Chronotropic and Inotropic Effects of Prostaglandins E_1, A_1, and $F_{2\alpha}$ on Isolated Mammalian Cardiac Tissue[1] (37507)

JUDY Y. SU,[2] CHARLES B. HIGGINS,[3] AND WILLIAM F. FRIEDMAN[4]
(Introduced by W. L. Nyhan)

Departments of Pediatrics and Medicine, University of California, San Diego, School of Medicine, La Jolla, California 92037

A large family of prostaglandins (PG) has been found to be ubiquitous in mammalian tissues and to have diverse physiological effects on numerous organs, including profound actions on the cardiovascular system (1, 2). The cardiovascular responses to the various prostaglandins appear to differ considerably among mammalian species (1–13). Berti, Lentati and Usardi (4) observed that PGE_1 had positive chronotropic and inotropic effects on hearts isolated from both guinea pig and rat. Vergroesen, DeBoer and Gottenbos (7) demonstrated that $PGF_{1\alpha}$ and $PGF_{2\alpha}$, as well as PGE_1 increased myocardial contractile force of the isolated heart of the rat. On the other hand, Von Euler (3) found that crude PG did not alter the frequency of contraction of the isolated rabbit heart, and Lee *et al.* (5) and Hedqvist and Wennmalm (11) observed that PGA_2 was devoid of significant chronotropic or inotropic effects in the isolated perfused rabbit heart.

Some studies (10, 13) of the effects of various PG on the intact canine heart have suggested that the positive chronotropic and inotropic effects of the PG may not be limited to the guinea pig and rat. Intravenous administration of large doses of PGE_1, A_1, and $F_{2\alpha}$ increased heart rate and contractile force of the intact heart of anesthetized dogs (10, 13). In anesthetized, vagotomized dogs treated with propranolol, PGE_1, A_1, and $F_{2\alpha}$ produced no chronotropic effects but did increase myocardial contractile force and the rate of rise of force development (6). Direct infusion of PG into the coronary arteries at doses too small to elicit systemic and hence reflex effects on the heart, produced positive inotropic effects on the intact canine heart (13). In contradistinction Higgins and coworkers (8, 12) observed no chronotropic and only insignificant inotropic actions of PGA_1 in the conscious dog when the indirect effects of this agent on heart rate, after load and reflex beta adrenergic stimulation of the heart were prevented. In order to help clarify the direct cardiac effects of the PG in larger mammalian species, the present study evaluated the chronotropic and inotropic effects of representatives of the three major subgroups of prostaglandins, *i.e.*, PGE_1, PGA_1, and $PGF_{2\alpha}$ on cardiac tissue isolated from two species commonly employed for analyzing the actions of cardiovascular agents, the cat and the dog. The prostaglandins were administered over and above the dosage range which has been shown to produce direct cardiac effects on isolated cardiac tissue of the guinea pig (4) and rat (4, 7).

Methods and Materials. Cardiectomy was performed after pentobarbital anesthesia in the cat (ip, 40 mg/kg) and dog (iv, 30 mg/kg). Tissue isolated for study included the right atrium with SA node attached from both species, cat right ventricular papillary muscles, and dog right ventricular trabecular carnae. All muscles were suspended in a myograph containing oxygenated Krebs solution

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at pH 7.4 and 30°. The composition of the Krebs solution was Na^+, 146 m*M*; K^+, 3.6 m*M*; Ca^{2+}, 2.5 m*M*; Mg^{2+}, 1.2 m*M*; Cl^-, 126 m*M*; $H_2PO_4^-$, 1.2 m*M*; SO_4^{2-}, 1.2 m*M*; HCO_3^-, 25 m*M*, and glucose, 5.6 m*M*. The solution was bubbled with 95% oxygen and 5% CO_2 which resulted in a pH of 7.4.

One end of the muscle was tied with 4-0 silk and the other end was fixed with a plastic clip connected to a Statham (UC-3) force transducer as described previously (14). Isometric tension was measured at the apex of the length–active tension curve of each muscle and in the case of ventricular muscles corrected for cross-sectional area and expressed in grams per square millimeter. The ventricular muscles were 3–6 mm in length, and averaged 1.1 mm^2 (range 0.6 to 1.7) in cross-sectional area. Frequency of contraction was measured from spontaneously beating right atria. Quiescent papillary muscle and trabecular carnae were stimulated at a frequency of 12 contractions/min and left atria stimulated at 30 contractions/min by field electrodes with square wave dc impulses of 4 msec duration and voltage less than 10% above threshold. The stimulus artifact and active tension were recorded on a Clevite Brush 260 recorder. Muscles were equilibrated for 60 min prior to commencement of individual experiments. Initially, cumulative concentrations of diluent were added. Muscles were then washed repeatedly with Krebs solution and re-equilibrated for 30 min prior to addition of a PG compound to the myograph. Individual muscles were used to study the effects of one PG compound only. Spontaneous frequency of contraction and active tension development was measured at steady state levels existing before and after each intervention.

Stock solutions (Upjohn Co., Kalamazoo, MI) of PGE_1, A_1 and $F_{2\alpha}$ were prepared in 10% ethanol and 20 mg% Na_2CO_3 solution at a final concentration of 1 mg/ml. The responses to concentrations of each PG from 3×10^{-11} to 3×10^{-5} *M* were analyzed. The Student's *t* test was used to analyze the statistical significance of the difference between mean values.

Results. Cat—right atria, right ventricular papillary muscles. Prostaglandins E_1, A_1 and $F_{2\alpha}$ at the maximum concentration studied increased the spontaneous frequency of contraction of cat right atria (Fig. 1); the order of potency was $E_1 > A_1 > F_{2\alpha}$. The threshold concentrations for the chronotropic effect were 3×10^{-7} *M* for E_1, 3×10^{-6} *M* for A_1 and 3×10^{-6} *M* for $F_{2\alpha}$. However, none of the prostaglandin compounds produced significant changes in tension development of right atria or right ventricular papillary muscles over the range of concentrations studied; at the highest concentration of each compound (3×10^{-5} *M*) tension development was identical to control (Fig. 2).

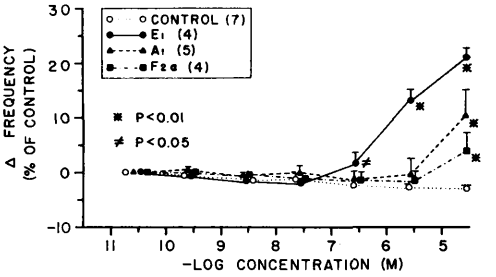

FIG. 1. Cumulative dose–response curves of prostaglandins E_1, A_1 and $F_{2\alpha}$ on the spontaneous frequency of contraction of right atria from cat. Number of experiments in parentheses. Each point and vertical bar = mean ± SEM.

Dog. Prostaglandins E_1, A_1 and $F_{2\alpha}$ produced no significant changes in either frequency of contraction of right atria or ten-

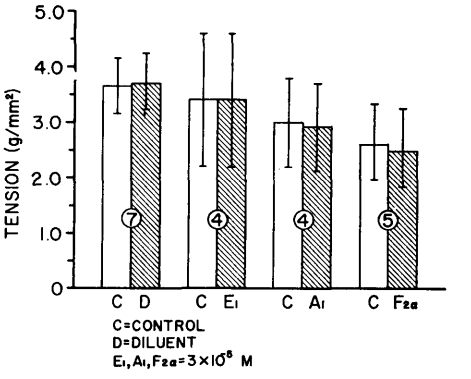

FIG. 2. Ventricular myocardium (cat). Effects of prostaglandins (3×10^{-5} *M*) on the tension development of cat papillary muscles. Number of experiments encircled.

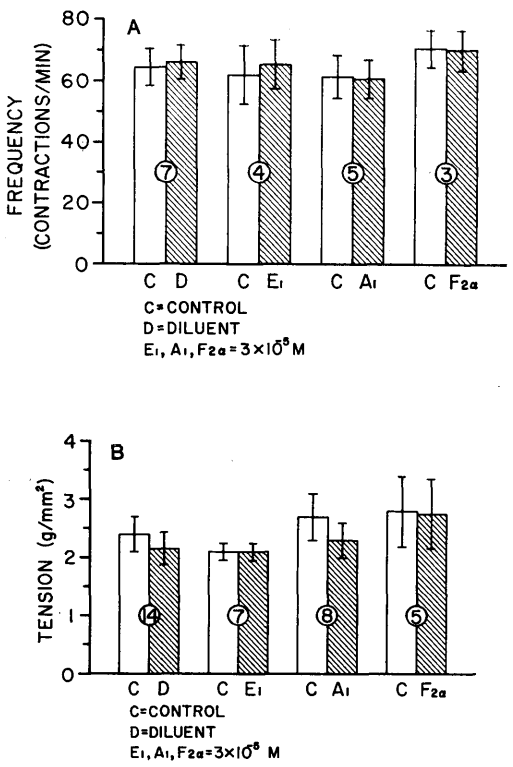

FIG. 3. A and B. Effects of prostaglandins (3×10^{-5} *M*) on the spontaneous frequency of contraction of dog right atria (A) and the tension development of trabecular carnae isolated with dog right ventriclar myocardium. (B).

sion development of right ventricular myocardium. At the highest concentration (3×10^{-5} *M*) frequency and tension development were unaltered (Fig. 3A and B).

Discussion. In the present study, PGE_1, PGA_1, and $PGF_{2\alpha}$ produced positive chronotropic effects on atrial tissue from the cat, but all three compounds were devoid of direct inotropic activity in this species. Each of the three PG lacked direct chronotropic or inotropic effects on cardiac tissue isolated from the dog.

The variability in the responses to prostaglandins among different species observed in the present studies is consonant with previous investigations of the direct stimulatory effects of prostaglandins on isolated hearts (3–5, 7). While previous studies have demonstrated that each of the prostaglandin compounds exert positive chronotropic and inotropic effects on isolated cardiac tissues of the guinea pig and rat (4, 7), they appear to be devoid of these actions on isolated cardiac tissue of other mammalian species (3–5, 11). In this regard, recent evidence indicates that the PGE and PGA, but not PGF, compounds markedly increase the accumulation of cyclic adenosine 3′,5′-monophosphate in guinea pig heart homogenates (9), while no effects on the accumulation of cyclic adenosine 3′,5′-monophosphate in particulate preparations of cat left ventricle were produced by PGE_2, A_1, A_2, F_1 and $F_{2\alpha}$ and only slight increases were observed with PGE_1. Since the inotropic and chronotropic actions of many hormones (15, 16) and perhaps most inotropic agents (17) may be mediated by the adenyl cyclase-cyclic 3′,5′-adenosine monophosphate system, it may be speculated that the direct cardiac actions of the prostaglandin compounds are a reflection of their variable effects on this myocardial enzyme system in different mammalian species. In this regard while some evidence suggests organ and species variability for the effects of various agonists and antagonists on the activity of the adenyl cyclase-cyclic adenosine 3′,5′-monophosphate system (18, 19); the range of doses at which two important inotropic agents, epinephrine and glucagon, stimulated myocardial adenyl cyclase activity was similar among various species (15, 20, 21).

In the intact dog controversy exists regarding the effect of prostaglandin compounds on heart rate and left ventricular contractility (6, 8, 10, 12, 13). Based upon the effects of prostaglandin compounds in this preparation, it has been suggested that the prostaglandins exert a strong inotropic effect on the canine myocardium (6, 8, 10). However, the present study supports the findings of Higgins and co-workers (8, 12) that the systemic administration of PGA_1 in the dog does not result in direct positive chronotropic and inotropic effects, but rather alters heart rate and cardiac performance indirectly via changes in arterial pressure and sympathetic tone. The absence of direct cardiostimulatory effects of PGE_1 and $PGF_{2\alpha}$ on cardiac tissue

isolated from the dog in the present study also supports the contention that these drugs alter the performance of the intact dog heart indirectly. In this regard, the heart rate response produced by PGA_1 in the conscious dog has been shown to result from the combination of withdrawal of vagal restraint and beta adrenergic stimulation on sinoatrial automaticity, which appear to be reflex responses to the systemic hypotension produced by this agent (13).

Summary. This study indicates that the chronotropic and inotropic effects of PG on isolated cardiac muscle are species dependent. While a direct chronotropic effect was observed on the atrial tissue of the cat, the PG appear to be devoid of direct chronotropic effects on canine cardiac tissue and of direct inotropic effects in both feline and canine cardiac tissue.

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