Succinylcholine does not worsen bupivacaine-induced cardiotoxicity in pentobarbital-anaesthetized dogs

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The intravascular injection of a large dose of bupivacaine induces electrophysiological cardiac impairment, mainly by slowing ventricular conduction velocity, and haemodynamic depression, by a decrease in myocardial contractility. When cardiotoxicity occurs, succinylcholine rapidly stops convulsions. However, the possible interactions between bupivacaine and succinylcholine on cardiac electrophysiology and haemodynamic status have never been investigated. Thus, we used an experimental electrophysiological model involving closed-chest dogs. Three groups (n = 6) of pentobarbital-anaesthetized dogs were given 0.2 mg $\cdot kg^{-1}$ atropine iv. Dogs in Group 1 were given saline. The others received 4 mg $\cdot kg^{-1}$ bupivacaine iv over ten seconds. Dogs in Group 2 were then given saline and those in Group 3 were then given 2 mg $\cdot kg^{-1}$ succinylcholine iv from one to two minutes after the administration of bupivacaine. The following electrophysiological variables were measured: heart rate represented by RR interval (RR), PR, atria-His (AH), and His-ventricle (HV) intervals, QRS duration, and QT interval corrected for heart rate (QTc). The following haemodynamic variables were measured: mean aortic pressure (MAoP), the peak of the first derivative of left ventricular pressure (LV dP/dt max), and LV end diastolic pressure (LVEDP). Comparison between Groups 1 and 2 showed that bupivacaine induced more than 100% HV interval lengthening and QRS widening (P < 0.01), prolonged QTc interval by more than 25% (P < 0.01), and decreased LV dP/dt max by more than 50% (P < 0.01). The only difference between Groups 2 and 3 was a transient shortening of QRS in the group given succinylcholine at four and five minutes (P < 0.05) and a shortening of QTc throughout the study period (P < 0.05 at two and three min, P < 0.01 at four to 30 min after the end of bupivacaine administration). We conclude that 2 mg $\cdot kg^{-1}$ succinylcholine did not worsen the previously impaired electrophysiological or a haemodynamic variables produced by a high dose of bupivacaine in anaesthetized dogs.

L'injection d'une forte dose de bupivacaïne est responsable d'altérations électrophysiologiques essentiellement dues au ralentissement majeur des vitesses de conduction ventriculaires et à l'atteinte hémodynamique par baisse de l'inotropisme. Lors d'accident toxique, la succinylcholine a été proposée pour supprimer rapidement l'expression des convulsions. Cependant les possibles interactions entre la bupivacaïne et la succinylcholine sur l'électrophysiologie et l'hémodynamique n'ont jamais été étudiées. Dans ce but, un modèle électrophysiologique de chien anesthésié à thorax fermé a été utilisé. Trois groupes de six chiens anesthésiés au pentobarbital reçoivent tous 0,2 mg $\cdot kg^{-1}$ iv d'atropine. Le groupe 1 ne reçoit ensuite qu'une perfusion continue de sérum salé isotonique afin de confirmer la stabilité du modèle. Les autres chiens reçoivent ensuite 4 mg $\cdot kg^{-1}$ iv de bupivacaïne en dix secondes. Le groupe 2 n'est plus perfusé que par du sérum salé isotonique alors que le groupe 3 reçoit en plus 2 mg $\cdot kg^{-1}$ iv de succinylcholine de la première à la deuxième minute après la fin de l'injection de bupivacaïne. Les paramètres électrophysiologiques mesurés sont les suivants : la fréquence cardiaque représentée par l'intervalle RR (RR), les intervalles PR (PR), AH et HV, la durée du complexe QRS et l'intervalle QT corrigé par la fréquence cardiaque (QTc). Les paramètres hémodynamiques mesurés sont les suivants : la pression aortique moyenne (MAoP), le pic de la dérivée première de la pression ventriculaire gauche (LV dP/dt max) et la pression télédiastolique ventriculaire gauche (LVEDP). La comparaison entre les groupes 1 et 2 montre que

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la bupivacaïne altère tous les paramètres électrophysiologiques et hémodynamiques. Ainsi, l'intervalle HV est allongé de plus de 100% (P < 0,01), le complexe QRS est élargi de plus de 100% (P < 0,01), l'intervalle QTc est prolongé de plus de 25% (P < 0,01) et LV dP/dt max est diminuée de plus de 50% (P < 0,01). Les seuls paramètres qui varient de manième significative après l'injection de succinylcholine sont le QRS qui se raccourcit à la quatrième et à la cinquième minute suivant la fin de l'injection de bupivacaïne (P < 0,05) et le QTc pendant toute l'étude (P < 0,05 à 2 et 3 min, P < 0,01 de 4 à 30 min). En conclusion, l'injection de 2 mg · kg⁻¹ de succinylcholine n'aggrave pas les paramètres électrophysiologiques et hémodynamiques préalablement altérés par la bupivacaïne sur ce modèle de chien anesthésié.

An overdose of bupivacaine is known to induce convulsions and cardiotoxicity.[1–4] Bupivacaine-induced cardiotoxicity is enhanced by seizures because they induce hypoxia and acidosis.[5–7] To resuscitate these patients, it is recommended that they be oxygenated, the convulsions stopped with pentobarbital, the trachea intubated and the lungs ventilated mechanically.[4,8–11] Succinylcholine has also been proposed to stop the seizures and to facilitate intubation of the trachea.[9] However, succinylcholine has many deleterious cardiovascular actions:[12] it may induce cardiac dysrhythmias and hyperkalaemia. Since bupivacaine overdosage is known to induce dysrhythmias[1–4] and since hyperkalaemia enhances bupivacaine cardiotoxicity,[13,14] one could argue that the use of succinylcholine in the resuscitation of bupivacaine toxicity might be dangerous.

Moore and Bridenbaugh[15] reported that succinylcholine did not worsen bupivacaine toxicity in three patients. However, possible interactions between bupivacaine and succinylcholine on cardiac electrophysiology and haemodynamic status have never been investigated. The aim of this study was to determine whether succinylcholine worsened the electrophysiological and haemodynamic impairment induced by a high dose of bupivacaine. We used an anaesthetized dog model[16,17] given a high dose of bupivacaine.[18,19]

Methods

Animal preparation

Eighteen mongrel dogs of either sex, weighing 10 to 15 kg, were anaesthetized with sodium pentobarbital (40 mg · kg⁻¹ iv). The tracheas were then intubated and the lungs were mechanically ventilated with room air (74052, B. Braun, Germany). Body temperature was maintained at 38° C ± 0.5 with an MR 450 rewarming humidifier device (Fisher and Paykel Ltd., New Zealand).

Instrumentation of the animals was as previously described.[20] ECG recordings were taken from standard lead II. A 6-Fr. bipolar electrode catheter (USCI, C.R. Bard, Inc., Billerica, MA) was introduced via the femoral vein under fluoroscopy into the right ventricle, close to the interventricular septum near the tricuspid valve to record the His-bundle ECG.[17] Drugs were administered through a venous catheter placed in the contralateral femoral vein. A 5-Fr. teflon catheter (Plastimed, France) was inserted into the femoral artery and advanced into the descending aorta to monitor mean aortic pressure (MAoP, P10 EZ pressure transducer, Gould Inc., Oxnard, CA) and to withdraw blood samples to verify blood gas stability (pH > 7.35, PaO_2 > 80 mmHg, $PaCO_2$ < 40 mmHg). The contralateral femoral artery was canulated with 5-Fr. high fidelity micromanometer (Millar Instruments, Houston, TX) that was advanced into the left ventricle under fluoroscopy to measure left ventricular pressures. The duration of the animal preparation was about 30 min.

Measurements

The following electrophysiological measurements (expressed in msec) were made: cardiac cycle length (RR interval), PR interval measured from the onset of the P wave to the Q wave of the QRS complex, AH interval measured from the onset of the atrial depolarization to the His bundle ECG of the endocavitary lead, HV interval measured from the His bundle electrogram of the endocavitary lead to the Q wave of ECG lead II, QRS duration, and QT interval corrected by heart rate (QTc, Bazett formula: QTc = $QT/\sqrt{RR}$). The following haemodynamic variables were measured: mean aortic pressure (MAoP, mmHg), left ventricular end diastolic pressure (LVEDP, mmHg) and the peak of the first derivative of left ventricular pressure (LV dP/dt max, mmHg · sec⁻¹) as an index of contractility[21] derived with a Gould differentiator. All these variables were recorded on an ES 1000 polygraph (100 mm · sec⁻¹) (Gould Inc., Oxnard, CA). PaO_2, $PaCO_2$, pH and acid-base status were measured from arterial blood samples (Instrument Laboratory 1306 pH/blood gas analyzer, Italy).

Experimental protocol

Three groups of six dogs were studied. In each animal, a 30-min period was allowed to verify stability of the preparation. Each animal was then given 0.2 mg · kg⁻¹ atropine sulfate iv to prevent vagal reactivity on sinus and atrioventricular nodes.[22] Atropine does not modify the electrophysiological and mechanical changes induced by bupivacaine.[23]

The control group (Group 1) served to determine the stability of the model. These dogs were given only a saline solution (3.5 ml · kg⁻¹ · hr⁻¹, iv). Each of the other two

groups received the same saline solution, and $4 \text{ mg} \cdot \text{kg}^{-1}$ bupivacaine iv over ten seconds, five minutes after atropine. This dose of bupivacaine induces marked myocardial depression and major electrophysiological changes without causing immediate cardiac death.[24] Group 2 was given bupivacaine only. Group 3 was given $2 \text{ mg} \cdot \text{kg}^{-1}$ succinylcholine iv from one minute to two minutes after the administration of bupivacaine.

For Group 1, electrophysiological and haemodynamic data were measured before the administration of atropine sulfate and five minutes later (0 min), and then at 1, 2, 3, 4, 5, 10, 15, and 30 min. For the other groups, electrophysiological and haemodynamic variables were recorded five minutes after atropine administration just before bupivacaine administration (0 min) and then at 1, 2, 3, 4, 5, 10, 15, and 30 min after the end of bupivacaine administration.

Data analysis
Results are expressed as mean ± SEM. Group 2 was compared with the control Group (Group 1) at each time for each variable to test the effects of bupivacaine on the experimental model. Data from Group 3 were compared with those from Group 2 to test the effects of succinylcholine.

Statistical analysis
The stability of each variable over time was verified in the control Group using the Kruskal-Wallis test. The comparisons between groups were performed with the Kruskal-Wallis test followed by the Mann-Whitney test with Bonferroni's correction. Statistical analysis was performed using the differences from the baseline values, to reduce systematic variations between animals. Values of $P < 0.05$ were considered to indicate statistical significance. All the results were analyzed with a 1983 BMDP computer program (BMDP Statistical Software Inc., Los Angeles, CA).

Results
In the control Group (Group 1), each measured variable remained stable over time. Since there were no differences between each variable measured at 1, 2, 3, 4, 5, 10, 15, and 30 min and the baseline value (0 min) (Figures 1–3), atropine sulfate did not modify the electrophysiological and haemodynamic variables in any groups.

Comparing Groups 1 and 2, bupivacaine induced bradycardia ($P < 0.01$), more than 50% PR interval lengthening ($P < 0.01$), and more than 30% AH interval lengthening ($P < 0.01$) from 1 to 30 min after the end of bupivacaine administration (Figure 1). Bupivacaine prolonged the HV interval by more than 100% ($P < 0.01$), caused a widening (>100%) of the QRS complex ($P <$
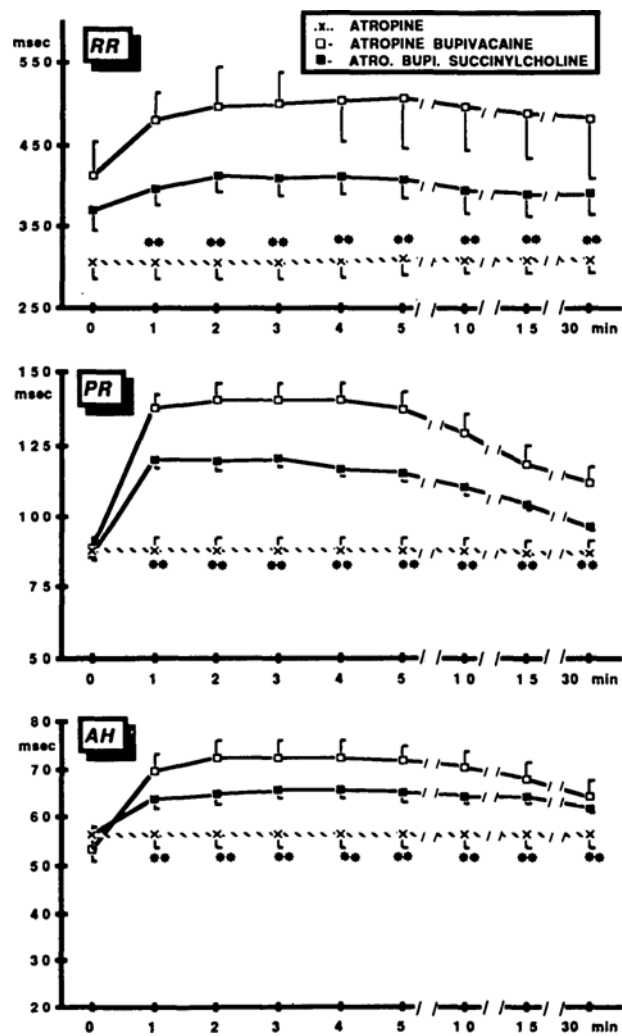

FIGURE 1   Effects of bupivacaine alone (Group 2, -□-) and bupivacaine plus succinylcholine (Group 3, -■-) on the course of electrophysiological variables: RR interval (RR), PR interval (PR) and AH interval (AH). Data are expressed as mean ± SEM. *Control Group, (· · x · ·) versus Group 2. **$P < 0.01$.

0.01), and prolonged QTc interval ($P < 0.01$) from 1 to 30 min after the end of bupivacaine administration (Figure 2). Similarly, bupivacaine impaired the haemodynamic variables, i.e., it decreased LV dP/dt max ($P < 0.01$ from 1 to 15 min, $P < 0.05$ at 30 min) and transiently increased LVEDP ($P < 0.05$ at two to four minutes) by more than 50% (Figure 3). Bupivacaine decreased MAoP, yet the change was not significant. Similar effects of bupivacaine were observed in Group 3 at one minute before succinylcholine administration.

Succinylcholine did not modify the RR, PR and AH intervals previously impaired by bupivacaine (Figure 1). Of the variables of ventricular conduction velocities, HV interval was not modified by succinylcholine, but the QRS
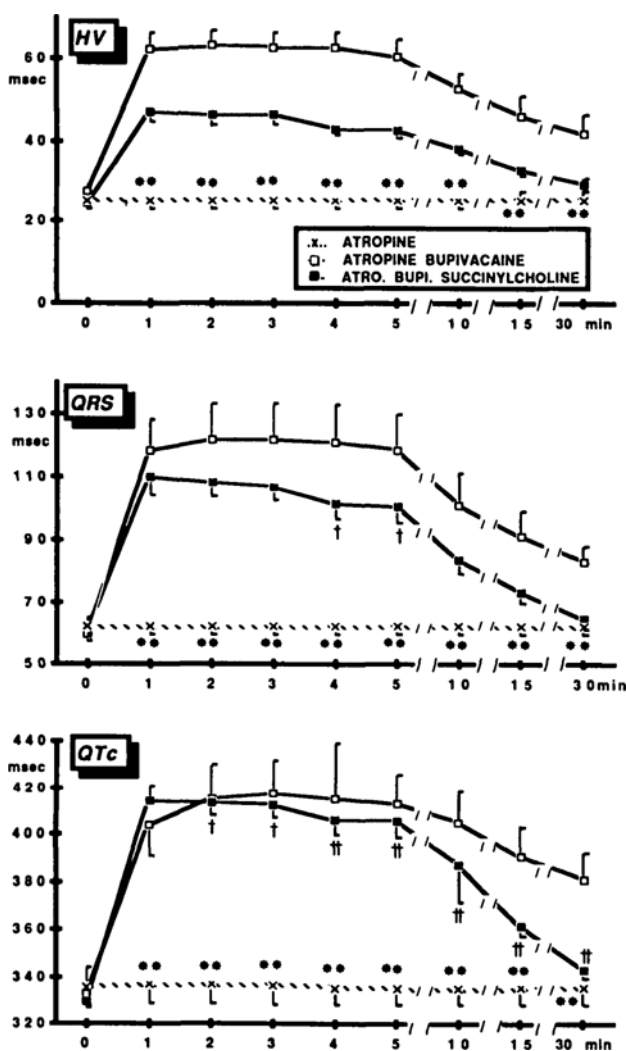
FIGURE 2   Effects of bupivacaine alone (Group 2, -□-) and bup-
ivacaine plus succinylcholine (Group 3, -■-) on the course of the
following ventricular variables: HV interval (HV), QRS duration, and
QTC interval. Data are expressed as mean ± SEM. *Control Group,
(· ·x · ·) versus Group 2. †Group 2 versus Group 3; †$P < 0.05$, **,
††$P < 0.01$

FIGURE 3   Effects of bupivacaine alone (Group 2, -□-) and bupiva-
caine plus succinylcholine (Group 3, -■-) on the course of the follow-
ing haemodynamic variables: mean aortic pressure (MAoP), peak of
the first derivative of left ventricular pressure (LV dP/dt max), and left
ventricular end diastolic pressure (LVEDP). Data are expressed as
mean ± SEM. *Control Group (· ·x · ·) versus Group 2.
*$P < 0.05$, **$P < 0.01$.

duration was reduced at four and five minutes after
succinylcholine (Figure 2). The QTC interval was shorter
in Group 3 than in Group 2 (Figure 2). Finally, succinyl-
choline did not modify the haemodynamic variables
previously impaired by bupivacaine (Figure 3).

Discussion

This study demonstrates that succinylcholine did not
worsen the electrophysiological and haemodynamic effects
induced by a high dose of bupivacaine in anaesthetized
dogs.

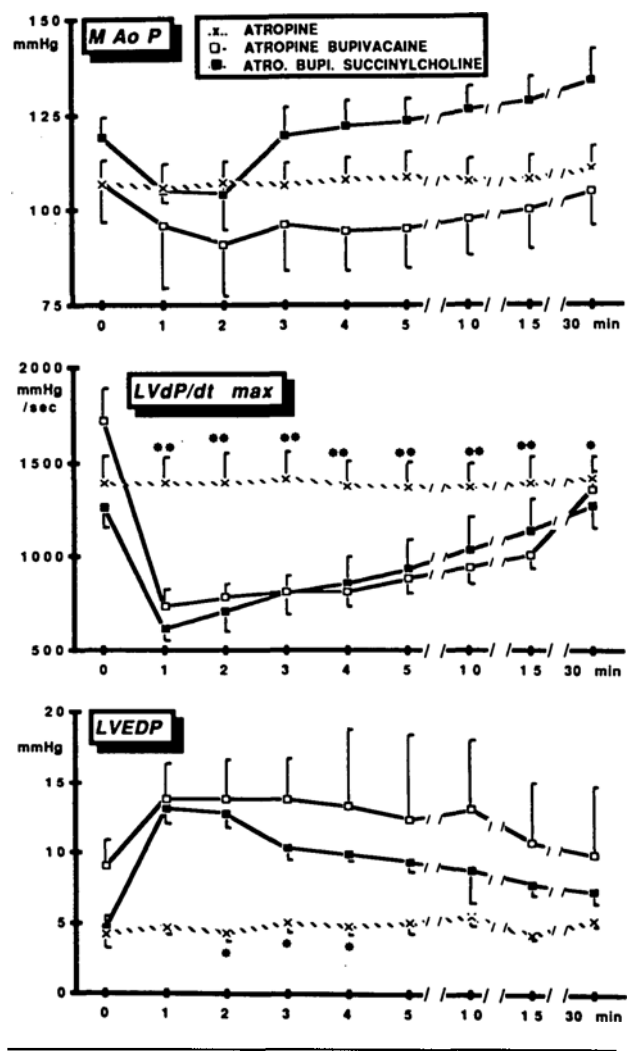All the dogs were given a single dose of sodium pen-

tobarbital. No additional anaesthesia was needed and the
electrophysiological and haemodynamic variables re-
mained stable throughout the experimental period in the
control group. Sodium pentobarbital protects against
episodes of convulsions which can accentuate direct
bupivacaine-induced cardiotoxicity by inducing hypoxia
and acidosis.[5-7] It has also been demonstrated that the
central nervous system can partially mediate bupivacaine
cardiotoxicity.[25-27] Nevertheless, the mortality of bupiva-
caine is mainly due to its cardiotoxicity.

Comparison between the control group and the group
given 4 mg · kg^{-1} bupivacaine *iv* alone showed that bupi-
vacaine induced bradycardia, AV block, and intraventri-

cular block which are similar to the ECG disturbances previously reported.[3,4,13,24,28-30] LV dP/dt max was also reduced and LVEDP increased. In contrast, mean aortic pressure decreased but to a lesser extent. Similar phenomena have been reported in man[31] and in anaesthetized[32] or conscious animals[33] so it can be concluded that the experimental model was appropriate.

Succinylcholine induced a slight shortening of QRS duration at four and five minutes after the administration of bupivacaine. No explanation can be given for this transient improvement. Moreover, it was the only variable of ventricular conduction velocity which was altered; in particular, no change was observed in the evolution of HV interval between Groups 2 and 3. The QTc interval was also shortened after succinylcholine throughout the study. Since it has been reported that a high dose of bupivacaine prolongs QT interval and can induce torsades de pointe, it could be speculated that succinylcholine might protect against such ventricular arrhythmias.[34] However, the dramatic slowing of ventricular conduction velocities represented by HV lengthening and QRS widening is sufficient to induce ventricular arrhythmias by a reentry phenomenon. It is well established that reentrant ventricular arrhythmias can occur when ventricular conduction velocities are slowed and when the drug induces ventricular conduction block.[28,35] For example, Anderson et al.[36] using increasing doses of lidocaine in anaesthetized dogs reported that ventricular arrhythmias occurred with high concentrations of lidocaine. Moreover, these authors using ventricular epicardic mapping demonstrated that ventricular arrhythmias occurred just after lidocaine-induced slowing of ventricular conduction velocities, ventricular conduction blocks and QRS widening. Since the QRS duration is correlated with ventricular conduction velocity,[37] and since it is well established that bupivacaine impairs the maximum upstroke velocity of fast action potentials[38] and therefore impairs ventricular conduction velocity,[39] it could be argued that the main mechanism of bupivacaine-induced ventricular arrhythmias is based on reentry phenomenon.[28,35] Therefore, despite slight QRS and QTc improvements induced by succinylcholine, we postulated that succinylcholine did not protect against the occurrence of reentrant ventricular arrhythmias. In other words, we cannot conclude that succinylcholine improved the cardiac electrophysiology previously altered by bupivacaine.

Finally, care must be taken in extrapolating our results to the clinical setting. It must be emphasized that the dogs did not suffer either cardiovascular collapse or ventricular arrhythmias throughout the study. They were also previously anaesthetized and were given atropine sulfate. These experimental procedures were used to introduce a degree of homogeneity in the model. Moreover, the

arrhythmogenic effects of succinylcholine are partially mediated by its cholinergic actions.[12] Nevertheless, succinylcholine never induced ventricular arrhythmias during the study. The results of our study are in agreement with those reported by Moore and Bridenbaugh.[15] These authors observed that succinylcholine did not worsen bupivacaine cardiotoxicity in three patients who suffered bupivacaine overdose. Taking into account the limitations of the model described above, these results confirmed that succinylcholine does not worsen the cardiotoxicity of bupivacaine.

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