two of the authors (S. M. Sattler and A. F. Lubberding) to determine the effect of different drugs on VF during ≥60 min of coronary occlusion. All pigs were randomized into treatment or control groups the day before the experiment using a randomization list. The combined control groups consisted of 47 pigs. After excluding pigs with pericarditis ($n = 1$) or procedural failure before AMI was induced ($n = 4$), 42 pigs were included in the present study. The open-chest group consisted of 20 pigs, and the closed-chest group consisted of 22 pigs. An overview on the study procedure is given in Fig. 1*A*.

Animals were stabled together in pens for at least 1 wk before experiments and fed according to requirements. All experiments were authorized by the Danish Animal Inspectorate in accordance with European Union legislations for animal protection and care and carried out under license number 2015-15-0201-00613. The experiments are reported in accordance with the ARRIVE guidelines modified for ischemia studies (21).

Procedure

All pigs were treated equally apart from the mode of infarct induction (Fig. 1*B*). Pigs were premedicated in their pens by intramuscular injection with 5 mL tiletamine-zolazepam (50 mg/mL; Zoletil 50 Vet, Virbac Danmark, Denmark), 6.25 mL xylazine (20 mg/mL; ScanVet Animal Health, Denmark), 1.25 mL ketamine (100 mg/mL; MSD Animal Health, Denmark), 2.0 mL butorphanol (10 mg/mL; Biovet, Denmark), and 2 mL methadone (10 mg/mL; Dechra Veterinary Products, Denmark) and brought to the operation theater. Anesthesia was maintained with continuous intravenous infusion of 12.5 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol (10 mg/mL Propolipid; Fresenius Kabi, Sweden) and 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl (50 μg/mL Fentanyl-Hameln; Germany). Pigs were intubated and ventilated in volume-controlled mode (tidal volume 10 mL/kg, frequency 14/min, and inspirational concentration of oxygen 0.3) using a Siesta I TS ventilator (Dameca, Denmark). An arterial catheter (22-gauge; Arrow International) was inserted into a femoral artery for continuous arterial blood pressure measurement. Arterial blood gas measurements [including acid base homeostasis, partial pressure of O_2 (Po_2), CO_2, electrolytes, glucose, and lactate] were performed with a bedside analyzer (ABL-90, Radiometer, Denmark) during the experiment, and ventilation was adjusted if necessary.

The internal jugular vein (on the left side for the open-chest and on both sides for the closed-chest procedure) and carotid arteries on both sides were dissected free and 8-French sheaths (Check-Flo Performer Introducer, Cook) were implanted. Before further placement of catheters, 10,000 IU heparin (Heparin LEO 5,000 IU/mL, Leopharma, Denmark) was administered. A Swan-Ganz catheter (Swan-Ganz VIP, Edwards Lifesciences) was placed into the pulmonary vein until wedge position was reached. The catheter was used to continuously measure central venous pressure (CVP) and pulmonary artery pressure (PAP). Cardiac output (CO) measurements were made by thermo dilution (REF-1, Baxter International) at baseline, before occlusion, and every 15 min during occlusion together with wedge pressure. All pressure measurements were continuously monitored using a patient monitor (Agilent, Hewlett-Packard, Santa Clara, CA) and subsequently recorded with a PowerLab 16/30 (AD Instruments, New

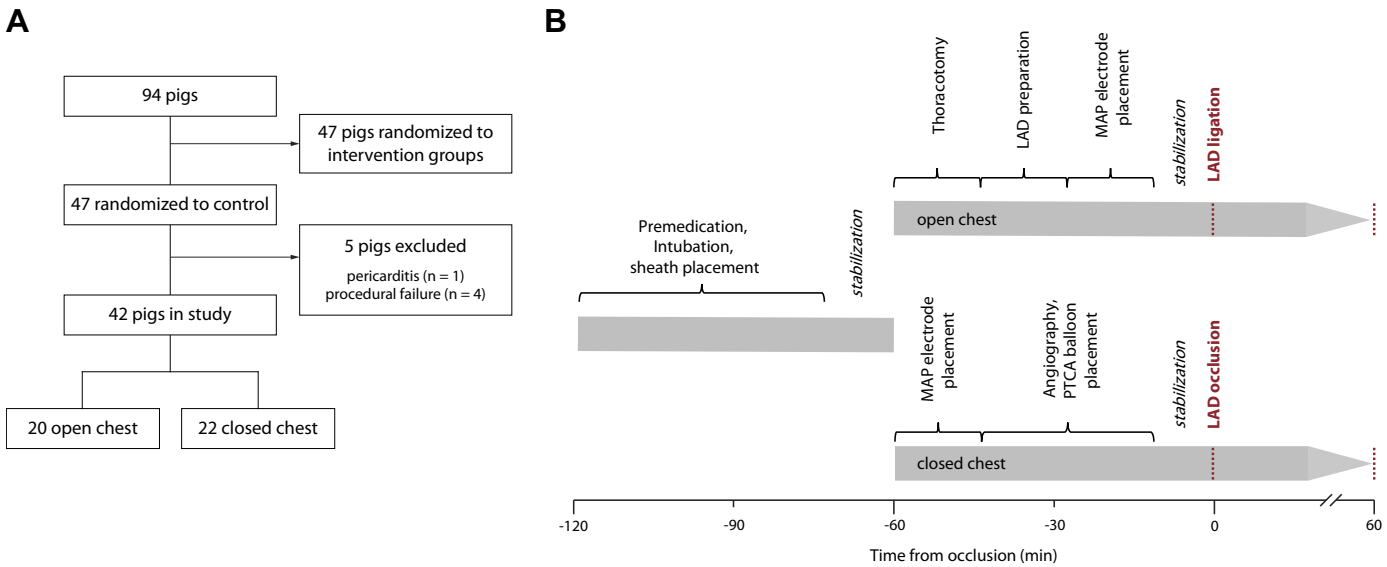

Fig. 1. Experimental design and time line. In this study, 47 pigs randomized to control group were used. After excluding diseased pigs or procedure failure, 42 pigs were included in the study (*A*). After preparation of pigs, either thoracotomy with dissection of the left anterior descending coronary artery (LAD) (upper pathway) or an angiogram and placement of a balloon catheter (lower pathway) was performed (*B*). MAP, monophasic action potential; PTCA, percutaneous transluminal coronary angioplasty.

Zealand). The temperature was kept stable at 37 ± 0.5°C throughout the whole procedure.

Open-chest procedure. In the open-chest procedure, a midline incision along the sternum and surgical preparation toward the sternum were performed, with electrical coagulation where necessary. Before the sternum was cut along its midline, the pericardium was dissected free using the index finger. The sternum was then cut and spread ~5–8 cm. To record monophasic action potentials (MAP) in the noninfarcted and infarcted tissue, two Franz electrode catheters (Easy MAP, Föhr Medical Instruments, Germany) were placed into the lateral and apical-septal regions of the left ventricle, respectively, under fluoroscopic guidance. The pericardium was cut open 5–8 cm, and the left anterior descending artery (LAD) was isolated at the midline. A ligature with Ethicon 2-0 Vicryl suture (Johnson & Johnson) was placed around the LAD, allowing for occlusion of the vessel against a counter bearing. To apply pressure, the two ends of the ligature were led through a flexible tube and a hemostat was used to tighten the ligature. The ligature was tightened and occlusion was confirmed by collapsed distal LAD and changes on the electrocardiogram (ECG).

Closed-chest procedure. In the closed-chest procedure, one Franz electrode was placed in the apical-septal region of the left ventricle for measurement of MAPs in the infarcted region. Because the other arterial access was used for angiogram and balloon placement, the second Franz electrode was placed in the free wall of the right ventricle for measurement of MAPs in the noninfarcted region. An angiogram was performed using a Judkins Left 3.5, 6-French catheter (Launcher, Medtronic, Minneapolis, MN), positioned into the left main coronary artery by injecting 10 mL Iomeron (350 mg iodine/mL Iomeron, Braco Imaging, Milano, Italy). The LAD and its midposition were identified and a percutaneous transluminal coronary angioplasty (PTCA) wire (PT Graphics, Boston Scientific, Natick, MA) was placed into the LAD. A PTCA balloon (3.5 × 12 mm; TREK, Abbott Vascular, Santa Clara, CA) was positioned into the LAD at its mid position, the balloon was inflated with 12 bar, and occlusion was confirmed by angiogram. The guiding catheter was pulled back into the ascending aorta to avoid flow reduction in the left main coronary artery.

Electrophysiology and Hemodynamic Measurements

A bipolar vector ECG was recorded in *x-y-z* configuration (0.1–1,000 Hz hardware filtering) with three BioAmps (AD Instruments, New Zealand). The MAP electrodes were connected to an amplifier (Bio Potential Amp, BPA 79232, Hugo Sachs Elektronik–Harvard Apparatus, Germany; Filter: 0.05–10,000 Hz). All signals were recorded in LabChart 8.0 (AD Instruments, New Zealand) at 2–4 kHz sampling rate using a PowerLab system.

We manually analyzed ECG, MAP, and pressure recordings in LabChart. Four consecutive heartbeats were used to measure RR, PQ, QT, and corrected QT intervals [QTc = $(QT/RR)^{1/3}$], vector magnitude of ST elevation [STVM, with STVM = STVM = $(ST_x^2 + ST_y^2 + ST_z^2)^{1/2}$], and P and QRS duration at baseline (−60 min from occlusion), before coronary occlusion (−5 min from occlusion with ligation or PTCA balloon placed), and during occlusion at *minute 1*, *3*, *5*, *10*, *15*, *20*, *30*, *45*, and *60*. MAPs were analyzed at both positions, and duration of MAP at 90% repolarization ($MAPD_{90}$) in 4 consecutive beats before occlusion and during occlusion at *minute 1*, *3*, *5*, *10*, *15*, and *20* was measured. Arterial blood pressure, CVP, PAP, wedge pressure, and CO measurements were performed at baseline, before occlusion, and every 15 min during occlusion. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated according to SVR = 80 × (mean arterial pressure − CVP) × CO^{-1} and PVR = 80 × (mean PAP – wedge pressure) × CO^{-1}. Stroke volume (SV) was calculated as SV = CO/heart rate × 1,000.

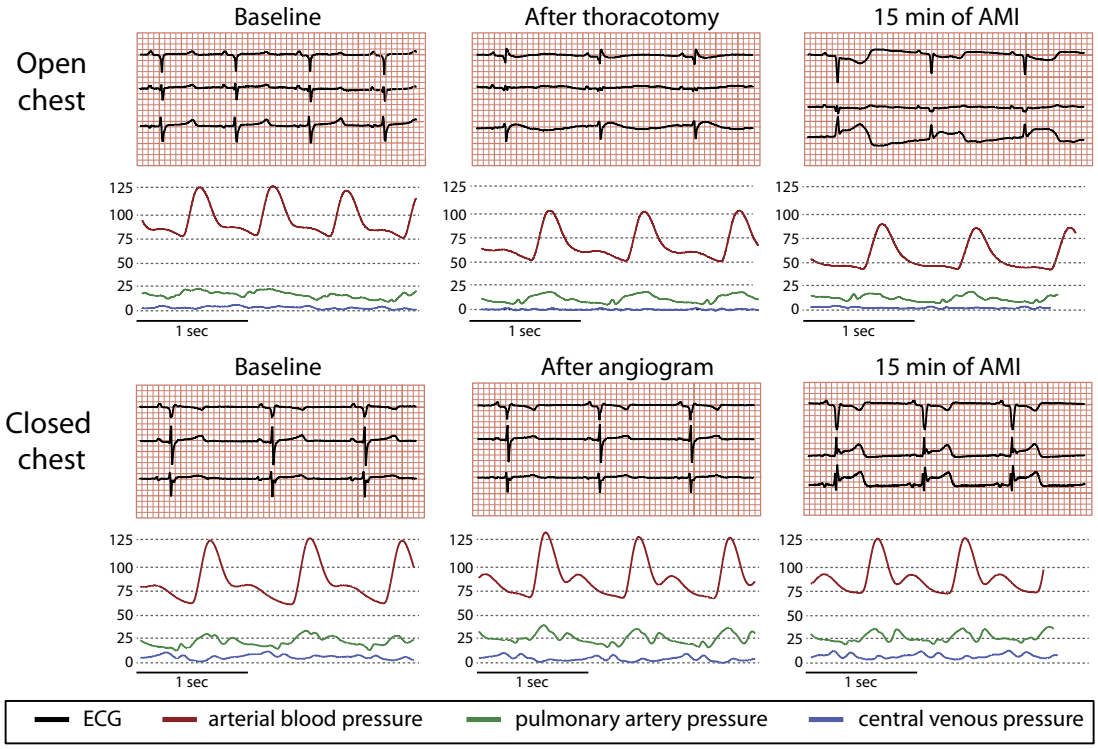

Fig. 2. Representative traces in open- and closed-chest procedures at baseline, after thoracotomy or angiogram and during acute myocardial infarction (AMI). On the grid paper, the electrocardiogram (ECG) is shown in *x*, *y*, and *z* axes. Note the heart rate reduction after thoracotomy in the open-chest group and the ST elevation at 15 min of AMI in both groups. Below the ECGs, the arterial blood pressure (red), pulmonary artery pressure (green), and central venous pressure (blue) are shown (in mmHg). Note the reduction in arterial blood pressure in the open-chest group, which is absent in the closed-chest group.

ECG during occlusion was manually reviewed, and premature ventricular contractions (PVCs) and arrhythmias were counted as single PVCs, couplets, or triplets. More than 3 consecutive PVCs with a rate $>$ 120 min^{-1} were defined as nonsustained ventricular tachycardia or VT when lasting $>$30 s. The coupling interval of the VF-initiating PVC was measured and corrected for heart rate, similarly to QT interval (Fridericia). Additionally, the dominant frequency of VF was analyzed using MATLAB (Version R2019a, MatWorks). A fast Fourier transformation (FFT) using a 6-s sliding window was performed. The dominant frequency was taken from each FFT spectrum for the first 45 s of VF.

Statistics

Continuous variables are reported as means ± SE. Data were censored post-VF. Statistical analysis was done using R software (28). A two-tailed Fisher's exact test was used to compare proportion of VF and a two-tailed Student's *t*-test was used to compare coupling interval and mean time from occlusion to VF. Hemodynamics (heart rate, mean arterial pressure, PAP, CO, SV, CVP, wedge pressure, SVR, and PVR), electrophysiological data (RR, P, PQ, QTc, STVM, $\Delta MAPD_{90}$, and $\Delta MAPD_{90}$ alternans), number of PVCs in *phase 1a*, *1b*, and *extended phase 1b*, and dominant frequency were compared using a permutation test. Our null hypothesis was as follows: there is no difference between open and closed chest at *1*) baseline ($t = -60$), *2*) before ligation/occlusion ($t = -5$), and *3*) during AMI ($t = 1$ to $t = 60$). P values < 0.05 were considered statistically different.

RESULTS

Baseline Characteristics

Mean body weight was 50.8 ± 0.5 and 51.2 ± 0.5 kg, and mean heart weight was 227 ± 4 and 232 ± 4 g in the open- and closed-chest groups, respectively. Representative traces of ECG and blood pressure are shown in Fig. 2 at baseline, after

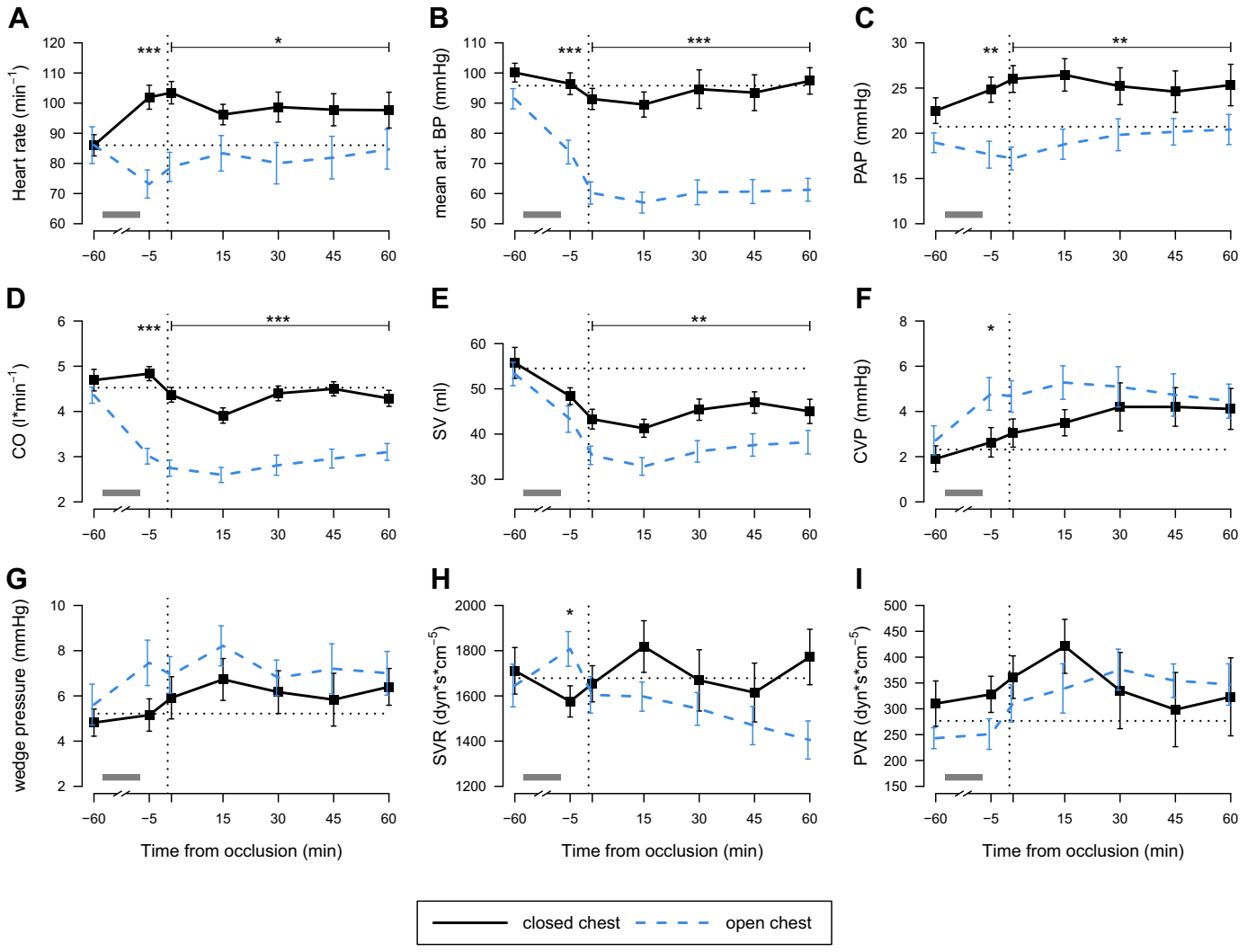

Fig. 3. Hemodynamics. *A–I*: hemodynamic parameters were recorded during baseline and before and after acute myocardial infarction (AMI) induction in an open- ($n = 20$) and a closed-chest ($n = 22$) porcine AMI model during sinus rhythm. Opening of the chest reduced heart rate, whereas angiogram and balloon placement increased heart rate (*A*). Mean arterial blood pressure (mean art. BP, *B*) decreased with opening the chest, and so did cardiac output (CO, *D*). Pulmonary artery pressure (PAP) increased with angiogram (*C*). Along with CO, stroke volume (SV) was reduced in the open chest (*E*). Preload parameters [central venous pressure (CVP), *F*, and wedge pressure, *G*] were slightly increased in the open-chest model but only significantly different for CVP before occlusion. Systemic (SVR, *H*) and pulmonary vascular resistance (PVR, *I*) fluctuated. Gray bar indicates closed- or open-chest procedure. The dotted vertical line indicates coronary AMI induction and the dotted horizontal line indicates mean at baseline. Open compared with closed: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (permutation test).

thoracotomy or angiogram, and after 15 min of AMI for open and closed chest.

At baseline (before any procedure was performed, $t = -60$), hemodynamic and electrophysiological parameters were comparable (all $P > 0.05$). Only STVM had a statistical difference (0.12 ± 0.04 and 0.15 ± 0.04 for open and closed chest, respectively; $P = 0.032$), but this was not regarded as clinically relevant (Figs. 3 and 4). Mean values including SE at baseline ($t = -60$) and before occlusion ($t = -5$) can be seen in Table 1.

Hemodynamics

To assess the effects of open- and closed-chest procedures on hemodynamics, comparisons were made before occlusion ($t = -5$, Table 1 and Fig. 3) and during AMI ($t = 1$ to $t = 60$, Fig. 3).

Heart rate increased during angiogram and stayed increased during AMI in the closed-chest group. In contrast, thoracotomy and subsequent pericardectomy led to an initial drop in heart rate, which returned almost to baseline during AMI. This

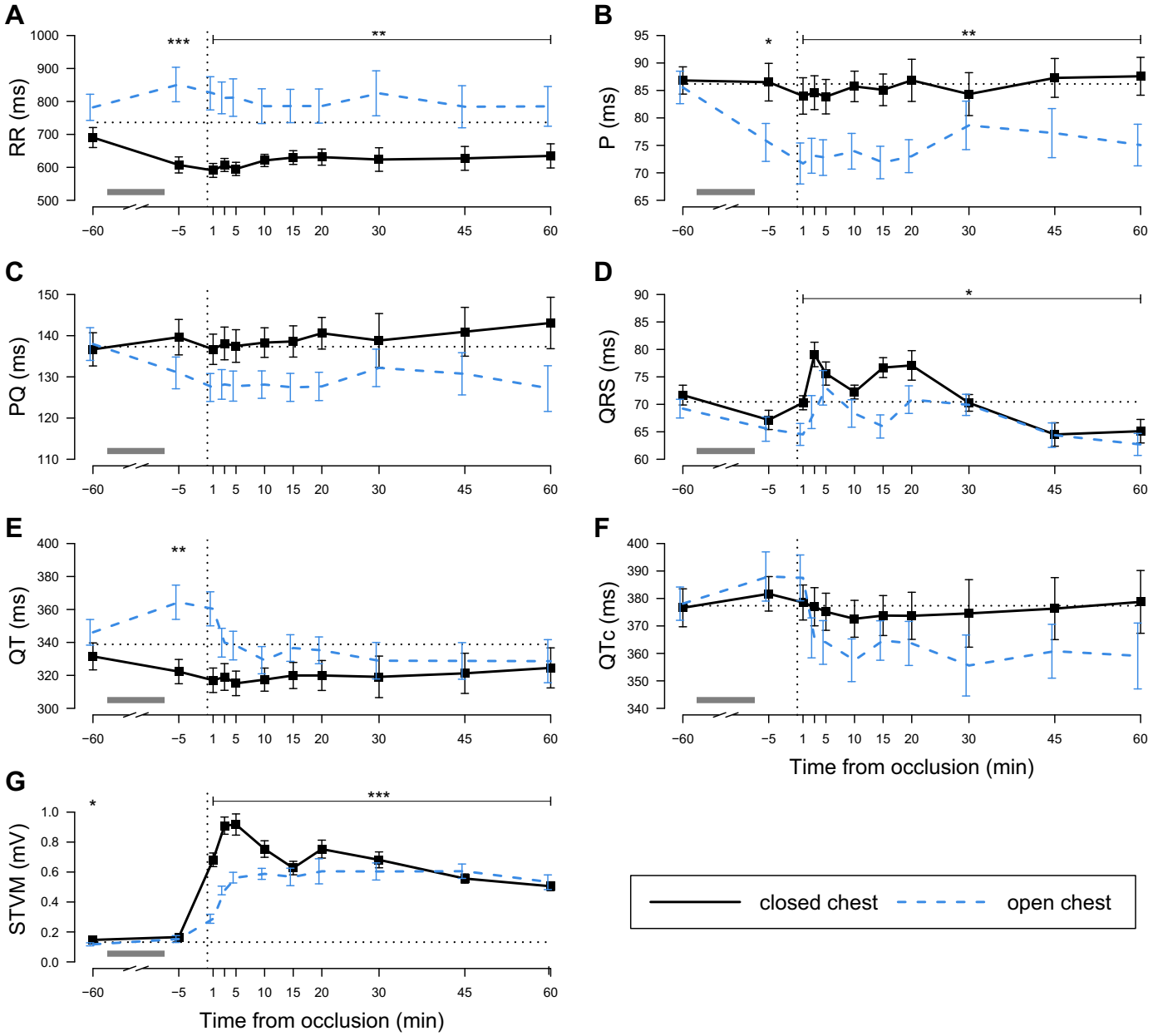

Fig. 4. Electrocardiogram. *A–G*: electrocardiogram was recorded during baseline and before and after acute myocardial infarction (AMI) induction in an open- ($n = 20$) and a closed-chest ($n = 22$) porcine AMI model during sinus rhythm. Opening the chest and subsequent AMI resulted in a prolongation of RR intervals, whereas angiography and balloon occlusion shortened RR intervals (*A*). Open-chest pigs had a shortening of P waves (*B*) and a trend toward shorter PQ intervals ($P = 0.056$, *C*). QRS complex prolonged during AMI with a first peak from 3–10 min and a second peak from 10 or 15–45 min, which was more pronounced in the closed-chest group (*D*). There were no differences in QT (*E*) and corrected QT (QTc, *F*). ST vector magnitude (STVM) reached a higher peak magnitude in the closed-chest group with similar magnitudes after 15 min of AMI (*G*). Gray bar indicates closed- or open-chest procedure. The dotted vertical line indicates AMI induction and the dotted horizontal line indicates mean at baseline. Open compared with closed: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ (permutation test).

Table 1. *Hemodynamic and electrophysiological parameters at baseline and before occlusion*

	Baseline	Open Chest	Closed Chest	*P* Value
n	42	20	22	
Hemodynamic parameters				
CVP, mmHg	2 ± 3	5 ± 3	3 ± 3	0.034
LAP, mmHg	5 ± 3	8 ± 4	5 ± 3	0.075
PAP, mmHg	21 ± 6	18 ± 6	25 ± 7	0.001
Mean art. BP, mmHg	96 ± 15	74 ± 18	96 ± 17	<0.001
Cardiac output, L/min	4.5 ± 0.8	3.0 ± 0.8	4.8 ± 0.7	<0.001
Stroke volume, mL	54 ± 12	43 ± 13	48 ± 9	0.146
SVR, dyn·s·cm^{-5}	1,674 ± 389	1,807 ± 316	1,575 ± 323	0.031
Electrophysiological parameters				
RR interval, ms	734 ± 165	851 ± 234	607 ± 114	<0.001
P duration, ms	86 ± 12	75 ± 15	87 ± 16	0.032
PQ interval, ms	137 ± 18	131 ± 17	139 ± 20	0.141
QRS duration, ms	71 ± 8	65 ± 10	67 ± 8	0.559
QT interval, ms	335 ± 37	364 ± 47	322 ± 35	0.002
QTc interval, ms	377 ± 29	388 ± 40	382 ± 29	0.573
STVM, mV	0.13 ± 0.04	0.15 ± 0.10	0.17 ± 0.07	0.643
$MAPD_{90}$, ms		307 ± 37	259 ± 33	<0.001

Values are means ± SD; permutation test comparing open vs. closed chest (at $t = -5$). CVP, mean central venous pressure; LAP; mean left atrial pressure; $MAPD_{90}$, duration of monophasic action potentials at 90% repolarization; mean art. BP, mean arterial blood pressure; PAP, mean pulmonary artery pressure; STVM, ST vector magnitude, SVR, systemic vascular resistance.

resulted in lower heart rates in the open-chest pigs before occlusion and during AMI compared with the closed-chest pigs ($t = -5$, $P < 0.001$; during AMI, $P = 0.015$; Fig. 3*A*). Mean arterial blood pressure was reduced with thoracotomy and decreased further with AMI (both $P < 0.001$; Fig. 3*B*), whereas PAP increased during angiography and stayed elevated during AMI ($t = -5$, $P = 0.001$; during AMI, $P = 0.003$; Fig. 3*C*). Although CO was relatively stable during the entire experiment in the closed-chest group, it dropped significantly upon opening of the chest and stayed reduced during AMI (both $P < 0.001$; Fig. 3*D*). In line with CO, SV was also decreased in the open-chest group during AMI ($P = 0.008$; Fig. 3*E*). Opening the chest slightly increased preload (CVP and wedge pressure) before infarct induction, but this was only significantly different for CVP before occlusion ($P = 0.034$), whereas no difference for either was seen during AMI (Fig. 3, *F* and *G*, respectively). Finally, SVR (Fig. 3*H*) and PVR (Fig. 3*I*) showed no clear behavior during the experiment.

Electrocardiography

To assess the effects of open- and closed-chest procedures on global cardiac electrophysiology, ECG parameters were compared before occlusion ($t = -5$, see Table 1 and Fig. 4) and during AMI ($t = 1$ to $t = 60$, Fig. 4).

RR interval was longer in the open-chest group before AMI ($t = -5$, $P = 0.001$; Fig. 4*A*) and remained longer during AMI ($P = 0.002$). P duration was decreased upon opening of the chest ($P = 0.032$; Fig. 4*B*), and also remained decreased during AMI ($P = 0.008$). PQ intervals were similar in both groups ($t = -5$, $P = 0.141$; during AMI, $P = 0.056$; Fig. 4*C*). No differences in QTc (Fridericia) could be observed after correcting for heart rate ($t = -5$, $P = 0.573$; during AMI, $P = 0.312$; Fig. 4*F*). QRS complexes broadened with AMI in both groups, but QRS broadening occurred later and was less pronounced in the open-chest group ($P = 0.037$; Fig. 4*D*). AMI led to ST segment elevation in both groups (Fig. 4*G*). The increase in STVM had a slower progression and reached a lower amplitude within the first minute in the open-chest group ($P < 0.001$). Maximum STVM was 0.58 ± 0.04 and 0.92 ± 0.07 mV and was reached after 10 and 5 min after AMI induction in the open- and closed-chest group, respectively.

Monophasic Action Potential

MAPs were recorded continuously beginning 5 min before AMI was induced and during the first 20 min of AMI. $MAPD_{90}$ did not change in the noninfarcted region in either group (Fig. 5*A*). In the infarcted region, $MAPD_{90}$ shortened less in the closed-chest group (Fig. 5*A*; $P = 0.003$). However, $MAPD_{90}$ was shorter at baseline in the closed-chest group, and MAPs from both groups shortened to comparable durations during AMI (Fig. 5*B*). Alternans of MAPD was not different between groups ($P = 0.084$; Fig. 5*C*). Representative traces of MAPs in the infarcted and the noninfarcted regions show the stability of MAPs in the healthy tissue compared with the MAPD shortening in the infarcted tissue in both groups (Fig. 5*D*).

Arrhythmia

The majority of PVCs were single in both groups, with only a small number of couplets (open chest: 0.18 ± 0.02, closed chest: 0.22 ± 0.02) and triplets (open chest: 0.04 ± 0.01, closed chest: 0.08 ± 0.01) in either group. The PVCs were therefore pooled. PVCs occurred in two distinct phases, *1a* (0–15 min) and *1b* (16–30 min) during AMI (Fig. 6*A*). There was no difference in the distribution of PVCs in *phase 1a* between the two groups ($P = 0.520$), whereas PVCs in *phase 1b* occurred earlier in the closed-chest group ($P = 0.001$). Because *phase 1b* in the open-chest group spanned from 16–40 min, we compared the groups using an alternative definition of *phase 1b* (16–40 min) with the same result ($P = 0.005$). However, the mean number of PVCs per minute was similar between the groups in *phase 1a*, *phase 1b*, and *extended phase 1b* (*1a*: 4.0 ± 1.1 and 4.2 ± 0.7, $P = 0.899$; *1b*: 3.4 ± 0.7 and 4.9 ± 0.8, $P = 0.163$; *extended 1b*: 3.3 ± 0.6 and 4.7 ± 0.8, $P = 0.165$; for open and closed chest, respectively). Nonsustained ventricular tachycardia was rare in both groups (open chest: 0.04 ± 0.01, closed chest: 0.04 ± 0.01).

In the 60 min of coronary occlusion, 7 out of 20 pigs in the open-chest and 12 out of 22 pigs in the closed-chest groups experienced VF ($P = 0.232$). Mean time to VF from occlusion was 23.4 ± 1.2 min and 17.8 ± 1.4 min in the open- and closed-chest groups, respectively ($P = 0.007$, Fig. 6*B*). The coupling interval of the initiating PVC was significantly longer in the open-chest group compared with the closed-chest group (0.34 ± 0.03 and 0.25 ± 0.01 s, respectively; $P = 0.002$), also when corrected for heart rate (0.41 ± 0.04 and 0.30 ± 0.01 s, respectively; $P = 0.003$). Additionally, the dominant frequency of VF was slower in the open-chest group (Fig. 6*C*; $P = 0.046$).

DISCUSSION

The present study investigated the effects of open- and closed-chest AMI procedures on hemodynamics, electrophysiology, and the incidence and time course of ventricular ar-

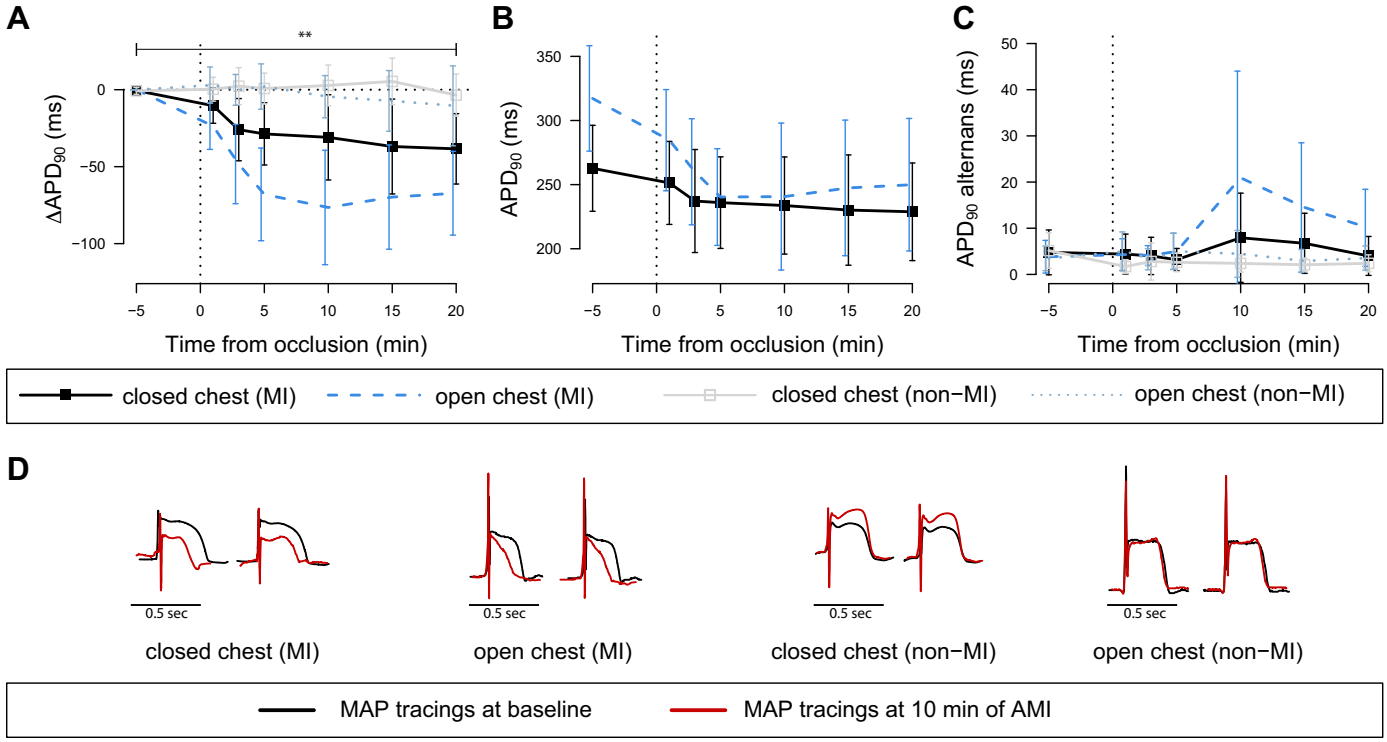

Fig. 5. Monophasic action potentials (MAPs). *A–D*: MAPs were recorded before and after acute myocardial infarction (AMI) induction in an open- and a closed-chest porcine AMI model during sinus rhythm in the infarcted (MI; open: $n = 12$; closed: $n = 17$) and noninfarcted area (non-MI; open: $n = 11$; closed: $n = 13$). Changes from baseline in MAP duration at 90% repolarization ($\Delta MAPD_{90}$) in the MI and non-MI area (*A*). Absolute $MAPD_{90}$ in the infarcted area was longer in the open-chest model, in line with slower heart rate (*B*). $MAPD_{90}$ alternans was only present in the infarcted area and was similar in the 2 groups (*C*). Representative traces of MAPs show shortening in the MI area but not in the non-MI area (*D*). Dotted vertical line indicates coronary ligation/occlusion. Open compared with closed: $^{**}P < 0.01$ (permutation test).

rhythmias in the early phase of AMI induced at the same occlusion site. Both open- and closed-chest AMI models have been used extensively over the last few decades in search of mechanisms and treatments for AMI-induced arrhythmia, yet the consequence of model choice on the development of such arrhythmias has not been directly evaluated. In the present study, we observed changes in hemodynamic and ECG parameters that were more pronounced in the open-chest group. Interestingly, the observed differences between the two models did not significantly affect the incidence of ventricular arrhythmias, including PVCs, VT, and VF. However, development of ventricular arrhythmias was delayed in the open-chest pigs, suggesting that substrate and triggers for AMI-induced arrhythmia appear similarly in the two models, but develop later in the open-chest configuration.

Arrhythmic Delay

PVCs during AMI are common and occur in two phases with distinct peaks in the first hour of AMI: *phase 1a* (2–10 min) and *phase 1b* (18–30 min) (16). Both models showed these phases without a difference in the number of PVCs. However, the arrhythmic peaks occurred later in the open-chest model. Consistent with PVCs, incidence of VF was comparable (although with a tendency toward fewer VF cases in the open-chest model), but VF occurred ~5 min later in open-chest pigs. Although no data on PVC incidence for these two models exist, VF incidence rates are likely to be comparable between the two models, as data from a recent systematic meta-analysis on large animal AMI models suggest (32).

Major contributors to AMI-induced arrhythmia are local electrophysiological changes in the myocardium, such as action potential duration (APD) shortening and repolarization heterogeneity (3). In the present study, we used MAP recordings in the infarcted and noninfarcted region to evaluate these changes. Although $MAPD_{90}$ was longer to begin with in the open-chest pigs, it shortened in both groups within the first 5 min of AMI and stayed shortened for the following 15 min. The temporal differences in arrhythmia development are therefore unlikely to be related to changes in APD shortening, as this happened within the first 2–3 min of AMI and stabilized afterward. However, AMI prolongs the effective refractory period (ERP) between ~15 and 20 min after AMI onset (3). Although we did not measure ERP in the present study, we found that the coupling interval of the VF-initiating PVC was longer in the open-chest group and the dominant frequency of VF was lower. This could be indicative of prolonged activation/repolarization properties of the myocardium in the open-chest group during VF. The involvement of these properties and possible changes in ERP on the arrhythmic delay cannot be excluded.

Cardiac ischemic preconditioning has been reported to influence the timing of ventricular arrhythmia during AMI. Cinca et al. (6) showed that LAD occlusion-reperfusion sequences preceding full LAD occlusion in a porcine AMI model delayed development of *phase 1b* arrhythmias due to a delay in steep changes in intra-myocardial resistance. The delay in myocardial resistance change was linked to activation of K_{ATP}-channels (30), as well as to a delay in intracellular Ca^{2+} accumu-

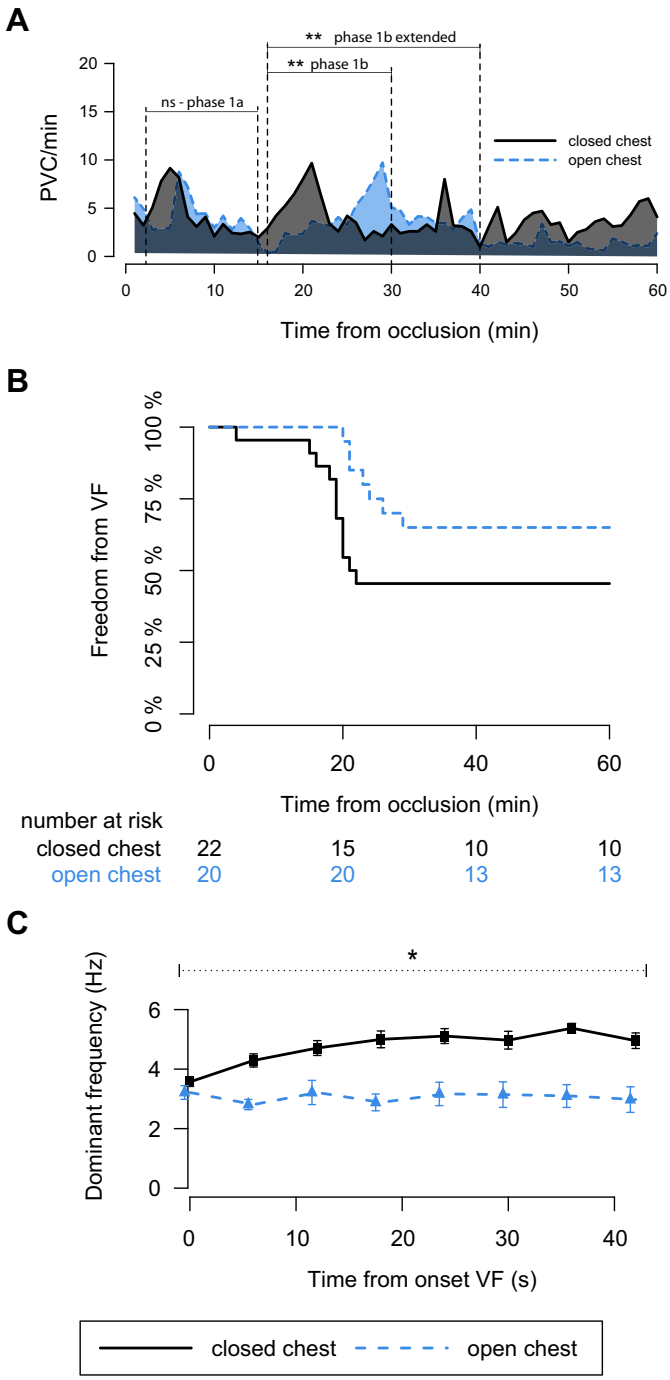

Fig. 6. Ventricular arrhythmias. *A–C*: premature ventricular contractions (PVCs) and ventricular fibrillation (VF) were analyzed during 1 h of acute myocardial infarction (AMI) in an open- ($n = 20$) and a closed-chest ($n = 22$) porcine AMI model. Distribution of PVCs shows distinct peaks in both groups, with a delay in PVCs in the open-chest model (*A*). Freedom from VF was similar in both groups, with a time delay in VF in the open-chest group (*B*). The dominant frequency of VF was increased in the closed-chest group (*C*). Open compared with closed: $*P < 0.05$, $**P < 0.01$ (permutation test); ns, nonsignificant.

lation (8). On the other hand, a study in pigs reported shorter time to VF in preconditioned pigs, despite smaller infarct size (27). In our study, direct ischemic preconditioning is unlikely to occur, although ligation placement could cause short ischemic episodes and balloon placement provides some impedance to blood flow. However, remote preconditioning or preconditioning by trauma could potentially have a similar influence on the time frame of arrhythmia development, as it has positive effects on infarct size (4, 13, 18). However, arrhythmia development was not addressed in these studies.

The heart rate differences between the two groups could be involved in the delayed arrhythmia development. A high heart rate, induced by atrial pacing, decreases the threshold for VF in AMI (15). Additionally, a high heart rate is commonly related to high sympathetic tone, which is linked to arrhythmias and SCD (3), also during AMI (17). In AMI, inhibition of systemic sympathetic nerve activity, as well as local cardiac denervation, can reduce arrhythmia incidence during ischemia (5, 22). Specifically in the development of *phase 1b* arrhythmias, the release of catecholamines has been proposed as a major contributor (9). The higher heart rate in the closed-chest model could reflect a proarrhythmic setting during AMI, although we do not see a significant difference in incidence, only a time shift. Whether heart rate and autonomic tone could contribute to this time shift is unclear.

Hemodynamics

We observed numerous hemodynamic changes after opening the thorax and pericardium. Most importantly, we registered a hypodynamic state with reduced SV, CO, and blood pressure that was not adequately compensated by vascular constriction as measured by SVR.

Preload. CVP and wedge pressure showed a trend toward higher values in the open-chest model. Whether this can be seen as an increase in preload or just reflects changes in intrathoracic pressure (as a result of thoracotomy and mechanical ventilation with positive pressure) is debatable. Because SV, CO, and arterial blood pressure were reduced before AMI induction, a relevant increase in preload seems unlikely.

Cardiac work. In the open-chest model, CO and SV (and heart rate) were already reduced before AMI was induced, indicating a negative inotropic state with otherwise normal preload. These effects were aggravated during AMI.

In the open-chest experiments, the pericardium was opened and thereby its function disturbed. The pericardium acts as a noncompliant shell around a compliant heart muscle, and opening the pericardium alters the pressure-volume relationship between the right and left ventricles (11). Furthermore, stretch or bulging of the ischemic myocardium is considered to be related to AMI-induced VF (1, 2). Removing the pericardium's restraint on left ventricular filling might therefore negatively impact ventricular function and rhythm.

Afterload. Mean arterial pressure and PAP were decreased in the open-chest pigs, corresponding to reduced afterload to the left and right ventricles, respectively. Reduced afterload reduces the workload and O_2 demand of the heart, which is mechanically favorable, especially in a diseased heart. An acute increase in afterload (29), as well as chronically high afterload post-AMI (24), has been associated with increased ventricular arrhythmias. However, arterial hypertension was not different between patients experiencing AMI with and without VF in a clinical study looking at risk factors for AMI-induced VF (14).

Autonomic effects. Closed-chest pigs experienced an increase in heart rate throughout the procedure, whereas open-chest pigs showed an initial drop in heart rate with thoracotomy that almost returned to baseline upon AMI. In the wake of thoracotomy-induced low blood pressure, sympathetic tone would be expected to attempt to compensate by increasing heart rate, SV, and SVR. We observed a temporary response in SVR before AMI induction, but it decreased even further during AMI. It appears that the invasive surgery caused a vagal or reduced sympathetic tone. Propofol is known to reduce mean arterial pressure and SVR (7). Even though the same anesthesia was used in both models, propofol's contribution to the lack of compensation for the low blood pressure cannot be excluded.

Area at Risk and Infarct Size

Both models were feasible for AMI induction and mid-LAD occlusion. In our study, we did not use staining to identify area at risk and infarct size directly. Infarct size was estimated using STVM as a surrogate parameter (26). STVM showed an initial peak, an attenuated second peak, and a slow decay thereafter. In our experiments, pigs in the open-chest group reached their first peak later and had a decreased amplitude of both peaks, although STVM reached similar magnitudes after 45 min. The first peak in STVM was of clearly lower magnitude in the open-chest group giving reason to suspect slower progression of AMI or potentially reduced infarct size. In accordance with STVM, QRS widened later and to a lesser extent in the open-chest pigs. Preconditioning caused by a more extensive surgery in the open-chest group could potentially have influenced infarct size. Studies have shown that surgical incision can produce cardioprotective effects in mice (4), rats (18), and dogs (13). In all these studies, remote preconditioning of trauma led to a reduced infarct size despite comparable areas at risk.

Limitations and Future Perspectives

Several limitations are associated with the present study. First, we have limited information on the local and global electrophysiological changes of AMI in these models because we only placed two MAP catheters in each pig: one in infarcted and the other in noninfarcted tissue. Additionally, we did not perform pacing protocols to measure ERPs or conduction velocity to avoid interfering with the natural development of arrhythmia. Although $MAPD_{90}$ showed no temporal changes that could account for the delay in arrhythmic development in the open-chest pigs, we did observe other indications of differences in activation/repolarization properties between the two groups in the coupling interval of the VF-initiating PVC and the dominant frequency of VF. More detailed electrophysiological data could have potentially provided more information on these differences. Second, only indirect measurements of area of risk and infarct size were used. Finally, no left ventricular pressure measurements to assess contractility were performed.

Because we used pigs that served as control groups in other experiments, no specific interventions were performed to test hypotheses on heart-rate dependency, autonomic effects, or remote preconditioning on the hemodynamic and arrhythmic differences. Experiments using atrial pacing, vagal and sympathetic blockade with atropine and beta blocker, respectively, or controlled ischemic preconditioning could provide a more detailed understanding of the hemodynamic and cardiac electrophysiological differences of the two models.

Conclusion

We show that the open-chest AMI model causes pronounced effects on hemodynamic parameters and delays the onset of ventricular arrhythmias. Future studies to understand the mechanism behind the differences in the open- and closed-chest models may reveal underlying general principles of AMI-induced arrhythmia. Despite the delay in arrhythmias, the open- and closed-chest models both experienced the characteristic *phase 1a* and *1b* arrhythmias, and VF incidence was comparable. This supports the use of either one in preclinical studies on AMI-induced arrhythmias, although caution is advised when choosing or comparing results between open- and closed-chest AMI models.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.F.L., S.M.S., J.T.-H., and T.J. conceived and designed research; A.F.L., S.M.S., and M.F. performed experiments; A.F.L. and S.M.S. analyzed data; A.F.L. and S.M.S. interpreted results of experiments; A.F.L. and S.M.S. prepared figures; A.F.L. and S.M.S. drafted manuscript; A.F.L., S.M.S., M.F., J.T.-H., and T.J. edited and revised manuscript; A.F.L., S.M.S., M.F., J.T.-H., and T.J. approved final version of manuscript.

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