Title: COMPARATIVE INOTROPIC EFFECTS OF KETAMINE AND ISOFLURANE IN ISOLATED HUMAN ATRIAL TISSUES

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Introduction. Ketamine, structure related to phencyclidine, is a commonly used dissociative agent with significant cardiac electrophysiological effects. Its inotropic and chronotropic effects , however, are not consistent in different species. The major goal of the present study was to assess the electromechanical effects of ketamine in isolated human atrial fibers and to compare with those of isoflurane.

Methods. Human atrial tissues were obtained from the hearts of 30 patients undergoing open-heart surgery (with informed consent and approval by the Clinical Research Committee, Tri-Service General Hospital). Strands of free running atrial trabecular muscle fibers with a diameter of 0.4-1.5 mm and a length of 3-5 mm were removed and placed in a tissue bath maintained at 37±0.1 °C. Tyrode solution containing (in mM) NaCl 131, KCl 4, $NaHCO_3$ 18, $MgCl_2$ 0.5, NaH_2PO_4 0.5, $CaCl_2$ 2.7 and dextrose 5.5 was gassed with 97% O_2 and 3% CO_2 and had a pH of 7.4±0.05. The preparations were stimulated at twice threshold, a pulse width of 1-2 ms and a rate of 1 Hz. Transmembrane action potentials were detected using glass microelectrodes filled with 3M KCl (resistance 10-30 MΩ) and contractile force recorded by a force transducer. Both electrical and mechanical events were displayed on a digital oscilloscope and a chart recorder. Action potentials were photographed from the oscilloscope and resting membrane potential (RMP), action potential amplitude (APA) and action potential duration to 50% repolarization (APD_{50}) were measured. $\dot{V}_{max}$ of phase 0 was obtained by using a differential amplifier. After 1 hour equilibration period, 10^{-5} - 10^{-3} M ketamine (Parke-Davis) were administered in the absence and presence of 10^{-6} M epinephrine (Epi) or theophylline (Theo). To study the effects of inhalational anesthetic, 0.5-1.25% isoflurane (Anaquest) were added to the gas mixture through vaporizer. Anesthetic concentrations in the superfusate were measured using a gas chromatography method. Data were analyzed using Student's t test. All results were shown as mean±SEM and significance was assumed at the $p < .05$ level.

Results. In the human atrial fibers perfused with normal Tyrode solution, ketamine reduced the contractile force in a dose-related manner. This depression could be reversed by Epi or high $[Ca]_o$. In the background of Epi or Theo, ketamine significantly increased the force in lower concentrations (10^{-5} - 10^{-4} M) (Fig.1). During the positive inotropy, ketamine decreased the residual fast component of upstroke but elevated the plateau level, increased the peak twitch and shortened the twitch duration. When the fibers were depolarized in 27 mM $[K]_o$ with Epi, ketamine also increased the contractile force. The positive inotropy could be blocked by verapamil and propranolol , but not by atropine, adenosine or naloxone (all were given in 10^{-6} M). On the other hand, isoflurane (0.19 -0.53 mM) induced only negative inotropic effects both in the absence and in the presence of Epi. The upstroke velocity of phase 0 and the plateau level of action potential were suppressed dose-dependently. Isoflurane also shortened APD_{50} and slightly reduced the APA and RMP. The negative inotropy of isoflurane could be reversed by high $[Ca]_o$ or Epi.

Discussion. Our findings on the negative inotropic effects of ketamine in human atrial tissues agree with results of in-vivo study in dogs[1] that ketamine depressed myocardial contractility. This decrease in force, similar to that induced by isoflurane,[2] could be due to a reduction of Ca influx with the consequent depletion of intracellular Ca or cAMP. The positive inotropic response to ketamine, however, was observed in human atrial muscle concomitantly exposed to Epi or Theo. This selective inotropy could in some way be associated with an increased Ca influx, an enhanced release of Ca from intracellular stores or an altered disposition of cAMP.[3] Our results suggest: 1) ketamine, different from isoflurane, could produce either negative or positive inotropic effects in the same human atrial tissues; 2) the resultant net inotropic action of ketamine might be attributable to the algebraic sum of differing influences on the intracellular cyclic nucleotides and cellular Ca.

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References.

1. Schwartz DA, Horwitz LD: Effects of ketamine on left ventricular performance. J Pharmacol Exp Ther 194:410-414, 1975.
2. Lynch C: Differential depression of myocardial contractility by halothane and isoflurane in vitro. Anesthesiology 64:620-631, 1986.
3. Barrigon S, De Miguel B, Tamargo J, Tejerina T: The mechanism of the positive inotropic action of ketamine on isolated atria of the rat. Br J Pharmacol 76:085-093, 1982.

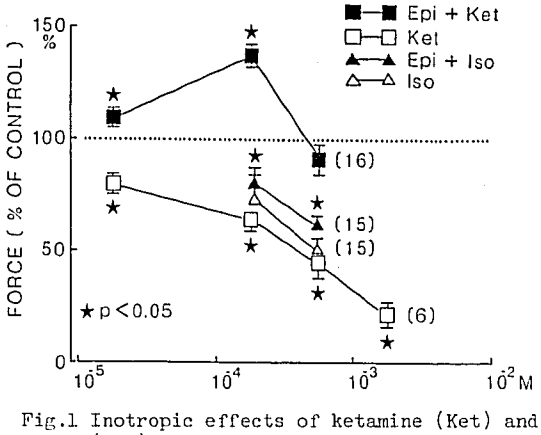

Fig.1 Inotropic effects of ketamine (Ket) and isoflurane (Iso) in the absence and presence of Epi. Numbers in parentheses indicate number of preparations