TITLE: VERAPAMIL DELAYS RECOVERY OF HALOTHANE-INDUCED DEPRESSION IN ISOLATED PAPILLARY MUSCLE

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Introduction. Many patients with cardiovascular disease now take calcium channel blockers on a chronic basis. Of concern for the anesthesiologist is the possibility that these new drugs may interact adversely with anesthetic agents. Systemic vasodilation has recently been identified as one of the effects of calcium channel blockers which may contribute to hypotension when inhalational agents are used. Less is known, however, about direct myocardial effects. The purpose of this study was to determine whether the combination of verapamil and halothane produced additive or synergistic depression of myocardial contractility. We studied this interaction in an isolated preparation of rabbit papillary muscle to eliminate reflex autonomic and vascular effects.

Methods. Papillary muscles were quickly isolated from rabbits killed by cervical dislocation. Muscles were placed in a Blinks' dual tissue bath containing Krebs' solution (equilibrated with 95% O_2 - 5% CO_2, 30°C, pH 7.4) and suspended between a punctate stimulating electrode and a Statham force transducer. Square-wave DC impulses of 4 msec duration and twice-threshold voltage were used to pace the papillary muscles at 0.2 Hz. Muscle length was adjusted to yield maximum peak developed tension. Each preparation was equilibrated until a steady state was achieved. Twitch tension was displayed continuously on a Gould 2400S four channel recorder.

To define the depressant effect of halothane alone, papillary muscles were exposed for 5 min to 1.5% halothane delivered through a vaporizor. At the end of 5 min, the bathing solution was quickly exchanged with fresh Krebs' solution and recovery of the muscle was observed for 20 min. To define the interaction of verapamil and halothane, papillary muscles were incubated for 30 min in Krebs' solution containing 10^{-6} M verapamil and then subjected to the same protocol for halothane exposure and recovery. Stability of the preparation was assessed using time-course controls. At least 3 papillary muscles were tested under each condition. The following measurements were obtained: percent depression of peak developed tension, time to 50% of maximum halothane-induced depression (t_D 1/2), and time to 50% recovery (t_R 1/2). All results were expressed as mean ± SEM. Student's t test was used to determine significance.

Results. The time-course effects of 1.5% halothane, 10^{-6} M verapamil, and the combination of halothane and verapamil are displayed in Figure 1. Mean values for maximum halothane-induced depression, time to 50% of maximum halothane-induced depression (t_D 1/2), and time to 50% recovery (t_R 1/2) are shown in Table 1.

Papillary muscles exhibited a slight increase in peak developed tension (2-3%) within the first minute of exposure to halothane. This was followed by rapid depression and slower but complete recovery. In the presence of verapamil alone, papillary muscles showed very slow depression at an average rate of 0.5 % of control tension/min. The combination of verapamil plus halothane did not differ from halothane alone in either the rate of onset of halothane-induced depression or the degree of maximum depression. During the first 10 min of recovery, however, muscles exposed to the combination of verapamil plus halothane showed significantly more depression than those exposed to halothane alone (Fig. 1). The time for 50% recovery was significantly longer for the combination of drugs (Table 1).

Discussion. In isolated papillary muscle, the combination of 1.5% halothane and 10^{-6} M verapamil produced the same degree of maximum depression as 1.5% halothane alone. Exposure to verapamil did not significantly accelerate the rate of halothane-induced depression. Recovery from halothane, however, was prolonged by verapamil and the effect appeared to be additive.

The absence of synergistic depression and the lack of acceleration in the onset of halothane-induced depression are two favorable aspects of the halothane-verapamil interaction. A worrisome feature, however, is the slower rate of recovery. The reversibility of halothane-induced myocardial depression may be impaired by calcium channel blockers.

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Table 1. Effect of verapamil on halothane-induced depression of papillary muscle contraction.

	Halothane	Verapamil + Halothane
% Max. Depression	75 ± 3	70 ± 3
t_D 1/2 (min)	2.7 ± 0.3	3.1 ± 0.1
t_R 1/2 (min)	3.9 ± 0.7	6.7 ± 0.5*

All values mean ± SEM; $n \geq 3$. * = $p < 0.05$.

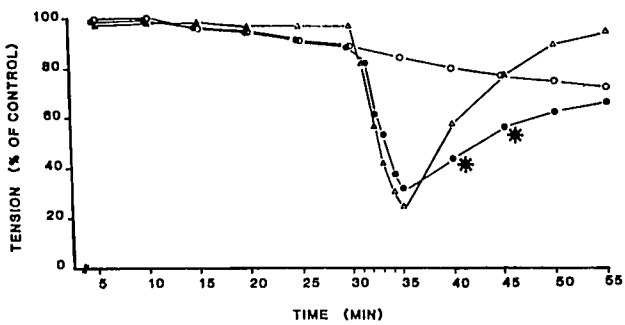

Figure 1. Time-course effects of 1.5% halothane (Δ-Δ). 10^{-6} verapamil (o-o), and verapamil plus halothane (●-●). All values are mean; $n \geq 3$. * = $p < 0.05$.