The Effects of Nifedipine on Ventricular Fibrillation Mean Frequency in a Porcine Model of Prolonged Cardiopulmonary Resuscitation

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We assessed the effects of a calcium channel blocker versus saline placebo on ventricular fibrillation mean frequency and hemodynamic variables during prolonged cardiopulmonary resuscitation (CPR). Before cardiac arrest, 10 animals were randomly assigned to receive either nifedipine (0.64 mg/kg; n = 5) or saline placebo (n = 5) over 10 min. Immediately after drug administration, ventricular fibrillation was induced. After 4 min of cardiac arrest and 18 min of basic life support CPR, defibrillation was attempted. Ninety seconds after the induction of cardiac arrest, ventricular fibrillation mean frequency was significantly (P < 0.01) increased in nifedipine versus placebo pigs (mean ± sd: 12.4 ± 2.1 Hz versus 8 ± 0.7 Hz). From 2 to 18.5 min after the induction of cardiac arrest, no differences in ventricular fibrillation mean frequency were detected between groups. Before defibrillation, ventricular fibrillation mean frequency was significantly (P < 0.05) increased in nifedipine versus placebo animals (9.7 ± 1.2 Hz versus 7.1 ± 1.3 Hz). Coronary perfusion pressure was significantly lower in the nifedipine than in the placebo group from the induction of ventricular fibrillation to 11.5 min of cardiac arrest; no animal had a return of spontaneous circulation after defibrillation. In conclusion, nifedipine, but not saline placebo, prevented a rapid decrease of ventricular fibrillation mean frequency after the induction of cardiac arrest and maintained ventricular fibrillation mean frequency at ~10 Hz during prolonged CPR; this was nevertheless associated with no defibrillation success.


Intracellular Ca\(^{2+}\) increases promptly with the induction of ventricular fibrillation (1). This increase in intracellular Ca\(^{2+}\) is several times more than the peak systolic intracellular Ca\(^{2+}\) content during normal sinus rhythm and has important metabolic and mechanical consequences. For example, a large concentration of intracellular Ca\(^{2+}\) increases activation of enzymes that actively transport Ca\(^{2+}\) into the sarcoplasmic reticulum and mitochondria (2–4), resulting in a significant intracellular energy deficit. Accordingly, calcium channel blockers may preserve metabolic machinery and reduce the production of cerebral catabolites, resulting in prolonged cell viability during global ischemia (5).

Although a randomized clinical trial using a calcium channel blocker in comatose survivors of cardiac arrest did not reveal beneficial effects of this drug with regard to neurologic outcome during a 6-mo follow-up, it is possible that the treatment effect was simply too small to be detectable in a clinical trial of only 520 cardiac arrest patients (6). Also, the calcium channel blocker was given after the return of spontaneous circulation, which may have limited the protective effects on the cerebrum. Thus, if calcium overloading is prevented early, beneficial effects may be more likely; further, if the goal of the treatment strategy is not an extremely difficult target, such as preventing...
postcardiac arrest brain damage, but a relatively simple one, such as protecting the fibrillating myocardium, the success of a given study may be more likely. In fact, Martin et al. (7) showed that a calcium channel blocker, but not saline placebo, maintained high ventricular fibrillation mean frequency in a cardiac arrest model and facilitated defibrillation. However, they observed this phenomenon only during the first 90 s of cardiac arrest, which may not be applicable to cardiopulmonary resuscitation (CPR) in humans, in whom basic and advanced cardiac life support are mostly initiated after approximately 5 min or even longer (8). Thus, it is unknown whether the underlying beneficial Ca\(^{2+}\) antagonist effect occurring 90 s after collapse may be present later as well. More knowledge about this physiology may improve the prediction of countershock success. Accordingly, the purpose of this study was to assess the effects of a calcium channel blocker versus saline placebo on ventricular fibrillation mean frequency and coronary perfusion pressure during prolonged CPR.

### Methods

This project was approved by the Austrian Federal Animal Investigational Committee, and the animals were managed in accordance with the American Physiological Society institutional guidelines and the Position of the American Heart Association on Research Animal Use, as adopted on November 11, 1984. Animal care and use were performed by qualified individuals who were supervised by veterinarians, and all facilities and transportation complied with current legal requirements and guidelines. Anesthesia was used in all surgical interventions, all unnecessary suffering was avoided, and research was terminated if unnecessary pain or fear resulted. Our animal facilities meet the standards of the American Association for Accreditation of Laboratory Animal Care. This study was performed according to Utstein-style guidelines (9) with 10 healthy, 12- to 16-wk-old swine weighing 30 to 40 kg. The animals were fasted overnight but had free access to water. The pigs were premedicated with azaperone (4 mg/kg IM) and atropine (0.1 mg/kg IM) 1 h before surgery, and anesthesia was induced with propofol (1–2 mg/kg IV). After intubation during spontaneous respiration, the pigs were ventilated with a volume-controlled ventilator (EV-A; Draeger, Lübeck, Germany) with 35% oxygen at 20 breaths/min and with a tidal volume adjusted to maintain normocapnia. Anesthesia was maintained with propofol (6–8 mg · kg\(^{-1}\) · h\(^{-1}\)) and a single injection of pirritramide (30 mg) (10). Muscle paralysis was achieved with 0.2 mg · kg\(^{-1}\) · h\(^{-1}\) of pancuronium after intubation. Ringer’s solution (6 mL · kg\(^{-1}\) · h\(^{-1}\)) and a 3% gelatin solution (4 mL · kg\(^{-1}\) · h\(^{-1}\)) were administered in the preparation phase. A standard Lead III electrocardiogram (ECG) was used to monitor cardiac rhythm; depth of anesthesia was judged according to blood pressure, heart rate, and electroencephalography (Engström, Munich, Germany). If cardiovascular variables or electroencephalography indicated a reduced depth of anesthesia, additional propofol and pirritramide were given. Body temperature was maintained between 38.0°C (100.4°F) and 39.0°C (102.2°F).

A 7F catheter was advanced into the descending aorta via femoral cutdown for withdrawal of arterial blood samples and measurement of arterial blood pressure. A 7.5F pulmonary artery catheter was placed via cutdown into the neck for measurement of right atrial and pulmonary artery pressure. Blood pressure was measured with a saline-filled catheter attached to a pressure transducer (Model 1290A; Hewlett-Packard, Böblingen, Germany) that was calibrated to atmospheric pressure at the level of the right atrium.

The ventricular fibrillation ECG signal (standard Lead III) and pressure tracings were monitored continuously and recorded on hard disk by a computer-based data acquisition system (Port 2000; Dewetron, Graz, Austria; and Datalogger [custom-made software]). Digitization was performed at a sampling rate of 1000 Hz and with an amplitude resolution of 12 bits (4096 equal steps between minimal and maximal amplitude). The recorded ECG signals were analyzed by using the mathematical software package Matlab (Math Works Inc., Natick, MA). The signals were divided into consecutive 10-s epochs; each epoch was transformed into the frequency domain by Fourier transformation. To filter out CPR-related artifacts, the frequency domain was restricted to the range from 4.33 to 30 Hz, as previously described (11). Mean fibrillation frequency for the 10-s epoch after 1.5, 7, 12, 18.5, and 22 min after the induction of cardiac arrest was calculated from the restricted spectrum. The mean ventricular fibrillation peak-to-trough amplitude (difference between a peak and the next trough of the ECG signal) was calculated at the same time segments as mean fibrillation frequency.

Fifteen minutes before cardiac arrest, 5000 U of heparin was administered IV to prevent intracardiac clot formation, and single doses of pirritramide 0.8 mg/kg and pancuronium 0.2 mg/kg were given. Subsequently, 10 animals were randomly assigned to receive either nifedipine (0.64 mg/kg; \(n = 5\)) (7) or saline placebo (\(n = 5\)) over 10 min (investigators were blinded to the drugs). Immediately after drug administration, ventricular fibrillation was induced with a 50-Hz alternating current applied via two subcutaneous needles, and ventilation was stopped. After 4 min of untreated ventricular fibrillation, closed-chest standard CPR was performed, and ventilation was resumed with the same ventilator setting as before the induction of cardiac arrest. Chest compressions were
always performed by the same investigator at a rate of 100/min, guided by acoustical audiotones. This investigator was blinded to hemodynamic monitor tracings. Hemodynamic variables were measured before the induction of cardiac arrest, as well as 1.5, 4.5, 8, 9.5, 13, 14.5, and 18 min after initiation of CPR. After 22 min of cardiac arrest, including 18 min of standard CPR, we attempted to restore spontaneous circulation with up to 5 countershocks (monophasic wave forms) with an energy of 3, 4, and 6 J/kg, respectively. If asystole or pulseless electrical activity was present after defibrillation, the experiment was terminated. Return of spontaneous circulation was defined as an unassisted pulse with a systolic arterial pressure of more than 80 mm Hg for longer than 5 min. After the experimental protocol was finished, the animals were killed with an overdose of potassium chloride and fentanyl; all pigs were necropsied to check correct positioning of the catheters and damage to the rib cage and internal organs.

Values are expressed as mean ± sd. The comparability of weight and baseline data was verified by using the unpaired Student’s t-test for continuous variables. To identify statistically significant differences of mean frequency, mean amplitude, and coronary perfusion pressure between groups, one-way analysis of variance was used, followed by a non-parametric Wilcoxon’s ranked sum test; all P values were corrected with the Bonferroni method for multiple comparisons, and values of P < 0.05 were considered significant. The association between coronary perfusion pressure and ventricular fibrillation mean frequency was examined with linear regression analyses.

Results

After the induction of cardiac arrest, the ventricular fibrillation mean frequency was higher in the nifedipine group than in the saline solution placebo group for approximately 2 min. From 2 to 18.5 min after the induction of cardiac arrest, including 14.5 min of CPR, no differences in ventricular fibrillation mean frequency could be detected. From 18.5 to 22 min of cardiac arrest, the ventricular fibrillation mean frequency of the placebo group deteriorated, and the mean frequency in the nifedipine group remained higher (Fig. 1). Ninety seconds after the induction of cardiac arrest, the ventricular fibrillation mean frequency was 12.4 ± 2.1 Hz in the nifedipine group versus 8.0 ± 0.7 Hz in the placebo group (P < 0.01) and 9.7 ± 1.2 Hz versus 7.1 ± 1.3 Hz shortly before defibrillation (P < 0.05), respectively. There were no significant differences in mean ventricular fibrillation peak-trough amplitude before defibrillation. Coronary perfusion pressure was lower in the nifedipine than in the placebo group from the induction of ventricular fibrillation to 11.5 min of cardiac arrest. From 11.5 to 22 min of cardiac arrest, coronary perfusion pressure in both groups was low and comparable (Fig. 2). There was a correlation index of r = 0.99 in the placebo group versus r = −0.15 in the nifedipine group between coronary perfusion pressure and ventricular fibrillation mean frequency. No animal had a return of spontaneous circulation after defibrillation; necropsy revealed proper instrumentation in all animals.

Discussion

Nifedipine, but not saline placebo, prevented a rapid decrease of ventricular fibrillation mean frequency immediately after the induction of cardiac arrest and maintained the ventricular fibrillation mean frequency at ~10 Hz during prolonged CPR. However, the significantly increased frequency values in the nifedipine group were not associated with increased defibrillation success.

Our observation is in full agreement, with respect to time course of ventricular fibrillation mean frequency, with an earlier study by Martin et al. (7), who also injected nifedipine during spontaneous circulation and then measured ventricular fibrillation mean frequency during CPR. Although Martin et al.’s results with regard to ventricular fibrillation mean frequency in the first 2 minutes were almost identical to those of our study, we continued the experiment for another 2 minutes of untreated ventricular fibrillation and, subsequently, 18 minutes of basic life support CPR. In Martin et al.’s study, nifedipine seemed to have a beneficial effect on the fibrillating myocardium by maintaining the ventricular fibrillation mean frequency on a high level and by prolonging the duration of cardiac arrest.
to convert ventricular fibrillation into a spontaneous rhythm, and not pulseless electrical activity, from ~60 to ~90 seconds. This experience is in agreement with both laboratory and clinical data, wherein high ventricular fibrillation mean frequencies correlated with high return of spontaneous circulation rates (12,13).

In previous studies, ventricular fibrillation mean frequency has been shown to correlate positively with coronary perfusion pressure (14). Interestingly, we observed a high mean frequency of ~9 to ~11 Hz during CPR in all nifedipine pigs, but coronary perfusion pressure was comparably low, at ~6 mm Hg. Accordingly, the correlation index between ventricular fibrillation mean frequency and coronary perfusion pressure was approximately ~0.15 throughout the CPR interval, whereas this value was at an established level of 0.99 in the saline placebo pigs. We deliberately did not attempt to defibrillate the animals until 22 minutes into the experiment to measure ventricular fibrillation mean frequency. Because of the prolonged interval of low coronary perfusion pressure, which may be at least partly due to the antihypertensive effects of calcium channel blocker such as nifedipine, it is not surprising that no animal could be converted from ventricular fibrillation to return of spontaneous circulation.

In a previous study, a ventricular fibrillation mean frequency >8.4 Hz predicted successful defibrillation with a sensitivity of 100% and a specificity of 80% (12). Conversely, although four of five nifedipine-treated animals had a ventricular fibrillation mean frequency >8.4 Hz, none was successfully defibrillated. Without doubt, the negative correlation between ventricular fibrillation mean frequency and coronary perfusion pressure and, therefore, the insufficient predictability of defibrillation success with ventricular fibrillation analysis in this experiment were due to the administration of nifedipine. However, it is unlikely that calcium channel blocker such as nifedipine is a significant source of false-positive ventricular fibrillation mean frequency values during CPR in humans. Nevertheless, the results of our experiment document that the present approach to analyzing ventricular fibrillation signals may be insufficient to adequately predict successful defibrillation. For example, analysis of ventricular fibrillation mean frequency in one clinical study achieved a sensitivity of only 73% and a specificity of only 67% (13), indicating that the move to >95% predictability of successful defibrillation may require more information than ventricular fibrillation analysis is capable of providing. Mean peak-to-trough amplitude would be a good predictive variable in our experiment; however, ventricular fibrillation amplitude depends on the direction of the main fibrillation vector, and, therefore, there is great individual variety. Other strategies to solve this dilemma may be to use alternative methods of ventricular fibrillation analysis, such as N(α) histograms (15), or other nonlinear modeling techniques (16,17). Furthermore, combined use of ventricular fibrillation variables leads to an improved forecast of defibrillation outcome, as we have shown in a previous study (18). For example, by using this new combination of mean frequency and amplitude (survival index) (18), the specificity for prediction of successful defibrillation would be improved in this example from 20% to 60%. However, both laboratory and clinical investigations would have to confirm the possible value of these strategies.

There are several limitations to this study. First, the absolute values of ventricular fibrillation mean frequency differ significantly between animals and humans (19). Also, we used young, healthy pigs that were free of atherosclerotic disease. Because of design limitations, we administered no vasopressor, which may have biased the results of ventricular fibrillation mean frequency analysis. Also, it is not possible to administer a calcium channel blocker before cardiac arrest.

In conclusion, nifedipine, but not saline placebo, prevented a rapid decrease of ventricular fibrillation mean frequency after the induction of cardiac arrest and maintained ventricular fibrillation mean frequency at ~10 Hz during prolonged CPR; this was nevertheless associated with no defibrillation success, which suggests that ventricular fibrillation-derived variables predicting defibrillation success are dependent on the study conditions.

References