# Cocaine-like effect of ketamine in frog myocardium

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*This study was undertaken to determine the effects of ketamine on sympathetic neurotransmission in frog myocardium. The effects of ketamine was compared with those ofdroperidol and thiopental.*

*In the electrically driven ventricular strips of frog heart, ketamine (10~$^{7}$-10$^{e}$M) was found to be ineffective on contractility but it produced negative inotropic effects at higher concentrations (>10$^{e}$M). Thiopental and droperidol also depressed the contractile activity of the frog myocardium. However, ketamine (10$^{e}$M) which has no direct positive inotropic effect, increased the positive inotropic responses to transient additional stimulations. Ketamine (10 M) did not change the positive inotropic effects of exogenously applied noradrenaline. Thiopental (10$^{e}$M) and droperidol (10$^{e}$M) did not increase the positive inotropic responses to transient additional stimulations.*

*These resuts suggest that ketamine facilitates sympathetic neurotransmission in frog myocardium by inhibiting neuronal uptake of the neurotransmitter in sympathetic nerve endings. [Turk J Med Res 1992, 10(4): 180-184]*

**Key Words:** Ketamine, Neuronal-uptake, Frog ventricle

The administration of ketamine is associated with an increase in arterial pressure and tachycardia (1,12). For these reasons ketamine has been recommended as the agent of choice in patients with hypovolemic shock (3) and for the aged and critically ill in order to avoid cardiovascular collapse after induction of anesthesia (4). The cardiovascular effects of ketamine may contraindicate its use in patients with hypertension (5).

Although evidence has been produced for a vagolytic action (6), the cardiovascular effects of ketamine appear to result mainly from its interaction with the sympathetic nervous system. Ketamine stimulates the central sympathetic nervous system directly (7) and indirectly by desensitization of baroreceptors (8). Ketamine has been shown to inhibit the uptake of noradrenaline into the isolated rat heart (9), rabbit heart (10) and into rabbit aorta and pulmonary artery strips (11).

It has been postulated that ketamine blocks neuronal re-uptake of noradrenaline (12). This study was designed to examine inhibition of re-uptake of neurotransmitter by ketamine and to compare its effects with cocaine in frog myocardium. We also aimed to study the effects of droperidol and theopental on sympathetic neuronal transmission using the same experimental condition.

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## MATERIALS AND METHODS

Ventricular strips prepared from the heart of the pithed frog Rana temporaria (25-75g) were used. Each strip was mounted vertically in an organ bath containing 20 ml of glucose-free, frog Ringer's solution of the following composition (mM): NaCI, 111.0;KCI, 1.9; CaCfe, 1.1;NaHC03, 2.4;NaH2P04, 0.07. The bathing solution was kept at room temperature and a gassed with **O2**. Each tissue was maintained at 0.5g resting tension and preparation was allowed to stabilize for 1 hr, the bathing fluid being replaced every 15 min. Muscle contractions were recorded isometrically by a force displacement transducer (Ugo Basile 7003) and displayed on a recorder (Ugo Basile 7070).

Ventricular strips were driven electrically through a pair of parallel platium electrodes by square-wave pulses of 3 msec duration and supramaximal voltage at a frequency of 0.3 Hz using a Grass 5SS stimulator. Transient additional stimulations were applied for 20 sec with following parameters of train stimulation 100V,5 msec duration and at 1,2,4 and 8 Hz. This

method of using transient additional stimulation has been used for the investigation of presynaptic adrenergic receptors in the guinea-pig left atrium (13) and in the frog ventricle strip (14). Concentration-response curves were obtained with step-wise cumulative addition of drugs.

The concentrations of drugs in the bathing medium were increased only when the response to the previous concentration had attained a maximal and steady level. After completion of the concentration-response curve, the strip was washed every 10 min for 3 times until the response returned to control level. Then the antagonist was added and 30 min later a new concentration-response curve to drugs was reobtained.

Following drugs were used

Ketamine (Parke Davis/Padeko), thiopental (Abbot), droperidol (Jannsen), cocaine (Geigy, phentolamine (Ciba), prazosin (Pfizer), atropine (Sigma), cimetidine (Sigma), propranolol (Ayerst), guanethidine (Ciba).

The mean values and their standard error (SE) were computed and subjected to statistical analysis for a significance of $p<0.05$ level using the Student's t test for paired observations.

## RESULTS

Effects of anaesthetic drugs on electrically driven strips of frog ventricle:

Ketamine ($10^{-7}$-$10^{-5}$M), thiopental and droperidol ($10^{-7}$-$10^{-5}$M) failed to produce a positive inotropic effect in isolated strips from the ventricle of the frog. Ketamine, thiopental and droperidol produced a marked negative inotropic effect at concentrations greater than $10^{-5}$M (Fig 1).

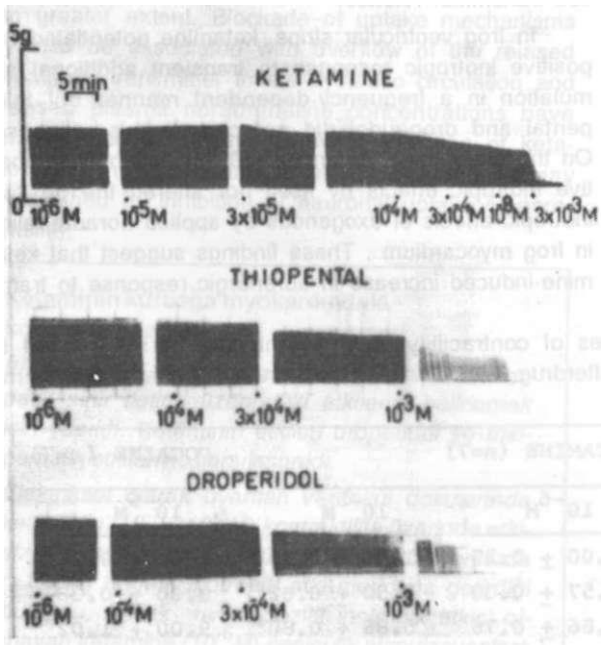


**Figure 1.** Effects of various concentrations of ketamine, thiopental and droperidol on the contractility of isolated frog ventricular strips.

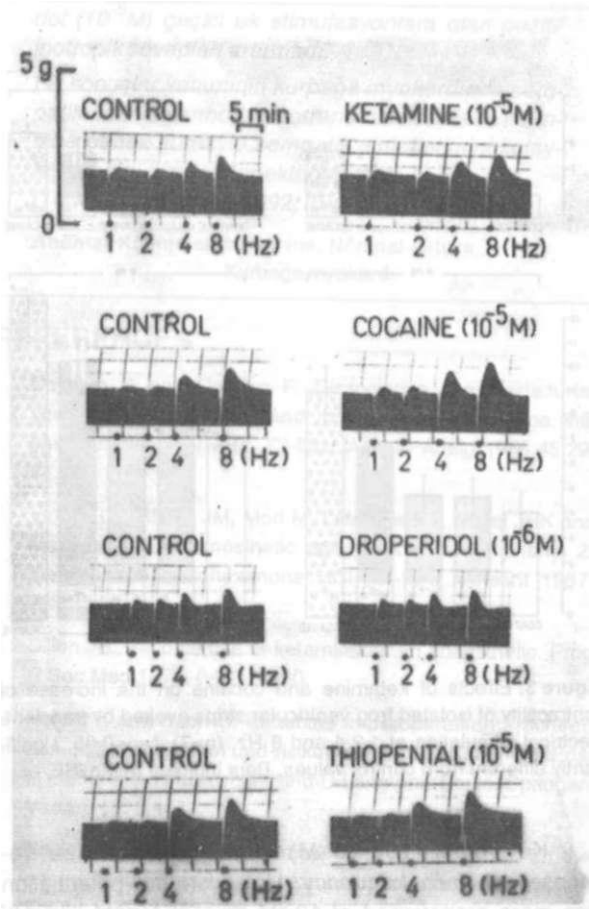


**Figure** 2. Effects of ketamine, cocaien, droperidol and thiopental on the increase of contractility of isolated frog ventricular strips evoked by transient-electrical stimulation.

These negative inotropic action of drugs was not prevented by phentolamine ($10^{-6}$M), atropine ($10^{-6}$M) and cimetidine ($10^{-5}$M). None of the antagonists used at these concentrations caused any inotropic effect on the ventricle strips.

Effects of anaesthetic drugs on the response to transient additional stimulation of electrically driven strips of frog ventricle:

Transient additional stimulations caused frequency-dependent increases in the contractions of isolated ventricular strips. Cocaine ($10^{-5}$M) significantly potentiated these increased contractions at all frequencies (Fig 2,3). These incremental responses were substantially inhibited by propranolol ($10^{-6}$M) and guanethidine ($10^{-4}$M).

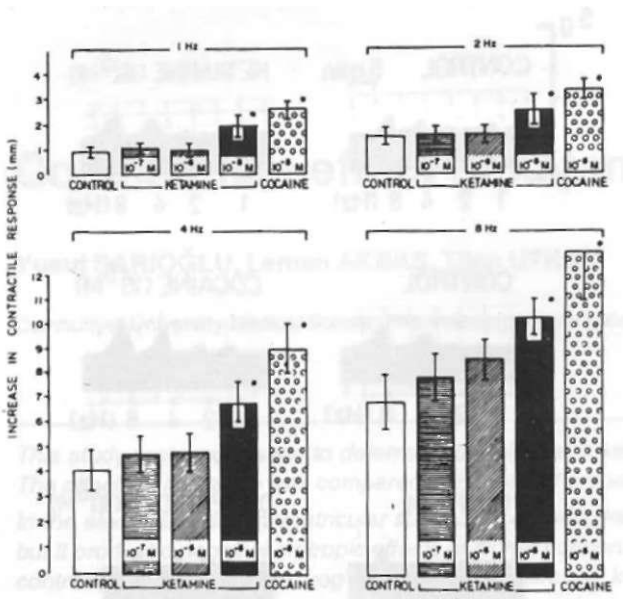


**Figure 3.** Effects of ketamine and cocaine on the increase of contractility of isolated frog ventricular strips evoked by transient-electrical stimulation at 1,2,4 and 8 Hz. (n*7), *=p<0.05, significantly different from control values. Bars indicate mean+SE.

Ketamine (10"$^{7}$-10"$^{5}$M) potentiated these responses at each frequency. However, the potentiation was more pronounced at 10"$^{5}$M than at 10-7M and 10"$^{6}$M (Fig 2,3, Table 1). Thiopental and droperidol (10"$^{6}$-10'$^{5}$M) did not change these responses at each frequency (Table 2).

## DISCUSSION

Ketamine is a dissociative anaesthetic agent which has been shown to produce marked increases in arterial blood pressure, heart rate and cardiac output in man and in several animal species (15, 16). Ketamine has also been shown to produce dose dependent negative chronotropic and inotropic effect in perfused rabbit heart (8), in left ventricular trabeculae of the rat (17), and in Guinea pig atrium (18). Various authors also reported the positive inotropic effect of ketamine on isolated dog right ventricular trabeculae (19), on isolated rat atrial (20) and on rat cardiac papilary muscle (21). It is clearly seen that previous studies have produced conflicting evidence concerning the direct effect of ketamine on the myocardium of different species and the inotropic effects of ketamine in frog ventricular muscle is not documented.

The results of the present study show that of 10"$^{7}$-10"$^{5}$M ketamine, thiopental and droperidol did not prodance on the isolated strips of frog ventricle. Higher concentrations (>10"$^{5}$M) of these drugs produced a depression of the contractile force in a dose-dependent manner. The negative inotropic effect of higher concentrations of ketamine in frog myocardium can not be due to activation of cholinergic and histamine-H2 receptors because it was not antagonized by atropine (10"$^{6}$M) and cimetidine (10"$^{5}$M). The negative inotropic effect of ketamine at the higher concentrations appers to be non-specific. The effect of ketamine may be attributed to its local anaesthetic properties in influencing surface membrane or protein structure functions as a non-specific effect (17).

The increase of the inotropic response to transient additional electrical stimulation is considered to be related to increased transmitter release from the adrenergic nerve terminals. Since the positive inotropic response to transient additional stimulation was abolished by a beta-adrenoceptor blocking agent propranolol or by 2-h exposure to guanethidine, it in due to increased transmitter release.

In frog ventricular strips, ketamine potentiated the positive inotropic response to transient additional stimulation in a frequency-dependent manner but thiopental and droperidol did not change this response. On the other hand, ketamine (10"$^{5}$M) had neither positive inotropic effects by itself nor altered the positive inotropic effects of exogenous by applied noradrenaline in frog myocardium . These findings suggest that ketamine-induced increase in adrenergic response to trans-

Table 1. Effects of ketamine and cocaine on the increases of contractility of frog ventricular strips evoked by transient-electrical stimulation at 1,2,4 and 8 Hz. Control and afterdrug values indicate the increase of contractility as mg. All values are mean±SE of number of experiments (n)

| | | KETAMINE (n=7) | | | COCAINE (n=7) |
|---|---|---|---|---|---|
| Frequency | Control | 10"$^{7}$M | 10"$^{6}$M | 10"$^{5}$M | 10"$^{5}$M |
| 1 Hz | 0.93 + 0.25 | 1'.07 ± 0'.23 | 1.00 + 0.27 | 1.93 + 0.45* | 2.60 + 0.29* |
| 2 Hz | 1.50 ± 0.33 | 1.57 ± 0.30 | 1.57 + 0.30 | 2.50 + 0.62* | 3.30 + 0.38* |
| 4 Hz | 4.14 ± 0.83 | 4.78 + 0.71 | 4.86 + 0.76 | 6.86 + 0.80* | 9.00 + T.02* |
| 8 Hz | 6.86 + 1.09 | 7.86 + 0.95 | 8.57 + 0.80 | 10.28 + 0.74* | 12'.40 + 1.44* |

)fc=Significantly different from control values ( p<0,.05).

Table 2. Effects of thiopental and droperidol on the increases of contractility of frog ventricular strips evoked by transient-electrical stimulation at 1,2,4 and 8 Hz. Control and afterdrug values indicate the increase of contractility as mg. All values are mean±SE of number of experiments (n)

| | | THIOPENTAL (n=5) | |
|---|---|---|---|
| Frequency | Control | $10^{-6}$M | $10^{-5}$M |
| 1 Hz. | 1.00 ± 0.20 | 1.00 ± 0.21 | 1.25 ± 0.40 |
| 2 Hz. | 1.50 ± 0.37 | 1.25 ± 0.25 | 1.25 ± 0.25 |
| 4 Hz. | 4.50 ± 0.50 | 4.25 ± 1.25 | 4.00 ± 2.00 |
| 8 Hz. | 7.52 ± 0.50 | 7.25 ± 0.75 | 7.50 ± 2.50 |

| | | DROPERİDOL (n=4) | |
|---|---|---|---|
| Frequency | Control | $10^{-6}$M | $10^{-5}$M |
| 1 Hz. | 1.87 ± 0.32 | 2.00 ± 0.21 | 1.50 ± 0.21 |
| 2 Hz. | 2.25 ± 0.15 | 2.25 ± 0.15 | 2.00 ± 0.21 |
| 4 Hz. | 5.87 ± 0.43 | 5.87 ± 0.90 | 5.62 ± 0.80 |
| 8 Hz. | 8.37 ± 0.90 | 9.25 ± 1.45 | 9.12 ± 1.23 |

ient stimulation in frog myocardium may result from the increased release of neurotransmitter from the presynaptic nerve endings.

The action of ketamine in frog neuroeffector junction confirms those of previous studies with respect to uptake, inhibition by ketamine on the isolated perfused rat heart and in the isolated rabbit heart (9,11,10,22).

When neuronal uptake mechanisms are inhibited with ketamine the potentiation of the response to noradrenaline might be expected to be amplified to an even greater extent. Blockade of uptake mechanisms may also be associated with overflow of the relased sympathetic transmitter in the systemic circulation and increased plasma noradrenaline concentrations have been reported in patients following injection of ketamine (23). The cardiovascular effects of ketamine may be explained by inhibition of neuronal uptake of noradrenaline.

Ketaminin kurbağa myokardındaki kokain-benzeri etkisi

*Bu çalışma kurbağa myokardında ketaminin sempatik sinir iletimi üzerindeki etkilerini belirlemek için yapıldı. Ketaminin etkileri droperidol ve thiopentalin etkileriyle karşılaştırıldı.*

*Elektriksel olarak uyarılan ventrikül dokularında ketaminin (W—10' M) kontraktilite üzerinde etkisiz olduğu fakat daha yüksek konsantrasyonlarda (>10°M) negatif inotropik etki meydana getirdiği bulundu. Ancak direkt pozitif inotropik etkisi olmayan ketamine (10°M) geçici ek stimulasyonlara olan pozitif inotropik cevapları arttırdı. Ketamine (W°M) ekzojen noradrenalinin pozitif inotropik etkilerini değiştirmedi. Thiopental (10°M) vedroperidol (W°M) geçici ek stimulasyonlara olan pozitif inotropik cevapları artırmadı.*

*Bu sonuçlar ketaminin kurbağa myokardında sempatik sinir uçlarında nörotransmitter uptake'ini inhibe etmek suretiyle sempatik sinir iletimini kolaylaştırdığını düşündürmektedir.*

*[Türk Tıp Araştırma 1992; 10(4): 180-184]*

**Anahtar Kelimeler:** Ketamine, Nöronal-uptake, Kurbağa myokardı

## REFERENCES

1. Corssen G and Domino F. Dissociative anasthesia:furter pharmacologic studies and first clinical experience with phencyclidine derivate CI-581. Anesth Analg 1966;45:29-31.
2. Virtue RW, Alanis JM, Mori M; Lafargue RT, Vogel JHK and Metcalg DR. An anesthetic agent: 2-orthochlorophenyl 2-methylamine cyclohexanone HCl (CI-581). Anesht 1967; 28:823-33.
3. Dillon JB. Rational use of ketamine as an anaesthetic. Prog R Soc Med 1971; 64:1153-60.
4. Horatz K and Speh B. Ketamine in deroparatiren Fracturen behanalung bei Alten und risikopatienten. in Ketamine. Eds. M Gemperle, H Kreuscher and D Langrehr. Berlin. Springer-Verlag, 1973:407.
5. Kaukinen S. Effects of antihypertensive medication on the cardiovascular response to ketamine in rats, acta Anaesth Scand 1978; 22:437-46.
6. Traber DL, Wilson RD and Prano LL. The effect of alpha-adrenergic blockade on the cardiopulmonary response to ketamine. Anesth Analg 1971; 50:737-43.
7. Slogoff S and Allen GW. The role of baroreceptors in the cardiovascular response to ketamine. Anesth Analg 1974; 53:704-11.
8. Dowdy EG and Kaya K. Studies of the mechanism of cardiovascular responses to CI-581 Anaest 1968; 29:931-43.
9. Miletch DJ, Ivankovic AD, Albrecht RF, Zahed B and Ilahi AA. The effect of ketamine on catecholamine metbolism in the isolated perfused rat heart. Anesth 1973; 39:271-7.
10. Hill GE, Wong KC, Shaw CL, Sentker CR and Blatnick RA. Interactions of ketamine with vasoactive amines at normothermia and hypothermia in the isolated rabbit heart. Anesth 1978; 48: 315-9.
11. Nedergard CA. Cocaine-like effect of ketamine on vascular adrenergic neurones. Eur J Pharmacol 1973; 23:152-61.
12. Mantell H, Starke K, Görlitz BD and Scumann HJ. Tierexperimentelle undersuchungen zur Wirkung des ketamine auf periphere sympathische nerven. Anaesth 1973; 22:111-6.
13. Vizi ES, Somogyi GT, Hadhazy P and Knell J. Effect of duration and frequency of stimulation on the presynaptic inhibition by alpha-adrenoceptor stimulation of the adrenergic transmission. Arch Pharmacol 1973; 280:79-91.

14. Sarıoğlu Y, İlhan M and Kayaalp SO. An evidence for presynaptic excitatory alpha2-adrenergic receptors in frog myocardium. Arch Int Physiol Biochem 1987; 96:35-40.

15. Domino EF, Chodoff P and Corssen G. Pharmacological effects of Cl-581 a new dissociative anesthetic in man. Clin Pharmac Ther 1965; 6:279-90.

16. Traber DL, Wilson RD and Priano LL Differentiation of the cardiovascular effects of Cl-581. Anesth Analg 1968; 47:769-78.

17. Goldberg AH, Keane WP and Phear WPC. Effects of ketamine on contractile performance and excitability of isolated heart muscle. J Pharmacol Exp Ther 1977; 201:171-83.

18. Adams HR, Parker JL, and Mathew BP. The influence of ketamine on inotrpic and chronotropic responsiveness of heart muscle. J Pharmacol Exp Ther 1977; 201:171-83.

19. Urthaler F, Walhor AA and Jamer TN. Comparison of the inotropic action of morphine and ketamine studied in canine cardiac muscle. J Thorac Cardivasc Surg 1976; 72:142-9.

20. Barrigon S, De Miguel B, Tamaro J and Tejerlna J. The mechanisms of the positive inotropic action of ketamine on isolated atria of the rat. Brit J Pharmacol 1982; 76:85-93.

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21. Riou B, Lcerpentier Y and Viars P. Inotropic effects of ketamine on rat cardiac papilary muscle. Anesth 1989; 71: 116-25.

22. Salt PJ. Inhibition of noradrenaline uptake2 in the isolated rat heart by steroids, clonidine and methoxylated phenylethylamines. Eur J Pharmacol 1972; 20:329-40.

23. Zsigmond EK. Comment. Anesth Analg (Cleve) 1972; 51:595.