TITLE: OXYGEN DEPENDENCY OF DOXORUBICIN CARDIOTOXICITY IN PERFUSED RAT HEARTS

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It is well known that the clinical usefulness of doxorubicin as an anti-cancer drug is limited by its cardiotoxicity; however, its mechanisms of toxicity remain elusive. It was demonstrated recently that hepatotoxicity due to doxorubicin was greater in periportal regions of the liver lobule where oxygen tension is higher.[1] To test whether O_2 tension also influences cardiotoxicity due to doxorubicin, isolated hearts were perfused at constant pressure by the method of Langendorff with Krebs-Henseleit solution saturated with 5%CO_2 and either 95%O_2 (high O_2 tension) or 20%O_2 (low O_2 tension). Toxicity due to doxorubicin was evaluated from changes in cardiac function (heart rate, the rate of change in developed pressure, and left ventricular systolic pressure), coronary flow, and uptake of trypan blue. Parameters of cardiac function were stable in control hearts perfused at high O_2 tension for 30 min. On the other hand, coronary flow increased and heart rate and the rate of the change in pressure decreased in hearts perfused at low O_2 tension. At high O_2 tension, doxorubicin (30 µM) increased O_2 uptake by about 50 µmol/g/h within 5 min. In contrast, doxorubicin had no effect on O_2 uptake in hearts perfused at low O_2 tension. Over 30 minutes of perfusion with doxorubicin, heart rate, left ventricular systolic pressure, the rate of change in ventricular pressure, and coronary flow decreased at both high and low O_2 tension. Compared to values for the respective untreated controls, the relative changes were greater at high than at low O2 tension. Irreversible cell damage as assessed by uptake of trypan blue was significantly different from control at high (34% staining) but not at low (26% staining) O_2 tension. In KCl-arrested hearts, O_2 uptake was increased by doxorubicin at high O_2 tension by 72 µmol/g/h, but was unaffected at low O_2 tension. Under these conditions cell death due to doxorubicin was significantly greater at high (35%) than at low (13%) O_2 tension. These data indicate that doxorubicin-induced cell death is three-fold greater at high O_2 tension, and are consistent with the hypothesis that O_2 tension is an important determinant of toxicity due to doxorubicin.

Reference

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A564

TITLE: NEGATIVE INOTROPIC EFFECTS OF PROPOFOL VS THIOPENTAL: ASSESSMENT IN AN ISOLATED VENTRICULAR SEPTUM MODEL

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Propofol depresses the hemodynamics in a dose-related manner. Negative inotropism is one of the mechanisms.[1] The rate of recovery of its cardiac depression is unclear. We quantified the negative inotropism of propofol and the rate of recovery in comparison with thiopental.

Seven isolated rabbit ventricular septa were studied. The septum was perfused via its first septal artery with Kreb-Ringer-Bicarbonate buffer solution equilibrated with 95% O_2 and 5% CO_2. The perfusion rate was 1 ml/gm/min and the tissue temperature was 34°C. The resting tension was 3-5 gm. Each septum was stimulated supramaximally, 5 volts for 5 msec, at 1.5-1.8 Hz with a pair of field electrodes. The isometric contraction was stabilized for 30 min before the experiment began. Baseline peak developed tension (T) was more than 2 times the resting tension in each preparation. The perfusates were propofol and thiopental each with concentration of 0.8×10^{-4}M, 1.7×10^{-4}M, and 3.5×10^{-4}M, individually given for 3 min at random sequence. T, peak dT/dt, time from stimulation to beginning of contraction (Latency), and time from beginning of contraction to peak tension (TPT) were recorded. Between perfusions, recovery to 95% of baseline T was timed. Data (mean± SEM) was analyzed with repeated measures ANOVA and Dunnett's contrast test for $p < 0.05$ between doses and between drugs.

At 0.8×10^{-4}M, 1.7×10^{-4}M, and 3.5×10^{-4}M, propofol significantly decreased T by 19%, 36% and 54%, respectively, while thiopental did so by 30%, 49% and 69%, respectively; $p < 0.05$ was also seen between drugs at all concentrations. Neither drugs changed the latency. Propofol shortened the TPT only at the high concentration (from 161±6msec to 137±3 msec), while thiopental did so at both the medium (to 141±4 msec) and the high (to 126±4 msec) concentrations, $p < 0.05$. On washout, propofol depression took much longer to recover at all concentrations (12±3 vs 2±1, 24±4 vs 5±1, 41±5 vs 6±1; in min, $p < 0.01$).

In conclusion, propofol and thiopental directly depress the myocardial contractility in a dose-related manner. Although propofol is less potent, it binds to the myocardial tissue longer than thiopental. The shortened TPT suggests a mechanism of inhibited availability of intracellular calcium caused by both drugs.

Reference

1. Anesthesiology 71:A29, 1989