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Effects of Dexmedetomidine on Contractility, Relaxation, and Intracellular Calcium Transients of Isolated Ventricular Myocardium

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The effects of the highly selective alpha$_2$-adrenoceptor agonist dexmedetomidine on contractility, relaxation, and the intracellular Ca^{2+} transients of isolated ventricular myocardium were studied in isolated right ventricular papillary muscles obtained from reserpinized ferrets. Dexmedetomidine (10^{-10}–10^{-5} M) did not alter amplitude and time variables of isometric, isotonic and zero-load-clamped twitches, except for a slight increase in maximal isotonic relaxation rate at 10^{-5} M. Dexmedetomidine (10^{-8}–10^{-5} M) caused no changes in the intracellular Ca^{2+} transient detected with aequorin. These results suggest that dexmedetomidine has no intrinsic myocardial contractile effects. (Key words: Aequorin. Sympathetic nervous system, alpha$_2$-adrenoceptor agonist: dexmedetomidine. Ions: calcium. Heart: contractility, relaxation.)

RECENT STUDIES have shown that a novel, highly specific alpha$_2$-adrenoceptor agonist, dexmedetomidine,[1] produces a hypnotic–anesthetic action in rats[2,3] and reduces halothane MAC in dogs[4] *via* activation of central alpha$_2$-adrenoceptors.[2] Dexmedetomidine causes a dose-dependent decrease in heart rate and cardiac output in halothane-anesthetized dogs[4] without affecting mean arterial pressure. It is uncertain whether these effects result from a direct effect on the myocardium or from peripheral effects. Therefore, this study was designed to investigate the effects of dexmedetomidine on the intrinsic contractility and relaxation properties of isolated ventricular myocardium.

Materials and Methods

This study was approved by the Institutional Animal Care and Use Committee.

Twelve papillary muscles of the right ventricle of adult male ferrets were used in this study. The experimental set-up, muscle transducer, recording apparatus, and criteria for selection of suitable preparations were identical to those described earlier,[5] except as noted below. The evening before the experiment, ferrets were given reserpine 5 mg/kg ip to deplete myocardial catecholamines. Ferrets were anesthetized with sodium pentobarbital (100 mg/kg ip), and the heart was quickly excised. Papillary muscles were mounted vertically in a temperature-controlled muscle chamber (30° C) filled with a physiologic salt solution of the following composition (millimolar concentrations): Na^+ 135, K^+ 5, Ca^{2+} 2.25, Mg^{2+} 1, Cl^- 103.5, HCO_3^- 24, $H_2PO_4^{2-}$ 1, SO_4^{2-} 1, acetate^{-1} 20, and glucose 10. The bathing solution was bubbled continuously with 95% O_2–5% CO_2 (500 ml/min). Muscles were held between a force–length servomechanism transducer (Innovi, Belgium) and a miniature Lucite clip with a built-in stimulation electrode (stimulus interval 4 s, voltage 5% above threshold).

After an initial period of stabilization (2–3 h) during which muscles contracted in alternating series of four isometric and four isotonic contractions, muscle length was set at L_{max}, *i.e.*, the length at which active force development was maximal. Each muscle was exposed to tyramine hydrochloride 10^{-6} and 10^{-5} M to ensure that adrenergic nerve endings were depleted of norepinephrine. After the bathing solution was changed, a new series of control contractions was recorded, and each of eight muscles was exposed to cumulative concentrations of dexmedetomidine (10^{-10}–10^{-5} M in 1 log M unit increments). The bathing solution was changed, and recovery was followed until steady state was achieved, usually after 30–60 min (n = 8). In five muscles, 10^{-6} and 10^{-5} M prazosin hydrochloride, an alpha$_1$-adrenoceptor antagonist, was added after exposure to 10^{-5} M dexmedetomidine.

In each of these conditions, variables of contraction and relaxation were recorded. Peak shortening (DL) and

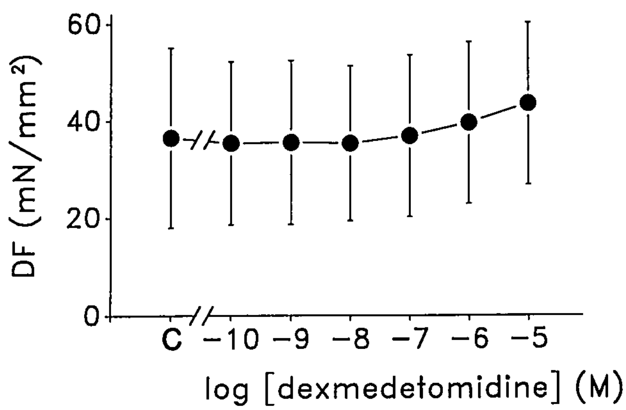

FIG. 1. Cumulative dose–response relationship to dexmedetomidine for developed force (DF) of isometric twitches (n = 8). C = control.

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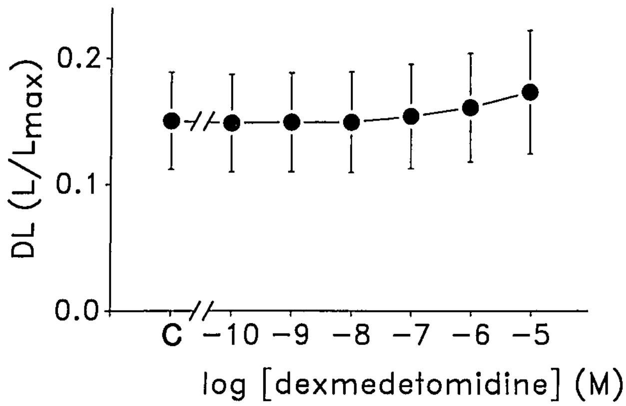

FIG. 2. Cumulative dose–response relationship to dexmedetomidine for peak shortening (DL) in isotonic preloaded twitches (n = 8). C = control.

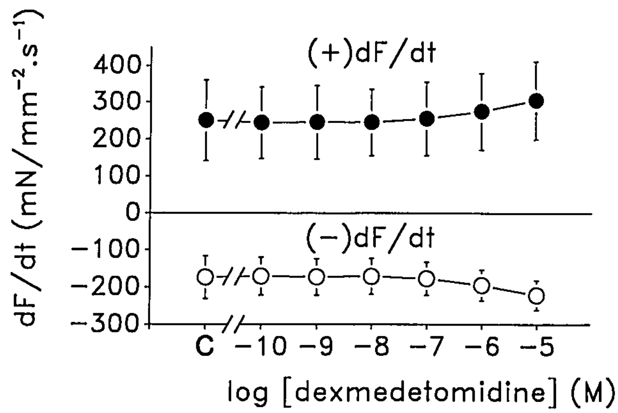

FIG. 4. Cumulative dose–response relationship to dexmedetomidine for maximal rate of rise ((+)dF/dt) and fall [(−)dF/dt] of force in isometric twitches (n = 8). C = control.

maximal velocity of lengthening (−V) were measured from a preloaded isotonic twitch; maximal unloaded velocity of shortening (MUVS) was determined from a zero-load-clamped twitch; peak developed force (DF), maximal rate of rise of force (+dF/dt), maximal rate of fall of force (−dF/dt), time to peak force (TPF), and time from peak force to half isometric relaxation (RTH) were determined from isometric twitches.[5] Each of these test contractions was separated by seven isotonic twitches at the preload of L_{max} to avoid long-term effects of load on contractile state.[6–8]

In four papillary muscles, the intracellular Ca^{2+} transient that accompanies contraction was detected with the Ca^{2+}-regulated bioluminescent protein aequorin.[9] Aequorin was microinjected into multiple (30–50) superficial cells. Aequorin light emission was detected against a background of total darkness with an EMI 9235QA photomultiplier tube selected for high gain and low dark current. Light, force, length, and dF/dt signals were recorded continuously on a pen recorder (Honeywell 1400) and on a four-channel digital oscilloscope (Nicolet 4094A). One hundred twenty-eight contractions were recorded to improve the signal-to-noise ratio in light signals.

At each drug concentration, variables were compared with control by means of repeated-measures analysis of variance (ANOVA) and with Duncan's multiple-range test when appropriate. $P < 0.05$ was considered significant. Data are presented as mean ± SD throughout.

Results

At the onset of the experiments, tyramine HCl 10^{-6} and 10^{-5} M did not change any of the measured variables ($P > 0.05$), except for TPF, which decreased from 257.6 ± 41.0 (control) to 252.0 ± 38.9 ms (tyramine HCl 10^{-6} M).

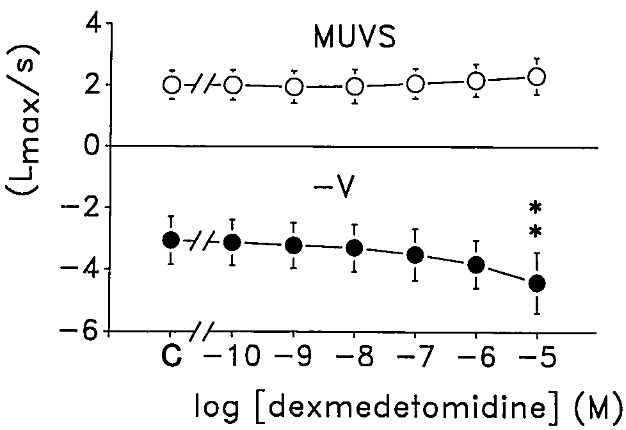

FIG. 3. Cumulative dose–response relationship to dexmedetomidine for maximal unloaded velocity of shortening (MUVS) in zero-load-clamped twitches and maximal lengthening velocity (−V) in preloaded isotonic twitches (n = 8). $**P < 0.01$.

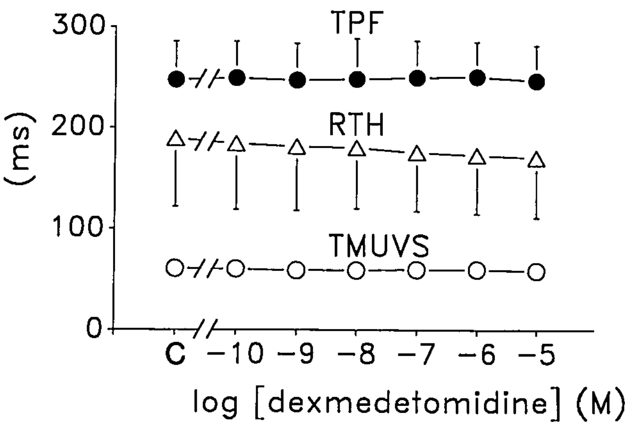

FIG. 5. Cumulative dose–response relationship to dexmedetomidine for time to peak force (TPF) and time to half isometric relaxation (RTH) in isometric twitches, and for time to maximal unloaded velocity of shortening (TMUVS) in zero-load-clamped twitches (n = 8). C = control.

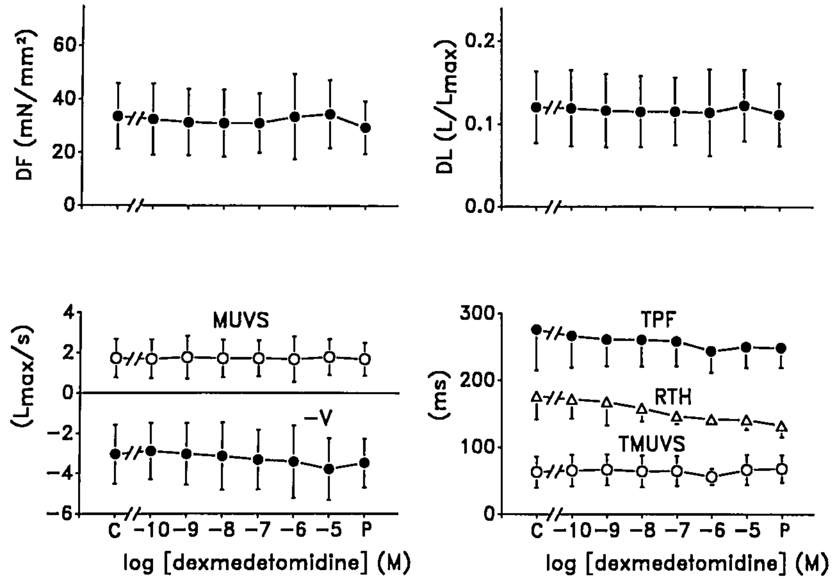

FIG. 6. Cumulative dose-response curve to dexmedetomidine for developed force (*top left*); for peak shortening (*top right*); for maximal unloaded velocity of shortening (MUVS) and maximal lengthening velocity (−V) (*bottom left*); and for time to MUVS (TMUVS), time to peak force (TPF), and time to half-isometric relaxation (RTH) (*bottom right*). After 10^{-5} M dexmedetomidine, muscles (n = 5) were exposed to prazosin HCl 10^{-6} M (P) in dexmedetomidine 10^{-5} M. C = control.

Figures 1 and 2 show the changes in DF and DL, respectively, during cumulative dose–response experiments with dexmedetomidine. Even though at 10^{-5} M dexmedetomidine DF and DL were increased over initial control values by 24.1 ± 18.9 and 14.8 ± 10.3%, respectively, the changes are not statistically significant. Figure 3 illustrates that MUVS was not affected by dexmedetomidine. Similarly, −V was not affected significantly until 10^{-5} M dexmedetomidine (a 47.8 ± 30.4% increase over control, $P < 0.01$). Figure 4 illustrates the lack of effect of dexmedetomidine on the maximal rates of rise and fall of force. In figure 5, the effects of dexmedetomidine on the time course of contraction and relaxation are illustrated. Dexmedetomidine changed neither TPF of the isometric twitch nor time to MUVS. However, at every concentration tested, dexmedetomidine decreased RTH in a dose-dependent fashion. The maximal abbreviation of isometric relaxation was from 189.3 ± 67.3 (control) to 170.3 ± 59.3 msec (10^{-5} M dexmedetomidine), but the changes were not statistically significant.

In five muscles, the addition of prazosin HCl 10^{-6} M in dexmedetomidine 10^{-5} M did not change any of the amplitude or time course variables significantly (fig. 6).

Figure 7 illustrates the isometric twitch and the aequorin signal during a cumulative dose–response experiment to dexmedetomidine (10^{-8}–10^{-5} M). The aequorin light signals that are representative of the intracellular Ca^{2+} transient did not change appreciably in dexmedetomidine 10^{-8}–10^{-5} M. Peak isometric force and peak light did not change significantly from control (repeated-measures ANOVA) during exposure to dexmedetomidine 10^{-8}–10^{-5} M (fig. 8).

Discussion

From this study I conclude that dexmedetomidine has no effect on contractility, relaxation, or the intracellular

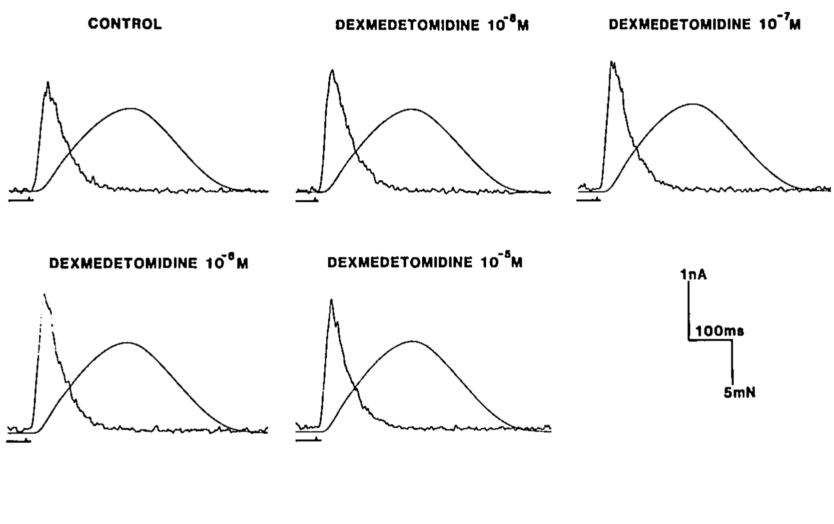

FIG. 7. Cumulative dose–response curves to dexmedetomidine. The aequorin signal and developed force are displayed in each panel. One hundred twenty-eight contractions were averaged in each drug concentration.

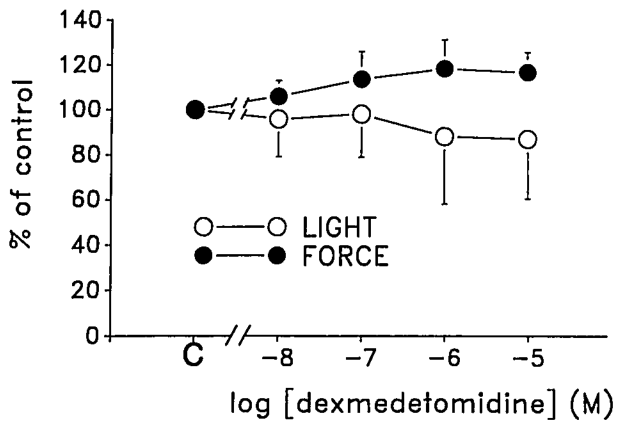

FIG. 8. Effects of dexmedetomidine on peak aequorin light and peak force of isometric twitches (n = 4). C = control.

Ca^{2+} transient of isolated ventricular myocardium. Dexmedetomidine is the D-isomer of a novel imidazoline compound that possesses hypnotic–sedative actions, and has a high affinity for $alpha_2$-adrenoceptors.[1]

Recent studies in rats have suggested that central $alpha_2$-adrenoceptors are involved in the hypnotic action of dexmedetomidine.[2] In volunteers, dexmedetomidine decreased systolic and diastolic blood pressure and caused a decrease in heart rate,[10,11] effects that may reflect a decreased sympathetic outflow consequent to activation of central $alpha_2$-adrenoceptors.

In the canine isolated heart–lung preparations, dexmedetomidine had no effect on cardiac function curves,[12] whereas in intact dogs it decreased cardiac output and increased systemic vascular resistance.[4] The decrease in cardiac output has been attributed to 1) the dexmedetomidine-induced bradycardia; 2) an increase in systemic vascular resistance by activation of peripheral $alpha_2$-adrenoceptors; and 3) a decrease in oxygen requirements.[4] Dexmedetomidine has a significant hypnotic–sedative action in doses of 0.5–1.5 mg/kg, which corresponds to approximately 10^{-7} M in humans.[10,11]

At these concentrations, dexmedetomidine had no measurable effects on isolated ferret ventricular myocardium. The lack of effects of this specific $alpha_2$-adrenoceptor agonist is consistent with an earlier observation that rabbit ventricular myocardium lacks functioning $alpha_2$-adrenoceptors.[13] At 10^{-5} M dexmedetomidine, isotonic relaxation velocity was slightly increased, but this may not be physiologically significant.

In conclusion, in clinically useful concentrations, dexmedetomidine has no detectable effects on contractility, relaxation, or the intracellular Ca^{2+} transient in ferret ventricular myocardium.

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