Dynamic Behavior of Endocardial Structures in the Baboon Heart[1] (36441)

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While precise patterns of efferent innervation of the heart have been extensively investigated, a large fraction of the studies have been made in the dog, cat, rabbit and a few other domestic animals with little or no information upon the primate. We have recently described the anatomical distribution of the autonomic cardiac nerves, together with functional responses to their electrical excitation in the baboon (1, 2). The emphasis of these reports, however was almost exclusively upon epicardial innervation. In subsequent experiments, after developing techniques for studies of endocardial structures in the dog (3, 4), strain gauge arches and/or intramyocardial pressure transducers were applied to the interventricular septum and papillary muscles in the intact baboon heart. The present report illustrates and compares changes in contractile force and in intramyocardial pressure development within the septum and epicardial portions of the left ventricle. To our knowledge, these data represent the first such direct experimental approaches to determination of endocardial functions in the primate heart.

Methods. Walton-Brodie strain gauge arches were carefully sutured to the endocardial surfaces of the interventricular septum and/or to the longitudinal surfaces of the papillary muscles of the left ventricle through left atriotomy, while the animal was on compete cardiac bypass and the heart was in fibrillation, in seven baboons (*Papio anubis*). After installation of the transducers, the animals were removed from the bypass pump with defibrillation and restoration of *in vivo* circulation. The small branchings of both sympathetic and parasympathetic cardiac nerves distal to the stellate and middle cervical ganglia and the cervical vagosympathetic trunk were carefully isolated and electrically stimulated using either a Nuclear Chicago constant current stimulator (model 7151) or a Grass S5 square wave voltage generator (2). Recordings were made upon either a Model R Beckman rectilinear or Offner Model R curvilinear recorder. In two additional animals, intramyocardial pressures were recorded by means of a Scientific Advances model SA-SA-M-7BW pressure transducer while intraventricular pressures were recorded from a special catheter whose tip was maintained in a fixed position at the endocardial surface (5). Specific experimental maneuvers are described in the Results section.

Results. Figure 1A illustrates the results of successively tying and cutting the vagi upon contractile force and arterial blood pressure in the baboon. Following left vagal transection (arrow), there occurred progressive elevation in force of contraction on each of the myocardial segments, including those of the interventricular septum (IVS) and posterior papillary muscle (PP). While the increment in force as measured on the left ventricular apex (LVA) amounted to 20%, that on the interventricular septum (IVS), left ventricular base (LVB), and posterior papillary muscle (PP) was 76, 100, and 150%, respectively. Arterial blood pressure simultaneously rose from 105/65 to 160/115 mm Hg, and heart rate increased from 165 to 200 per minute during the 7 min following the initial

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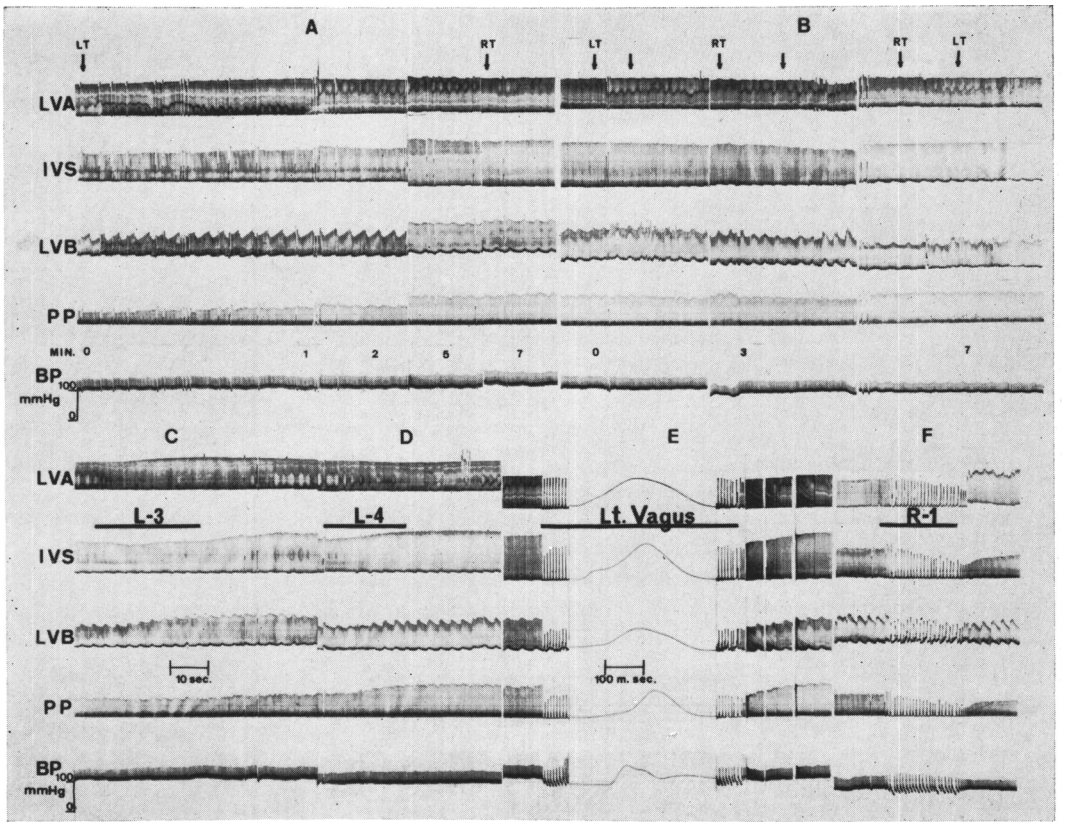

FIG. 1. Alterations in contractile force on small segments of the myocardium located at the anterior surface of the left ventricle (LVA), the endocardial surface on the left ventricular side of the interventricular septum (IVS), the epicardium at the base of the left ventricle, and the logitudinal surface of the left ventricular posterior papillary muscle (PP). Arterial blood pressure is shown at the bottom of each panel. In panel A, the left (LT, arrow) and right (RT, arrow) cervical vagosympathetic trunks were sectioned, and in panel B, the communicating rami from T3, T2, and T1 were successively cut on the left (LT), right (RT), and finally, the rami at C7 and C8 were cut (arrows, right portion, panel B). Two small branches of the left sympathetics (L3 and L4) were electrically stimulated (10 cps, 5 msec, 4 V) at the level of the arch of the aorta (panels C and D, respectively). In panels E and F the left and right (R-1) vagosympathetic trunks were electrically stimulated with an illustrative fast trace shown in E.

vagotomy. Right vagotomy elicited little further change. It should be noted that the sympathetic cardiac outflows were intact throughout these procedures.

Following bilateral vagotomy, the upper thoracic sympathetic trunk was then progressively decentralized, starting with unilateral transection of the left T3-T4 interganglionic segment (Fig. 1B). Communicating rami from T3 to T1 were then sectioned on the left (two arrows, left portion, panel B) with visible decline in contractile force and arterial blood pressure. The T3–T1 rami were next sectioned on the right side (middle of panel B) with further decrease in segmental contractile force and pressure. Finally, the C7 and C8 rami were cut successively on the right and left sides (right portion, panel B) with little or no additional alterations in muscle segment responses. Blood pressure declined from 150/110 to 115/80 during this relatively short (7 min) procedure, while heart rate did not change.

Figure 1C illustrates the muscle segment

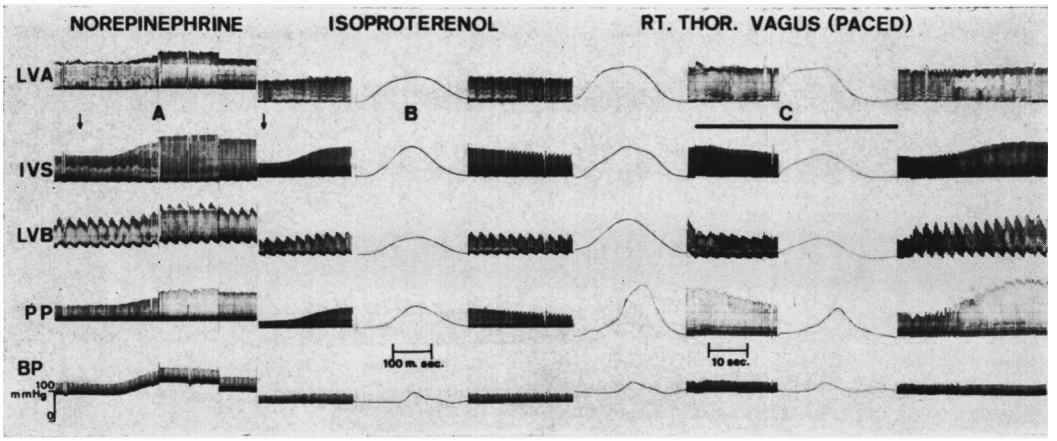

FIG. 2. Inotropic responses of epicardial (LVA and LVB) and endocardial (IVS and PP) muscular segments of the baboon heart to norepinephrine (A) and isoproterenol (B) and to electrical stimulation (10 cps, 5 msec, 5 V) of the right thoracic vagosympathetic trunk in the paced heart. Fast traces reveal change in *df/dt* during isoproterenol augmentation and during vagal inhibition in contractile force.

response to electrical excitation of a single small branch (L-3) of the left sympathetics at a point immediately proximal to its entry into the cardiopulmonary plexus. Augmentation in contractile force marked all of the test segments, including both epicardial and endocardial surfaces, although the least prominent change occurred in the papillary muscle. Figure 1D reveals responses to similar stimulation of another nerve branch (L-4) of the same left sympathetic complex, and in this instance the responses were most prominent upon the interventricular septum and papillary muscle. The LVA segment did not change. In Figure 1E and F, portions of the left and right thoracic vagi, respectively, were stimulated with prompt and profound alterations in contractile force, blood pressure, and heart rate. Whereas the response to left vagal stimulation developed almost instantaneously, that to right stimulation (R-1) was more gradual in onset and development. The particular point of these presentations is to reveal the direct influence of the thoracic vagi upon these prominent endocardial structures. Both the interventricular septum and the papillary muscle participated in the negative inotropic response. This depressor action is further substantiated by suppression in *df/dt* and in *dp/dt* as illustrated in Fig. 1E. Gradual recovery in contractile force following cessation of stimulation characterized each of the individual muscle segments, and was clearly apparent on the endocardial structures. Thus, a variety of experimental procedures convincingly demonstrate a direct influence of the autonomic nervous system upon endocardial as well as upon epicardial portions of the baboon heart.

The direct action of adrenergic agents upon the endocardial musculature is illustrated in Fig. 2, in which both norepinephrine (A) and isoproterenol (B) elicited strong inotropic influences. Norepinephrine indicated a markedly positive inotropic affect and was accompanied by a distinct elevation in arterial blood pressure. Isoproterenol, on the other hand, elicited moderate augmentation in contractile force without significant increase in systemic arterial blood pressure. Both agents stimulated simultaneous alterations in contractile force on all four of the test segments, with somewhat greater percentage changes in the endocardial structures. Panel C illustrates the negative inotropic influences of the vagus nerve upon both interventricular septum and the papillary muscle in the paced preparation. With the onset of electrical stimulation of the right thoracic vagus, contractile force progressively declined

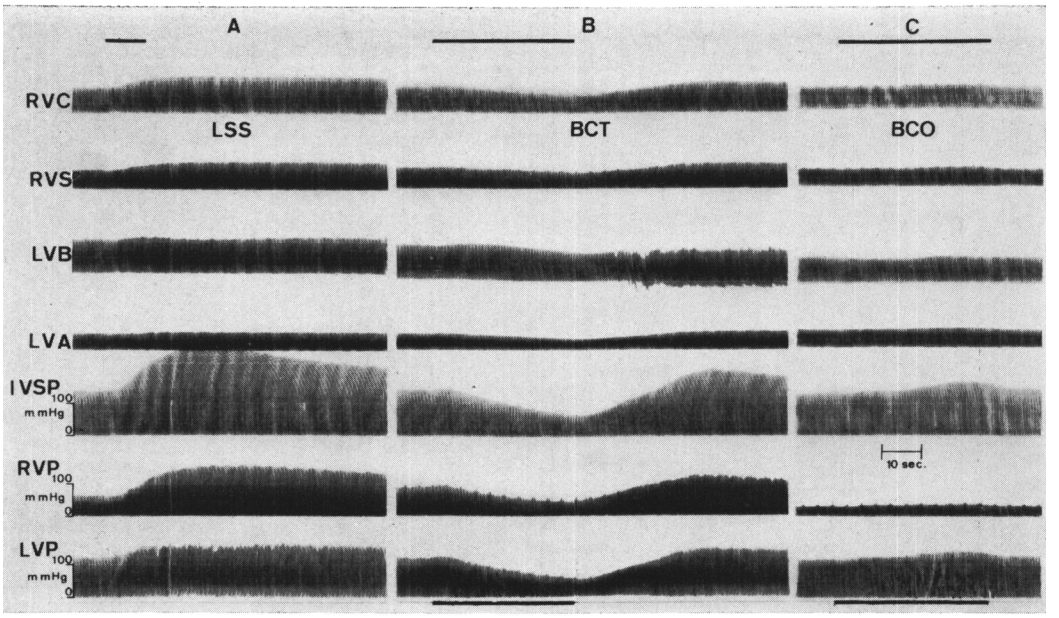

FIG. 3. Changes in contractile force on the epicardial surfaces of the right ventricular conus (RVC), right ventricular sinus (RVS), left ventricular base (LVB) and left ventricular apex (LVA) during left stellate stimulation (LSS), bilateral tug on the carotid arteries (BCT), and bilateral occlusion of the carotid arteries (BCO). Intramyocardial pressure was simultaneously recorded from a miniature Scientific Advances model SA-SA-M-7BW pressure transducer (IVSP), and from cannulas fixed in position on the endocardial surfaces of the right (RVP) and left (LVP) ventricles. Bilateral cervical vagotomy was performed before the experiment.

in both epicardial and endocardial segments, but in the absence of alterations in heart rate (illustrated in Fig. 1E and F), these changes were particularly apparent upon the endocardial structures. Fast traces before and during stimulation permit comparison of the rates of change in contractile force and pressure. In all instances these rates of change were markedly reduced. Following cessation of stimulation, and without change in heart rate, contractile force remained depressed for many cycles before beginning gradual recovery. The percentage changes in contractile force were relatively greater in the endocardial, compared with epicardial surfaces. Again, a brief period of exaggerated contractile force occurred during recovery in both the interventricular septum and in the papillary muscle.

Figure 3 extends these observations to include direct pressure recordings from miniature pressure transducers implanted within the middle portion of the interventricular septum (channel 5). Under control circumstances, systolic pressure within the interventricular septum was 135 mm Hg while that within the left ventricle cavity was 125 mm Hg. Simultaneous right ventricular systolic pressure was 65. Electrical excitation of the left stellate ganglion resulted in prompt and simultaneous elevations in all three pressures. However, the magnitude of systolic pressure achieved was markedly greater within the septum, thus creating an exaggerated gradient from the intramuscular to the intracavitary positions.

Figure 3B reveals the direct reflex inhibition of septal intramyocardial (IVSP) pressures as well as in intraventricular pressures as a result of tension applied bilaterally to the common carotid arteries in the vagotomized animal. Heart rate did not change although the identical procedure induced pronounced bradycardia as well as decreased inotropic response before vagotomy. While a "rebound" phenomenon was visible in all of

TABLE I.

Procedure	No. of animals	Heart rate/min		p	Systolic press (mmHg)		p	Contractile force (% change)		p
		Control	Experimental		Control	Experimental		Epicardium	Endocardium	
Stellate stimulation	7	156 ± 12	174 ± 15	.025	94 ± 6	114 ± 10	.025	20.6 ± 6.5	43 ± 8.4	.01
Bilateral carotid occlusion	8	155 ± 8	165 ± 9	.005	107 ± 11	136 ± 15	.025	16.1 ± 5.4	35.9 ± 8.2	.0005
Norepinephrine	7	160 ± 10	176 ± 11	.001	118 ± 13	166 ± 14	.001	49.3 ± 16.8	84.3 ± 25	.10
Vagal stimulation	5	147 ± 13	67 ± 15	.0005	106 ± 15	76 ± 18	.01	−24.6 ± 2.2	−37.8 ± 5.2	.01
Bilateral carotid traction	6	153 ± 11	121 ± 14	.01	114 ± 13	94 ± 12	.0005	− 7.8 ± 2.4	−26.0 ± 7.8	.01

the pressures following cessation of stimulation, it was distinctly greater in the IVS. Alterations in contractile force were present in all of the recorded channels, but were of lesser magnitude than were the changes in pressure. Finally, bilateral carotid occlusion (Fig. 3C) resulted in reflex elevations in septal intramyocardial and in left ventricular pressure with lesser change in right ventricular pressure. These experiments further demonstrate the active participation of endocardial tissues during both direct and reflex neural stimulation.

Table I presents comparative data upon responses in heart rate, systolic blood pressure, and contractile force of epicardial and endocardial muscle of the left ventricle during five different experimental manipulations. Only systolic pressures are illustrated because in several animals intraventricular pressures were recorded instead of systemic arterial pressure. The statistical differences (p values) between control and experimental data are shown for the responses in heart rate and blood pressure, and for the differences in responses (percentage change) in contractile force on the epicardial and endocardial surfaces. Changes in heart rate during each of the five experimental procedures were consistent and, except during stellate ganglion stimulation (including both right and left sides), were significant. Similarly, alterations in systolic blood pressure were generally significant. Segmental contractile force, as measured by the strain gauge arch, showed marked changes on both epicardial and endocardial surfaces as a result of direct electrical (stellate and vagus nerves) and reflex (bilateral carotid occlusion and traction) excitation. Emphasis is placed upon the comparative changes in contractile force of these two different myocardial segments, with clear evidence for more profound alterations in the myocardial muscle. The p values show highly significant differences for each of the neural manipulations. In contrast, these changes were not significantly different when the positive inotropic response was elicited by intravenous norepinephrine.

Discussion. It is clear from these data that endocardial structures of the baboon heart

possesses the capability of responding actively to many stimuli known to be involved in cardiovascular regulation. This is not surprising, of course, since they are structured from excitable and contractile myocardium. However, it is apparent that these regions may be even more responsive to both humoral and neural excitation than are comparable segments on the epicardium. For example, the interventricular septum shows a greater percentage change in both contractile force and intramyocardial pressure than do similar segments of the free-wall of the left ventricle (Table I). The true significance of these observations is not presently understood because functional studies of these intraventricular structures remain grossly incomplete (4, 6).

There is recent evidence for discrete distribution of efferent cardiac nerves to the endocardial surfaces in the dog in a manner comparable to that established for epicardial surfaces (4). It was shown in the dog that branches from the right and left sympathetic trunks are differentially distributed to the papillary muscles, and that even more specific, smaller branches of the left sympathetics may selectively activate either the anterior or posterior papillary muscle within the innervation of the papillary muscles in the baboon (Fig. 1). Whether the capabilities for such highly localized control holds physiological significance, and whether isolated inotropic events may in fact be restricted to such highly selected portions within a single chamber is not known. The structure–functional mechanisms exist for local control, but we are not yet prepared to state whether such mechanisms are actually operational under normal reflex activity.

In those primary control systems examined, therefore, the endocardial surfaces of the baboon heart appear to be regulated by beta adrenergic agents (norepinephrine, isoproterenol) in much the same way as in the dog and man. Also, the distribution and electrical activation of both sympathetic and parasympathetic nerves elicit comparable results. The left sympathetic cardiac nerves exert greater inotropic influences on the interventricular septum and the left ventricular papillary muscles than do those from the right. Both vagi are clearly distributed to those endocardial structures and exert very distinct negative inotropic affects. Direct electrical excitation of the sympathetic nerves induces marked and sustained elevation in contractile force and intramyocardial pressure. Following successive transection of the isolated left and right vagi both contractile force and pressure rises, presumably as a result of sudden "release" of cholinergic tone. With sympathetic outflows to the heart intact under such circumstances, it is probable that this system exerts simultaneous augmentation in contractile response. Reciprocally, successive transection of the sympathetic trunk between T3 and T4, accompanied by bilateral section of the individual white and gray rami at T3, T2, and T1 and C7 and 8 resulted in progressive decline in myocardial segmental contractile force. It is apparent, therefore, that at least a degree of balance is maintained between the two antagonistic outflows of the autonomic nervous system, and this implies a tonically active system of control within appropriate portions of the central nervous system of the baboon. In many experiments there appeared to be an excess of parasympathetic tone with correspondingly greater vagal influence compared with sympathetic. There is also tentative evidence to indicate an active role by the medulla in maintenance of adrenergic cardiovascular tone (7). However, we do not yet have sufficient data in which primates have been tested under varying levels of blood pressure, the influence of different anesthetics, use of sufficiently wide range of receptor blocking agents, etc., to arrive at more definitive statements in this regard.

Recent observations have amply demonstrated that the carotid sinus baroreceptors exert a reflex, negative inotropic influence upon left (8, 9) and right (10) ventricular performance in the dog. The present experiments confirm both the direct and reflex influences of the vagi upon ventricular contractile force as well as upon intraventricular pressures in the baboon. They further document the active participation of the interventricular septum and the papillary mus-

cles in these responses. To our knowledge, this represents the first report documenting such alterations in these endocardial structures in the primate. Figure 3 also elaborates an additional important detail of the overall suppressor action of the baroreceptor reflex upon ventricular musculature. Both vagi had been sectioned prior to the pressure stimulus delivered in Fig. 3B, thus eliminating this pathway for reflex inhibitory action. Withdrawal of sympathetic tone, coupled with decreased release of catecholamines from the adrenal medulla, remained as the primary responsible mechanism. Such participation by the sympathetic system is well known, of course, but is usually considered to be of lesser importance than the vagus outflows to the heart (9). It is apparent that interaction between cholinergic and adrenergic mechanisms may be of importance in the baboon, as they are in the dog (11). However, we have never elicited as marked alterations in force and pressure in the dog heart as were consistently observed in the baboon heart (Fig. 3B) during baroreceptor reflex maneuvers. It may be therefore, that moderator reflex mechanisms may play an even more important role in the cardiovascular adjustments required of the baboon under normal conditions.

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