# Comparative Inotropic Effects of Local Anesthetics in Isolated Cat Papillary Muscles

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The direct inotropic action of seven local anesthetics: procaine, mapivacaine, lidocaine, tetracaine, chloroprocaine, bupivacaine and etidocaine were compared in isolated cat papillary muscles. All of the local anesthetics produced a dose-related depression of maximal velocity of shortening (Vmax), maximal developed force (Fm) and maximal dF/dt. The more potent local anesthetics such as bupivacaine and etidocaine depressed myocardial contractility at significantly lower concentrations than the less potent local anesthetics such as lidocaine and mepivacaine. Depression of Vmax by bupivacaine or etidocaine was three times greater than that by lidocaine and ten times greater than that by procaine. At the same concentration ($10^{-4}$M), direct myocardial depression was demonstrated in the following order of severity: etidocaine $\geq$ bupivacaine $>$ tetracaine $>$ chloroprocaine $\geq$ lidocaine $>$ mepivacaine $>$ procaine. (Key words: isolated muscle preparation, local anesthetics, myocardial contractility)

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Much information has been obtained on the cardiac effects of local anesthetics, in particular lidocaine, owing to the current use of lidocaine for the treatment of cardiac arrhythmias[1–4]. Since Albright reported cardiac arrest associated with regional anesthesia by bupivacaine and etidocaine[5], a considerable amount of animal experimentation in order to clarify the mechanisms of cardiotoxicity of these local anesthetics[6–10]. Although there is a report on comparative cardiac effects of some local anesthetics utilizing the isolated perfused rabbit Langendorff heart preparation[11], no data, using the isolated muscle preparation, is available concerning the comparative inotopic effects of local anesthetics including procaine, mepivacaine and chloroprocaine which have been widely used in clinical anesthesia. We, therefore, evaluated the direct inotropic effect of seven local anesthetics:procaine, mepivacaine, lidocaine, tetracaine, chloroprocaine, bupivacaine and etidocaine in isolated cat papillary muscles.

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## Methods

Papillary muscles were quickly excised from the right ventricles of adult cats (2.6–3.5 kg) anesthetized with sodium pentobarbital 30 mg·kg$^{-1}$ i.p. The papillary muscle were suspended in Krebs-Henseleit solution with 1 mg·ml$^{-1}$ of dextrose. The bathing solution was kept at a constant temperature of 35°C and bubbled with 95 per cent $O_2$ – 5 per cent $CO_2$ gas mixture to maintain $P_{O_2}$ over 500 mmHg, $P_{CO_2}$ around 40 mmHg and pH 7.4. Sixty one muscles were studied : 6 muscles were treated with procaine, 9 with mepivacaine, 12 with lidocaine, 9 with tetracaine, 8 with chloroprocaine, 10 with

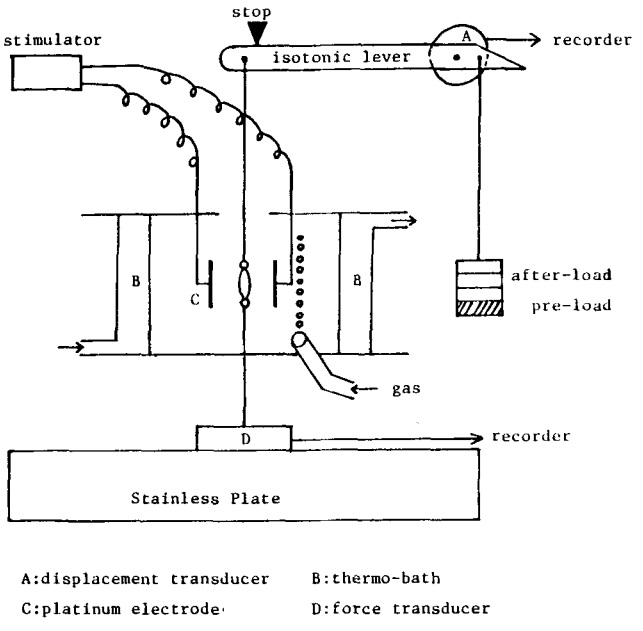


**Fig. 1.** A schema of experimental apparatus.

bupivacaine, 7 with etidocaine, respectively. The apparatus for muscle preparations, isotonic and isometric measurements of muscle mechanics, and recording systems were described in detail in the previous reports[12,13]. Muscles were stimulated at 0.2 Hz by parallel platinum electrodes delivering 5 msec square-wave pulses at voltages 20 per cent above threshold. The muscle length was set by a small preload and kept constant throughout the procedure for each muscle study (fig. 1). Maximal velocity of shortening (Vmax) was approximated by the value of the velocity of shortening at 0.5 $g \cdot mm^{-2}$. Maximal developed force (Fm) was obtained by the maximal afterload. Changes in muscle length and force of contraction with their first-time derivatives (dl/dt and dF/dt) obtained by R-C differentiators were recorded on a multichannel recorder at a paper speed of 100 $mm \cdot sec^{-1}$. Velocity of shortening was expressed in units of muscle length per second ($ml \cdot sec^{-1}$), and force was expressed in grams per unit of cross-sectional area ($g \cdot mm^{-2}$).

After equilibration for an hour, control measurements of Vmax ($ml \cdot sec^{-1}$), Fm ($g \cdot mm^{-2}$) and maximal dF/dt ($g \cdot mm^{-2} \cdot sec^{-1}$) were made. Each local anesthetic, which was diluted in perfused solution just prior to the study, was directly administered to bathing solution from a concentration of $10^{-6}$M to $3 \times 10^{-4}$M in a stepwise fashion. Determinations of the above components of muscle mechanics were repeated, at least 10 min after stabilization of contraction height, at concentrations of $10^{-6}$M, $10^{-5}$M, $3 \times 10^{-5}$M, $10^{-4}$M, and $3 \times 10^{-4}$M. Control measurements without anesthetics were repeated, after which the weight and length of the muscle were measured and cross-sectional area was calculated. Muscle preparations were included in these data only when repeated control measurements reached above 90 per cent of original control values. All values were expressed as mean ± SEM and statistical analysis was performed utilizing analysis of variance followed by Student t test for group mean data. $P$ values less than 0.05 were considered statistically significant.

## Results

The average length and cross-sectional area of 61 muscles were 7.2 ± 0.4 mm and 1.14 ± 0.09 $mm^2$, respectively. There were no significant differences in both muscle lengths and cross-sectional areas between local anesthetics studied.

**Table 1.** Effects of local anesthetics on Vmax, Fm and maximal dF/dt (part 1)

| | Vmax ($ml \cdot sec^{-1}$) | Fm ($g \cdot mm^{-2}$) | maximal dF/dt ($g \cdot mm^{-2} \cdot sec^{-1}$) |
|---|---|---|---|
| *procaine* ($n = 6$) | | | |
| control | 1.38 ± 0.08 | 4.42 ± 0.20 | 11.96 ± 0.94 |
| $10^{-6}$M | 1.37 ± 0.07 | 4.40 ± 0.23 | 11.83 ± 0.86 |
| $10^{-5}$M | 1.38 ± 0.09 | 4.41 ± 0.18 | 11.81 ± 1.03 |
| $3 \times 10^{-5}$M | 1.34 ± 0.08 | 4.31 ± 0.20 | 11.54 ± 1.05 |
| $10^{-4}$M | 1.31 ± 0.10* | 4.13 ± 0.22* | 11.15 ± 0.87* |
| $3 \times 10^{-4}$M | 1.27 ± 0.12* | 3.98 ± 0.25* | 10.86 ± 0.93* |
| *mepivacaine* ($n = 9$) | | | |
| control | 1.44 ± 0.07 | 4.33 ± 0.18 | 12.11 ± 0.54 |
| $10^{-6}$M | 1.44 ± 0.08 | 4.31 ± 0.19 | 12.12 ± 0.56 |
| $10^{-5}$M | 1.43 ± 0.08 | 4.16 ± 0.21 | 11.61 ± 0.56 |
| $3 \times 10^{-5}$M | 1.33 ± 0.08* | 3.89 ± 0.20* | 11.02 ± 0.47* |
| $10^{-4}$M | 1.26 ± 0.09* | 3.36 ± 0.22* | 9.43 ± 0.64* |
| $3 \times 10^{-4}$M | 1.06 ± 0.07* | 2.80 ± 0.16* | 8.19 ± 0.41* |
| *lidocaine* ($n = 12$) | | | |
| control | 1.43 ± 0.07 | 4.60 ± 0.20 | 12.29 ± 0.55 |
| $10^{-6}$M | 1.39 ± 0.07 | 4.54 ± 0.24 | 12.10 ± 0.57 |
| $10^{-5}$M | 1.37 ± 0.07* | 4.37 ± 0.26 | 11.91 ± 0.45 |
| $3 \times 10^{-5}$M | 1.21 ± 0.08* | 4.02 ± 0.19* | 11.42 ± 0.47* |
| $10^{-4}$M | 1.14 ± 0.06* | 3.26 ± 0.27* | 8.78 ± 0.50* |
| $3 \times 10^{-4}$M | 0.79 ± 0.07* | 2.58 ± 0.16* | 5.83 ± 0.44* |
| *tetracaine* ($n = 9$) | | | |
| control | 1.50 ± 0.15 | 4.29 ± 0.21 | 12.00 ± 0.93 |
| $10^{-6}$M | 1.51 ± 0.14 | 4.22 ± 0.23 | 11.84 ± 0.94 |
| $10^{-5}$M | 1.41 ± 0.12* | 3.95 ± 0.23* | 11.46 ± 1.03* |
| $3 \times 10^{-5}$M | 1.24 ± 0.07* | 3.45 ± 0.16* | 9.84 ± 0.86* |
| $10^{-4}$M | 1.07 ± 0.09* | 2.76 ± 0.24* | 7.95 ± 1.06* |
| $3 \times 10^{-4}$M | 0.65 ± 0.07* | 1.58 ± 0.20* | 4.65 ± 0.56* |

Mean values ± SEM are shown. $n$ = number of papillary muscle. Vmax = maximal velocity of shortening at $0.5 g \cdot mm^{-2}$. Fm = maximal developed force.

* significant difference vs control values.

The mean values for components of muscle mechanics before and after administration of anesthetics are summarized in table 1 and table 2. No significant differences were obtained in control values for each anesthetic in components of muscle mechanics between anesthetics. Per cent changes in Vmax for each anesthetic are shown in figure 2. No changes in Vmax were observed by procaine at $10^{-6}$M and $10^{-5}$M concentrations, mepivacaine, tetracaine and chloroprocaine at a $10^{-6}$M concentration, while dose-dependent decreases were obtained for all anesthetics at other concentrations. Decreases in Vmax for procaine, mepivacaine, lidocaine and chloroprocaine were significantly less than those for tetracaine, bupivacaine and etidocaine. In contrast to Vmax, Fm and maximal dF/dt were decreased progressively with increasing the concentrations of anesthetics even at the lowest cocentration of $10^{-6}$M (fig. 3 and fig. 4). Bupivacaine and etidocaine were most

**Table 2.** Effects of local anesthetics on Vmax, Fm and maximal dF/dt (part 2)

| | Vmax ($ml \cdot sec^{-1}$) | Fm ($g \cdot mm^{-2}$) | maximal dF/dt ($g \cdot mm^{-2} \cdot sec^{-1}$) |
|---|---|---|---|
| *chloroprocaine* ($n = 8$) | | | |
| control | 1.37 ± 0.06 | 4.37 ± 0.19 | 12.23 ± 0.98 |
| $10^{-6}$M | 1.36 ± 0.08 | 4.28 ± 0.21 | 11.98 ± 0.95 |
| $10^{-5}$M | 1.28 ± 0.12* | 4.17 ± 0.23 | 11.80 ± 0.86 |
| $3 \times 10^{-5}$M | 1.26 ± 0.09* | 3.98 ± 0.26* | 11.19 ± 0.85* |
| $10^{-4}$M | 1.02 ± 0.07* | 3.40 ± 0.24* | 9.53 ± 0.96* |
| $3 \times 10^{-4}$M | 0.88 ± 0.05* | 2.61 ± 0.18* | 7.55 ± 0.54* |
| *bupivacaine* ($n = 10$) | | | |
| control | 1.42 ± 0.10 | 4.53 ± 0.18 | 12.30 ± 0.62 |
| $10^{-6}$M | 1.35 ± 0.12* | 4.16 ± 0.22* | 11.25 ± 0.72* |
| $10^{-5}$M | 1.23 ± 0.09* | 3.70 ± 0.23* | 9.80 ± 0.86* |
| $3 \times 10^{-5}$M | 0.85 ± 0.08* | 3.22 ± 0.19* | 8.92 ± 0.96* |
| $10^{-4}$M | 0.75 ± 0.07* | 2.39 ± 0.20* | 6.88 ± 1.03* |
| $3 \times 10^{-4}$M | 0.47 ± 0.11* | 1.36 ± 0.24* | 4.06 ± 1.04* |
| *etidocaine* ($n = 7$) | | | |
| control | 1.46 ± 0.13 | 4.65 ± 0.27 | 12.15 ± 0.93 |
| $10^{-6}$M | 1.31 ± 0.09* | 4.13 ± 0.32* | 11.11 ± 1.01* |
| $10^{-5}$M | 1.27 ± 0.12* | 3.88 ± 0.27* | 9.20 ± 0.94* |
| $3 \times 10^{-5}$M | 1.09 ± 0.08* | 3.13 ± 0.28* | 9.02 ± 0.93* |
| $10^{-4}$M | 0.76 ± 0.07* | 2.72 ± 0.26* | 7.39 ± 0.86* |
| $3 \times 10^{-4}$M | 0.42 ± 0.06* | 1.16 ± 0.18* | 3.49 ± 0.48* |

Mean ± SEM are shown. $n$ = number of papillary muscle. Vmax = maximal velocity of shortening at $0.5 g \cdot mm^{-2}$. Fm = maximal developed force.

* significant difference vs control values.

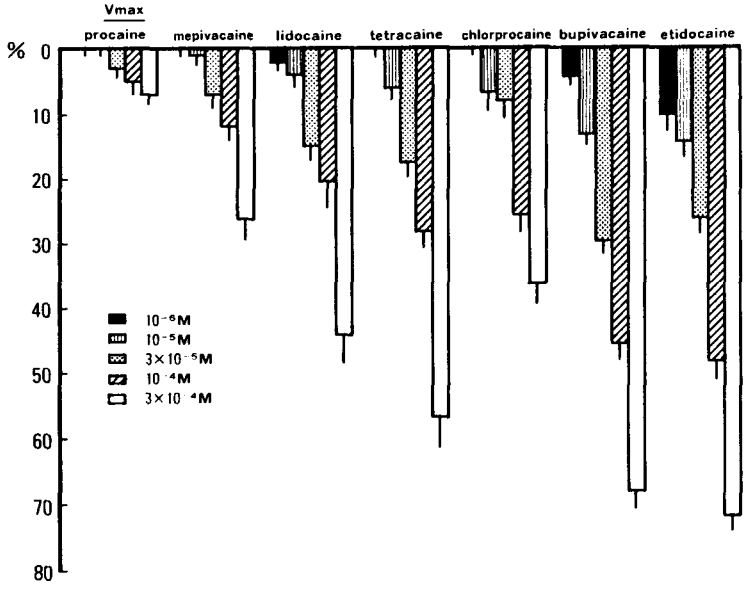


**Fig. 2.** Per cent depression in Vmax by various concentrations of seven local anesthetics.

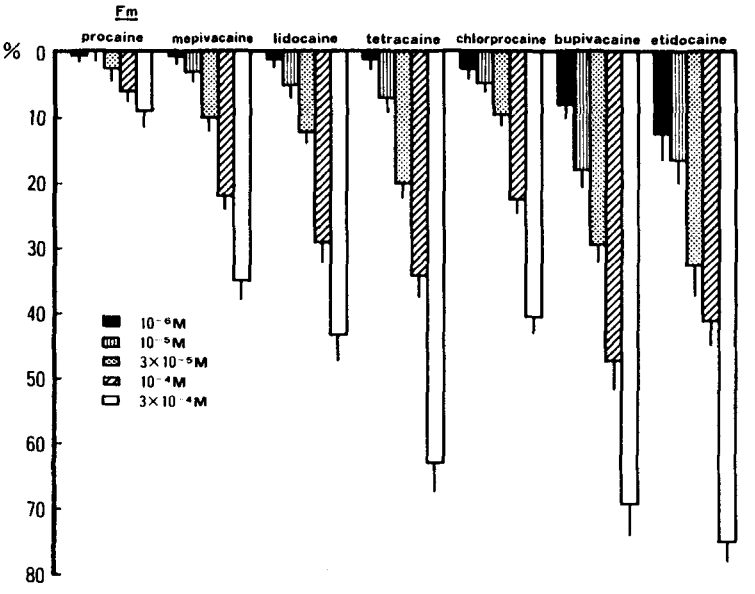


**Fig. 3.** Per cent depression in Fm by various concentrations of seven local anesthetics.

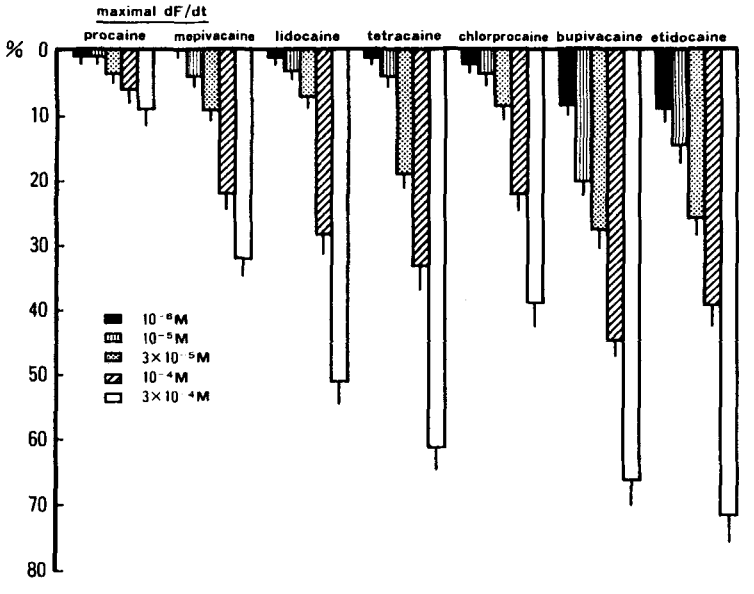


**Fig. 4.** Per cent depression in maximal dF/dt by various concentrations of seven local anesthetics.

potent in terms of depression in contractile performance, while procaine was significantly less depressant than other anesthetics.

After a negative inotropic action of each anesthetic was fully developed the bathing solution was replaced with fresh anesthetic-free solution, then the contraction increased gradually and almost complete recovery was established within 30 min even after a high concentration of a potent anesthetic was administered.

## Discussion

Our results indicate that all of the seven local anesthetics studied are capable of exerting a direct negative inotropic action. Tetracaine, bupivacaine and etidocaine comprise one group of local anesthetics that are significantly more cardiodepressant than procaine, mepivacaine, lidocaine and chloroprocaine. The effect of the seven drugs on myocardial contractility as determined by dose-response

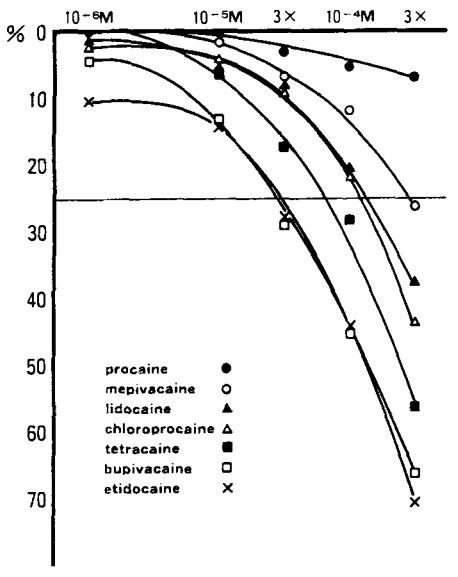


**Fig. 5.** Dose-response curves of Vmax for seven local anesthetics.

curves of Vmax is illustrated in figure 5. A 25 per cent depression of Vmax occurred at a concentration of $2.7 \times 10^{-5}$M of bupivacaine (7.8 $\mu g \cdot ml^{-1}$) and etidocaine (7.5 $\mu g \cdot ml^{-1}$). Tetracaine caused a similar depression at a concentration of $6.5 \times 10^{-5}$M (17.2 $\mu g \cdot ml^{-1}$). Mepivacaine, lidocaine and chloroprocaine required significantly higher concentration ($1.1\text{-}2.8 \times 10^{-4}$M:68.9 $\mu g \cdot ml^{-1}$ for mepivacaine, 28.0 $\mu g \cdot ml^{-1}$ for lidocaine and 32.5 $\mu g \cdot ml^{-1}$ for chloroprocaine) to produce a 25 per cent depression of myocardial contractility. Figure 6 provides a comparison of per cent depression of Vmax and Fm by seven drugs at a concentration of $10^{-4}$M, causing direct myocardial depression in the following order of severity:etidocaine $\geq$ bupivacaine > tetracaine > chloroprocaine $\geq$ lidocaine > mepivacaine > procaine.

This difference in in vitro cardiodepression between local aesthetics seems to be related to their affinity for and duration of binding to the sodium channels[14,15]. Bupivacaine possibly also blocks calcium channels, since this drug severely depresses automaticity which is a calcium dependent variable.

It has been suggested that cardiodepressant effects of local anesthetics are related to their physical chemical properties. Because more cardiodepressant local anesthetics, such as bupivacaine and etidocaine are extremely lipid soluble and extensively protein bound, they might penetrate cardiac membranes more readily, and then produce more myocardial depression than drugs which are less lipid soluble and less protein bound[11,16]. In our study, bupivacaine and etidocaine exerted a negative inotropic effect that was nine to ten times greater than that of procaine, and about four times greater than that of lidocaine as estimated by a 25 per cent depression in Vmax for each drug. It was reported that bupivacaine was four times more potent than lidocaine in depressing LV dp/dt in anesthetized pigs[17], so that our results in the isolated muscle preparation seems to support their data in intact animals. Bupivacaine and etidocaine were reported to be approximately four times more potent than lidocaine in producing conduction block in the isolated desheathed rabbit vagus C fibers[18]. Therefore, the relative anesthetic potency and a negative inotropic action of these two drugs seems to be similar. The relative myocardial depressant action of various local anesthetics is correlated with their intrinsic anesthetic potency[15]. We observed also some relationship between relative negative inotropism (procaine = 1) and relative anesthetics intrinsic potency (procaine = 1), when we compare relative negative inotropism for each drug from figure 5 and figure 6 (fig. 7). It will then be concluded that the more potent local anesthetics, such as bupivacaine and etidocaine may be relatively more cardiotoxic than the less potent local anesthetics as mepivacaine or lidocaine. The cardiotoxicity of bupivacaine has been pointed out by many investigators[7,10,17], and cardiac resuscitation is more difficult following bupivacaine-induced cardiovascular collapse[17,19]. It is also reported that acidosis with hypoxia markedly potentiates the cardiotoxicity of bupivacaine[8,20].

Since the present study was performed in vitro utilizing cat papillary muscles at contraction frequency of 0.2 Hz with provision of substrate and oxygen by diffusion, conclusions may not be directly applicable

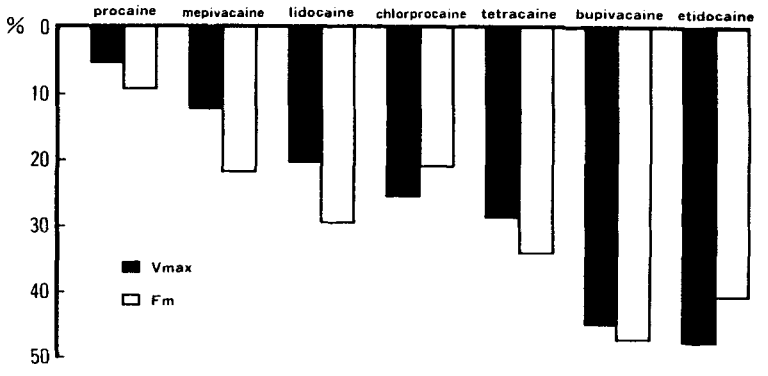


**Fig. 6.** Comparison of depression in Vmax and Fm at a concentration of $10^{-4}$M.

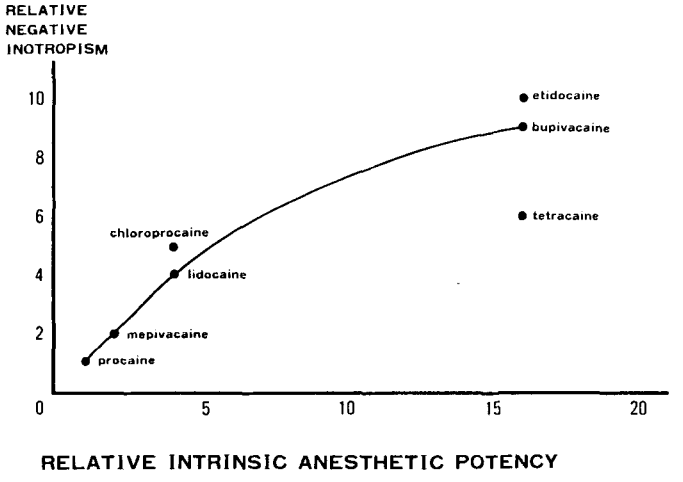


**Fig. 7.** Relationship between relative intrinsic anesthetic potency (procaine = 1) and relative negative inotropism (procaine = 1) of local anesthetics.

to clinical situation. However, our results suggest that the less cardiodepressant local anesthetics might be preferably selected for regional anesthesia especially in patients with impaired myocardial function. It will be recommended that epinephrine should be added to local anesthetics in order to reduce total amount of doses, particularly in cases where prolonged and continuous administrations of local anesthetics would be required. We agree with Mark's proposal[21] that the use of a test dose containing epinephrine, the use of repeated small doses instead of a large bolus and improved patient monitoring are mandatory to avoid cardiodepression by epidural anesthesia with the more potent local anesthetics such as bupivacaine.

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