AUTONOMIC CONTROL OF CLASSICALLY CONDITIONED HEART RATE AND BLOOD PRESSURE RESPONSES IN RESTRAINED AND UNRESTRAINED SPONTANEOUSLY HYPERTENSIVE RATS

by

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Table 1. Abbreviations used in text.

A-, refers to appendix table number
ANS, autonomic nervous system
bpm, beats per min
CR, conditioned response
CS, conditioned stimulus
dB, decibels
E, epinephrine
ECG, electrocardiogram
HR, heart rate
i.p., intraperitoneal
ISI, interstimulus interval
mg/kg, milligrams per kilogram of body weight
mm Hg, millimeters of Mercury pressure
NE, norepinephrine
OR, orienting response
pg/ml, picograms (10^{-12} g) per milliliter
R, restrained group
R-R, restrained-restrained subgroup
R-U, restrained-unrestrained subgroup
SHR, spontaneously hypertensive rat(s)
U, unrestrained group
UR, unconditioned response
US, unconditioned stimulus
U-R, unrestrained-restrained subgroup
U-U, unrestrained-unrestrained subgroup
WKY, Wistar-Kyoto normotensive rat strain from which SHRs were derived

INTRODUCTION

Classical conditioning of cardiovascular responses has been reported in a number of situations and species. Recently, attention has been turned towards conditioned modifications of heart rate and blood pressure in attempts to understand the nature of learned cardiovascular changes in hypertension. The experimental study of hypertension has been facilitated by the development of a genetically inbred strain of "spontaneously" hypertensive rats (Okamoto, 1969), a strain characterized as sympathetically dominated in terms of cardiovascular reactivity and responses to stress (Folkow, 1978). However, the importance of conditioned stress responses in these rats has been largely ignored. Broadly viewed, the present study was an attempt to provide information on the mechanisms involved in classically conditioned modifications of cardiovascular functioning in spontaneously hypertensive rats (SHRs). The experimental approaches that were employed included in-depth comparisons of conditioned heart rate (HR) and blood pressure (BP) reactions that were developed in either restrained or unrestrained SHRs, and of the changes in their reactions following pharmacological blockade of the autonomic nervous system (ANS).

More specifically, the objective of the present study was to determine whether classically conditioned HR and BP reactions (CRs) in SHRs varied according to the conditions of restraint that were imposed

during conditioning. Both conditioned increases of HR (McCarty, Chiueh & Kopin, 1978b) and conditioned decreases of HR (Hatton, Wilkin, Francisco, Hoffman, Buchholz & Fitzgerald, 1979; Hatton, Buchholz & Fitzgerald, 1981) have been reported in SHRs. Presently, degree of restraint stands as the one major difference between these studies. However, it remains unanswered as to how restraint could have contributed to opposing directions of HR conditioned reactions. Information concerning the dynamics of HR and BP responses of SHRs in restrained and unrestrained situations may prove to be of use in understanding the nature of the processes underlying stress induced modifications of cardiovascular reactions as well as help illuminate the generality of these processes in the hypertension syndrome.

The nature of autonomic responding in SHRs is reviewed in the material that follows. The first section reviews general outcomes concerning physiological findings relative to autonomic response patterns and sympathetic reactivity. The second section is concerned with the responses of SHRs to physiological and emotional stressors and is followed by a section discussing the effects of restraint on physiological and psychological responses. The intent of these sections is to illustrate the nature of autonomic dominance patterns in SHRs and to point out the necessity of obtaining an accurate description of the effects of restraint in cardiovascular conditioning for this strain.

Autonomic reactivity in SHRs has been examined in a variety of different situations. Due to the complex nature of autonomic control,

no single set of procedures has been employed. Those procedures most frequently used include: (1) measurement of plasma catecholamines, as circulating levels of epinephrine (E) in rats chiefly reflect neural activation of the adrenal medulla, while circulating norepinephrine (NE) mainly reflects overflow of sympathetically released NE to the capillaries and is linearly related to sympathetic nerve activity; (2) measurement of catecholamine synthesizing enzymes in plasma, as these enzymes are frequently released along with catecholamines; (3) measurement of sympathetic nerve fiber activity, which provides a direct assessment of sympathetic activity; (4) simple monitoring of HR and BP as SHRs appear to exhibit a close relationship between changes in sympathetic and vagal discharge rate and changes in HR (Folkow, 1960), such that changes in HR reflect shifts in autonomic activity, while blood pressure levels indicate the extent to which the differentiated autonomic pattern raises the net load on heart and resistance vessels; (5) tests of the effects of various pharmacological agents on HR and BP. Drugs that have been used in the latter capacity include sympathetic and parasympathetic blocking agents. Sympathetic blocking agents are subdivided into alpha- and beta-adrenergic antagonists. Alpha-adrenergic receptors, responsible for vasoconstriction of the arterioles, are inhibited by phentolamine and ergot alkaloids, whereas beta-adrenergic receptors, which increase HR, are blocked by propranolol and related compounds. Examples of parasympathetic blocking agents include atropine sulfate and methyl-atropine, both of which antagonize vagal influences on the heart.

Autonomic Activity of Spontaneously Hypertensive Rats

The "Okamoto" strain of spontaneously hypertensive rats is considered to be the most appropriate animal model of essential hypertension in humans (Hallback & Folkow, 1974; Weiss, 1974). Studies have shown that SHRs exhibit a polygenic inheritance pattern and a sequence of cardiovascular changes that are highly similar to human hypertension (Okamoto, 1972). Breeding experiments by Hansen (1972) indicated that several genetic factors interacted to produce hypertension in SHRs, with no one factor appearing to be exclusively responsible. Cross breeding experiments with SHRs did not result in simple dominance-recessive relationships in the control of BP. As in human essential hypertension, BP is relatively normal in young SHRs, increases with age, and terminates in heart failure, cerebrovascular accident, renal insufficiency, or the malignant phase of the disease (Grollman, 1972). The growth of increased BP is not mediated by a circulating renal pressor agent, but elevated plasma level of such an agent (possibly angiotensin I or II) has been found in the malignant phase (Grollman, 1972). Cardiac hypertrophy and arteriosclerosis in SHRs are comparable to that observed in clinical hypertension (Grollman, 1972; Limas, Westrum & Limas, 1980).

Physiological Studies. A central issue in the research surrounding hypertension in SHRs is the nature of autonomic activity underlying control of the cardiovascular system (Folkow, 1978). Several studies have indicated that SHRs have increased centrally elicited adrenal activity and sympathetic outflow. Grobecker, Saavedra, Roizen,

Weise, Kopin and Axelrod (1976) reported that plasma values of both NE and its synthetic enzyme dopamine-β-Hydroxylase were elevated in young SHRs compared to genetically matched normotensive rats. Judy, Watanabe, Henry, Besch, Murphy and Hockel (1976) found that SHRs exhibited increased levels of directly measured sympathetic nerve activity compared to normotensive rats and that older SHRs had impaired abilities to inhibit central sympathetic outflow in response to activation of the baroreceptor reflex by exogenous pressor agents. Vanhoutte (1980) reported hyperfunction of peripheral adrenergic nerve terminals and enhanced release of NE.

In a study of NE levels in the cardiovascular system of SHRs, Vetadzokoska, Gudeska, Glavas, Sukarova and Nikodijevic (1972) found that even though the total content of the heart was slightly lower in SHRs than in normal rats, the nerve terminal pool of NE available for release was higher. These investigators also found that alpha-adrenergic vascular reactivity in SHRs was increased compared to nephrectomized hypertensive rats. Increased sympathetic drive to the myocardium of SHRs was further indicated by the results of titrated beta-adrenergic pharmacological blockade in both SHRs and normotensive rats (Pfeffer, Pfeffer and Frohlich, 1976).

Recording studies of splanchnic nerve discharge rates have indicated that SHRs have higher than normal levels of this sympathetically mediated activity (Okamoto, Nosaka, Yamori & Matsumoto, 1967). After severing the splanchic nerve, Iriuchijima (1973, 1976) found that a much higher rate of splanchic-nerve stimulation was needed in SHRs

than in normotensive rats to maintain resting levels of arterial pressure.

The arterial vasculature of SHRs has been shown to be somewhat more reactive to sympathetic activity than that of normotensive rats. Bohlen (1979) and Berecek, Schwertschlag and Gross (1980) tested the responsiveness of different vascular beds to exogenously applied NE and found that SHRs showed greater vascular constrictive responses than normal rats. Sub-maximal responses were increased at all doses tested and response thresholds were lowered in SHRs. Webb and Vanhoutte (1979) also found increased sensitivity to NE in isolated tail arteries of SHRs.

The picture that emerges from the preceding studies is one of sympathetic lability in SHRs. Sympathetic activity appears to be enhanced and cardiovascular responses to sympathomimetic agents are exaggerated. Such a pattern may suggest that baroreceptor feedback in SHRs is inadequate or that central baroreflex control mechanisms are offset to allow for a higher level of sympathetic outflow (Guyton, 1980).

Behavioral Studies. In addition to physiologically elevated levels of resting sympathetic activities, other investigations have indicated that SHRs exhibit exaggerated behavioral and sympathetic reactions to environmental stressors and other stimuli. In most studies demonstrating phasic sympathetic hyperreactivity in SHRs, HR, BP, or plasma catecholamine responses to acute, unconditioned environmental stressors have been examined. Some of these studies will be

reviewed briefly in order to gain an understanding of typical reaction patterns and the role of sympathetic nervous activity in the cardiovascular responses of SHRs.

Hallback and Folkow (1974) investigated the cardiovascular reaction patterns of unrestrained SHRs to "sudden alerting" stimuli including intense noise, light and vibration. The exact type and intensity of the noise was not specified; the light was flashing but the intensity was not given; the vibration consisted of motor-driven shaking of the spring mounted box in which the animals were located. Each stimulus lasted 30 seconds with 10-15 minutes of recovery allowed between stimulations. They found that SHRs exhibited larger pressor responses and HR increases than normotensive rats. SHRs also responded more frequently to mild stimuli (lights), which was interpreted as indicating lower reaction thresholds in SHRs than in normotensive controls. Pharmacological manipulations, including β-adrenergic blockade with alprenolol and vagal cardiac blockade with atropine indicated that the cardiovascular reaction patterns of SHRs were exaggerated in terms of both sympathetic outflow and central suppression of vagal outflow.

In another psychological stress experiment exposing SHRs to 30 seconds of loud noise and to a jet of air, Hallback-Nordlander and Lundin (1979) monitored cardiac output, BP and HR responses. Here again, the type and intensity of the noise were unspecified; the air jet was directed to the animal's head. SHRs had higher resting levels of cardiac output and HR than normal rats, but nevertheless showed

greater increments in both of these measures in response to stress. Both rat strains displayed pressor BP responses. Elimination of the environmental influences by barbiturate anesthesia resulted in fall towards baseline HR and cardiac output in SHRs than in normotensive rats.

Several investigations have been conducted to examine the reactions of SHRs to more intense, physiological stressors. McCarty, Chiueh and Kopin (1978a) examined behavioral and cardiovascular reactions of SHRs and normotensive rats to inescapable electric foot-shock. Rats in this experiment received 10 min habituation to a Plexiglas chamber with an electrifiable grid floor. Blood samples were drawn and HR and BP were measured before, during and after 5 min of 2.5mA, .4 second footshocks (intershock interval of 5 sec). The SHRs displayed greater behavioral reactivity to shock than the normotensive animals, as well as larger cardiovascular responses to handling and transfer. Heart rate and BP responses to shock, which were equivalent in both strains of rats, consisted of increases of HR and pressor BP responses. In a separate account of the plasma catecholamine responses of this same experiment, Chiueh, McCarty and Kopin (1977) reported that SHRs had significantly higher post-shock levels of NE and E than normotensive rats.

In a study very similar to the one just cited, McCarty and Kopin (1978a) measured plasma catecholamine responses to footshock in several ages of SHRs and normotensive rats. Additionally, the investigators in this study reported on resting catecholamine levels in naive animals prior to handling and then transfer to the shock

chamber. Handling and transfer induced significant catecholamine responses in SHRs of every age, as well as in the oldest normotensive rats (48 weeks). As in the earlier report by Chiueh, et al. (1977), SHRs displayed larger plasma NE and E increases in response to foot-shock than normotensive rats, and this was found at every age tested.

In another series of experiments, the effects of immobilization on SHRs were studied (Kvetnansky, McCarty, Thoa, Lake & Kopin, 1979). Both SHR and normotensive rats were immobilized up to 2.5h/day in a prone position with head and limbs secured. The results of these investigations showed that SHRs exhibited significantly more sympathetic activity in response to this type of stress than did normotensive rats. SHRs had greater increments in plasma NE and plasma E during initial exposure to this stress, and had greater increments in BP after repeated exposures. Baselevel HR responses were increased in both SHRs and normotensive rats, but did not differ between the two strains.

Yamori, Matsumoto, Yamabe and Okamoto (1969) studied the effects of chronic exposure to several stressors including immobilization, combined visual, auditory and electric shock, and cold exposure. The immobilization group received 2-10 h/day exposure over 20-30 days for a total of 100-130 h. The combined stimuli group was exposed to randomly combined high pitched buzzing (3-7 sec, 5-6 times/min), flickering 100 W lights (40-60 flashes/min), and 20-40 V, 60 HŻ, .5-1 sec shocks through the grid floor (5-6 shocks/min), for 1-4 h/day from 6 to 18 weeks of age. The cold stress group was housed in a 2-10° C

environment from 13 to 20 weeks of age. It was found that SHRs showed greater chronic augmentations of BP than normal controls. SHRs also showed higher incidence of aggravated hypertensive lesions following chronic exposure to stress.

The results of the preceding studies indicate that SHRs, relative to normotensive rats, display exaggerated behavioral and sympathetic defense reactions to environmental, physiological and mental stressors. While there were some variations among individual experiments, these reaction patterns have generally included magnified HR increases, pressor BP changes and increased plasma catecholamine levels. This pattern of generally higher sympathetic outflow in SHRs exposed to unconditioned stress supports a neurogenic hypertension model proposed by Folkow (1975, 1978; Hallback & Folkow, 1974). In this model, sympathetic defensive reactions are thought to contribute to vascular structural changes that are important in maintaining hypertension. Some studies have indicated that increased sympathetic activities, in the form of overall increased pressor load, can be translated into permanent structural changes of the vasculature (see Weiss, 1974, for a review). These structural changes then play an important role in maintaining high levels of peripheral vascular resistance which figure prominently in hypertension.

Conditioning Studies. Many of the cardiovascular stress reactions of humans are not triggered by actual physiological stressors, but are conditioned responses based on previous stressors (Gutman & Benson, 1971; Wolf, 1970). In keeping with attempts to use SHRs

as models of human essential hypertension, it becomes important to examine the nature of conditioned cardiovascular stress responses in SHRs. Sympathetically mediated conditioned stress reactions in SHRs might provide an important link between a type of stress that is frequently encountered by humans and the type of structural change associated with increased vascular resistance. Therefore, investigators have recently become concerned with whether or not SHRs display sympathetically dominated responses when the response complex is triggered by a conditioned rather than an unconditioned stimulus event (Hatton, et al. 1979, 1981; McCarty, Chiueh & Kopin, 1978b).

McCarty et al. (1978b) studied cardiovascular and plasma catecholamine responses of SHR and normotensive rats in an "anticipatory" stress situation. In this experiment, unrestrained rats were placed into a special shock chamber (the CS) and allowed to rest for 5 minutes prior to receiving 5 min of 2.5mA, .4 sec footshocks every 5 sec (the unconditioned stimulus, US). After four daily exposures to the "5-min wait, 5-min shock" protocol, animals were tested on the fifth day to monitor cardiovascular and plasma catecholamine responses during the 5-min anticipatory period. It was found that transfer from the home cage to the shock chamber resulted in HR increases in experimental SHRs and that these increases were larger than those shown by control SHRs and normotensive rats. Plasma catecholamines were also significantly elevated in SHRs. This study seemed to indicate that, as with unconditioned stressors, SHRs display a sympathetic response pattern to conditioned stimuli associated with stress.

The conditioning controls used by McCarty et al. (1978b), however, were inadequate. The control groups were exposed to daily handling and placement into the shock chamber, but never received exposure to the shock US. It is difficult to tell, therefore, whether the responses of the experimental groups represented only the effects of conditioning or whether nonassociative processes such as sensitization resulting from shock experience also contributed to the cardiovascular reactions (Mackintosh, 1974). In light of the hyperreactive nature of SHRs, this is a crucial issue in interpreting the outcomes of the McCarty et al. (1978b) study.

The conditioning paradigm employed by McCarty et al. (1978b), too, was not the type of procedure that has been typically employed by other investigators in the study of classically conditioned cardiovascular responses (Black & Black, 1967; Cohen & Obrist, 1975; Dykman, 1967; Fitzgerald & Martin, 1971; Gantt, 1960; Holdstock & Schwartzbaum, 1965; Schneiderman, 1974). In a well controlled cardiovascular classical conditioning experiment, the CS typically consists of a discrete stimulus event such as the onset of a tone, light, or other stimulus, and the interval leading to the onset of the US is on the order of seconds rather than minutes (Cohen & Obrist, 1975; Fitzgerald & Martin, 1971; Schneiderman, 1974). Thus, it was deemed important in the present study to investigate the nature of classically conditioned cardiovascular responses of SHRs within the context of a well controlled conditioning paradigm that provided assessment of nonassociative influences on HR and BP.

In the experiments by Hatton et al. (1979, 1981), restrained SHRs and normotensive Wistar-Kyoto rats received 30 classical conditioning trials in which a tone CS was followed 10 seconds later by a shock US. Control groups in these studies received exposure to both the CS and the US in an explicitly unpaired fashion. Hatton et al. (1979) monitored HR responses that developed to the tone CS, while Hatton et al. (1981) monitored both HR and BP. Additionally, pharmacological blockade of the autonomic nervous system was carried out in the later study in order to determine the underlying nature of the cardiovascular conditioned responses that were developed.

The results of the studies by Hatton et al. (1979, 1981) did not correspond with the results of the McCarty et al. (1978b) study. While the normotensive rats showed conditioned accelerations, SHRs developed conditioned decelerations of HR in both studies by Hatton et al. (1979, 1981), as opposed to the accelerations noted by McCarty et al. (1978b). Moreover, Hatton et al. (1981) found that the decelerative HR CRs of SHRs were mediated principally by increased vagal output which was not secondary to sympathetically mediated pressor BP CRs. The SHRs showed pressor BP CRs similar in direction to the BP increases that have occurred in unrestrained SHRs to various forms of stimulation. Why the SHR HR CR was a deceleration instead of an acceleration like that frequently shown by unrestrained SHRs to external stimulation remains an important question.

The occurrence of a vagally mediated decelerative HR CR coupled with a sympathetically mediated pressor BP CR strongly suggests that

it may be inappropriate to characterize stress induced cardiovascular reactions in SHRs as being dominated by sympathetic influences. It seems likely that there may be a variety of circumstances under which SHRs as well as other rat strains may demonstrate different patterns of cardiovascular changes, and that relative autonomic control of response components in the pattern will also vary (Martin & Fitzgerald, 1980). So far, conditioned and unconditioned cardiovascular responses of SHRs have been examined only under a relatively narrow range of conditions.

In this connection it should be noted that several differences existed between the experiments of Hatton et al. (1979, 1981) and McCarty et al. (1978b). Many of these differences were minor methodological points that were unlikely to have produced the divergent HR CRs. However, one major difference was the factor of restraint, which has been thought to influence profoundly the direction of conditioned HR responses in normotensive rats (Fitzgerald & Teyler, 1970; Martin & Fitzgerald, 1980; Teyler, 1971). In keeping with what has been found in unrestrained SHRs, unrestrained normotensive rats have been shown to develop conditioned HR accelerations (Black & Black, 1967), while restrained normal rats have consistently been shown to develop conditioned HR decelerations (Fitzgerald & Martin, 1971; Fitzgerald & Teyler, 1970; Martin & Fitzgerald, 1980). At present, it is not possible to specify the mechanisms or processes underlying the different types of responding that occur under the two conditions of restraint. The following section provides a survey of some of the known physiological and behavioral effects of restraint.

Restraint

Physiological Effects of Restraint. It is traditional in many physiological investigations to restrain laboratory animals during the course of experimental manipulations and recordings (Fowler, 1978). However, the experience of being restrained is not an innocuous event. Physical restraint and immobilization of an animal acts as a potent unconditioned stressor, activating many physiological, hormonal and sympathetic reactions (Fowler, 1978). It is worthwhile, therefore, to mention some of the physiological responses induced by restraint and consider how they might interact with the development of conditioned cardiovascular responses.

Restraint usually refers to the manipulation of an animal in order to restrict movement during the course of an experimental investigation. Several devices are used to effect restraint in rats, but a majority of these devices consist of some type of plastic tube into which a rat can be inserted. These devices fit snugly around the rat and frequently have adjustable inserts in front of and behind the animal to restrict forward and backward movement. Typical descriptions refer to circular plastic tubes or to inverted-U-shaped plastic restrainers (Fowler, 1978).

Another type of restraint that is commonly used is referred to as immobilization. Immobilization is frequently employed as a form of stress in rats and mice (Dallman & Jones, 1973). A typical immobilization procedure consists of taping or otherwise securing a rat to a bench, cage top, or wooden block. Physiological, hormonal or

biochemical stress responses are usually monitored during and/or after immobilization.

While not identical to the type of restraint that is imposed to restrict movement for other experimental investigations, immobilization might be thought of as comparable to restraint. Though the magnitudes of stress responses seen during immobilization may be somewhat larger than those seen during restraint, they are directionally similar and consist of the same response configuration (cf. Chiueh & Lopin, 1978, and Kvetnansky et al. 1979). Emotional and sympathetic arousal result from both procedures. Because of its frequent use as a physiological stressor, immobilization has been well characterized. On the other hand, the effects of restraint have not been frequently described (Chiueh & Kopin, 1978). The outcomes of immobilization experiments must be relied upon, therefore, to supplement knowledge of the effects of restraint.

Immobilization results in diffuse activation of sympatho-adrenal responses in both normotensive and SHR rats. In normotensive rats, immobilization has been reported to increase HR by 150-175 bpm and to increase BP by 10-30 mm Hg (Kvetnansky et al. 1979; Popper, Chiueh & Kopin, 1977). Plasma NE and E levels have been reported to increase 4 to 12 times resting levels (DeTurck & Vogel, 1980; Kvetnansky et al. 1977, 1979; Popper et al. 1977). Adrenalmedullectomy reportedly blocked the immobilization-induced rise in plasma E, but did not affect plasma NE increases (Kvetnansky et al. 1977). In SHRs, immobilization has resulted in HR

increases of 110-160 bpm and in BP increases of up to 15 mm Hg, while plasma catecholamine levels also increased by 10-20 times. Strangely, initial exposure to immobilization in that study did not elicit a BP increase in SHRs, although a BP response did occur on later exposures (Kvetnansky et al., 1979). Plasma corticosterone levels, another stress indicator, were increased 3-5 times in both SHRs and normotensive rats (Kvetnansky et al. 1979).

Restraint has been shown to exert effects similar to immobilization in SHRs, although restraint effects were less pronounced in normotensive rats (Chiueh & Kopin, 1978). In a study of the effects of normal experimental restraint Chiueh & Kopin (1978) found that normotensive rats displayed HR increases of 50-55 bpm and SHRs increases of 120-130 bpm. Restraint induced BP increases of only 2-10 mm Hg in the normotensive rats, while BP increases of 25-30 mm Hg were seen in the SHRs. Plasma catecholamine levels were increased by 2-3 times in normotensive rats, while increases of 4-12 times were seen in the SHRs. Finally, another study showed that restraint induced increases of plasma corticosterone to 6 times resting levels in normotensive rats (Dallman & Jones, 1973). SHRs were not included in that study, however. It would appear that restraint is a fairly stressful procedure, especially in SHRs.

Chronic exposure to immobilization has resulted in long-term physiological changes in normotensive as well as SHR rats. Kvetnansky et al. (1970) found that relative to pretreatment baselines, two catecholamine synthesizing enzymes, tyrosine hydroxylase and

phenylethanolamine-N-methyl transferase, were 2 to 3 times higher in the adrenal medulla of normotensive rats after one or two weeks of exposure to immobilization. Another catecholamine synthesizing enzyme, dopamine-β-Hydroxylase, also has been found to be elevated following long term exposure to immobilization (Lamprecht, Williams & Kopin, 1973). Normotensive rats reportedly became hypertensive during the course of repeated daily immobilizations in the study by Lamprecht et al. (1973). This hypertensive condition persisted for several weeks after the termination of the stress treatments. Similar results were found in both normotensive and SHR rats in another study of chronic immobilization and BP (Yamori et al. 1969). In that study, previously existing hypertension in SHRs was augmented by approximately 30 mm Hg over unstressed SHRs. Normotensive rats developed chronic BP elevations that were 15-20 mm Hg higher than unstressed controls.

Many experimenters disregard the possible effects of restraint when considering the outcomes of their investigations. A particularly flagrant example of this type of disregard was found in an experiment by Buccafusco and Spector (1980) on possible neurochemical differences in the control of BP between SHRs and normotensive rats. In their study, BP was recorded from rats while they were restrained or unrestrained during different experimental manipulations. The details of when restraint was used were not specified. It was not possible to tell which experimental outcomes of their study were obtained during restraint or how restraint may have influenced the results that were reported.

Another example pertains to an investigation of the effects of thermal stress on the BP of SHRs (Yen et al. 1977). Both SHRs and normotensive rats were restrained during the application of heat stress. Restraint was clearly described, but possible interactions with the experimental manipulations were ignored. This prompted Chiueh and Kopin (1978) to comment that the heat stress responses must not be considered alone, but as further augmentations of the BP elevation produced by restraint.

Restraint in Cardiovascular Conditioning. In contrast to many physiological studies, restraint has for some time been suspected to play a role in the development of conditioned cardiovascular responses (Fitzgerald & Teyler, 1970; Teyler, 1971). Teyler (1971), in an examination of the development of conditioned HR responses in normotensive rats, found that restraint exerted a pronounced effect. Restrained rats developed large magnitude conditioned cardiodecelerations, while unrestrained rats that were shocked through attached chest electrodes showed much smaller HR decreases. Another unrestrained group that was shocked through the grid floor of the test chamber showed mixed responding consisting of accelerations and decelerations. In general, the results provided some support for the view that inescapability of the shock US might contribute to the HR conditioning process. Teyler (1971) found no correlation between movement and HR changes during the CS in most of the groups, tending to rule out gross skeletal-motor activity as an important factor in the CRs.

Further studies on the relationship between US escapability and movement in restrained and unrestrained rats were carried out by Martin and Fitzgerald (1980). This investigation consisted of three experiments in which both restrained and unrestrained rats were required to perform escape responses at the end of the CS in order to terminate electric shock. In the first study, restrained and unrestrained rats receiving regular classical conditioning trials with no opportunity to escape shock were yoked to animals performing a wheel-turn escape response. The directions of conditioned HR responses were accelerative in the unrestrained groups and decelerative in the restrained groups, regardless of the presence or absence of the escape contingency. In an additional experiment, the somatomotor activity associated with escape was sharply increased in restrained rats, but this failed to modify the decelerative direction of the HR CRs. In the third experiment rats ran from an enclosed shock box following shock and the HR change to the CS signalling shock remained decelerative. Overall, the findings failed to indicate an important role for US escapability or anticipation of movement in determining HR CR direction. It was hypothesized instead that restraint might provide a peculiarly powerful influence on cardiovascular control systems within the CNS when rats are exposed to strong stress. Different brain systems serving specific defense behaviors were identified as possible sources of cardiovascular variability.

In addition to decelerative HR CRs, restrained normotensive rats have been found to develop depressor BP CRs. Hoffman (1977) examined

the conditioned HR and BP responses of restrained normotensive rats based on either electric shock or ammonia fumes reinforcements that produced entirely different unconditioned cardiovascular reaction patterns. The focus of that study mainly concerned the relationship between cardiovascular CRs and URs, but the results are relevant to the present issue. Regardless of the type of reaction pattern produced by the US, the HR and BP CRs were highly similar. The CR pattern consisted of HR deceleration associated with a biphasic pressor/depressor BP change. This study seemed to indicate, again, that restraint exerts a pre-potent influence on the development of conditioned cardiovascular responses in normotensive rats and promotes a pattern of cardiovascular CRs that is parasympathetically dominated.

Hallback and Folkow (1974) reported that accelerative HR responses of SHRs to mild and intense stimuli involved both accentuated sympathetic as well as centrally suppressed vagal discharge. They stated that this pattern reflected a "truly intensified defence reaction in SHR". These researchers went on to suggest that SHRs display a dominance of "sympathotonic" reaction patterns along with sympathetic hyperreactivity.

Certainly, the study by McCarty et al. (1978b) indicated that conditioned as well as unconditioned cardiovascular reactions of SHRs may be dominated by sympathetic influences. However, the findings of Hatton et al. (1979, 1981) in which restrained SHRs displayed decelerative HR CRs provided some evidence to indicate that conditioned cardiovascular reaction patterns of these rats may not always be subject to complete sympathetic dominance.

There are several ways in which a potent stressor such as restraint might encourage parasympathetically dominated cardiovascular responses in SHRs in place of normally occurring sympathetic reactions. Possibly, the high level of sympathetic background activity produced by restraint may prevent further increases of sympathetic output when the CS is presented. This type of argument has been referred to as the "Law of initial values" (Wilder, 1957). Evidence against this argument in restrained SHRs and normotensive rats has been provided by the fact that magnitudes of conditioned HR decreases have been found to be independent of major fluctuations in baselevel HR (Hatton et al. 1980; Fitzgerald & Martin, 1971; Fitzgerald, Martin & O'Brien, 1973; Fitzgerald & Teyler, 1970; Hoffman, 1977). Another possibility is that restraint may prime certain CNS pathways that normally control specific behavior patterns during stress (Martin & Fitzgerald, 1980). According to this view, any type of learned stress event might trigger cardiodeceleration given that the rat is restrained. For example, it may be possible to generate a certain pattern of conditioned cardiovascular responding and then modify that pattern simply by changing the conditions of restraint. The present experiment provides information on processes that may be involved in such a transformation of cardiovascular reactivity in SHRs.

Specific Objectives and Experimental Design

The present experiment, then, was designed to provide a detailed assessment of the effects of restraint on classically conditioned cardiovascular responses in SHRs. The SHR strain of rats has become

a major model for the study of human hypertension and it has become important to have accurate information concerning influences on HR and BP reactions to conditioned stress within this strain. The first objective of the study was to provide information on the similarities and differences of HR and BP responses of restrained and unrestrained SHRs receiving aversive classical conditioning. The second objective was to determine whether changing restraint conditions would influence the nature of previously established HR and BP CRs. The third and final objective was to assess the relative contributions of sympathetic and parasympathetic activity controlling the HR and BP CRs and URs that occurred under the different conditions of restraint. This objective was accomplished through the use of pharmacological agents that selectively blocked sympathetic or parasympathetic autonomic activity.

The effects of restraint were examined in several different phases. Each phase included groups of rats that were restrained and groups that were unrestrained. These phases included CS-alone trials, paired conditioning trials, non-reinforced test trials in which restraint was changed, reinforced trials under the changed restraint, and pharmacological autonomic blockade. These phases provided a complete picture of the effects of restraint on unconditioned and conditioned responses to the CS, the persistence of previous restraint effects on learned responses, and differences of autonomic control under different types of restraint.

METHODS

Subjects

Sixty naive, male, Okamoto-Aoki spontaneously hypertensive rats (SHR) obtained from Taconic Farms, Germantown, New York, were used. The rats ranged in age from 11 to 13 weeks and were individually caged under conditions of a 12-hr light-dark cycle, with food and water available ad libitum. The experiment was conducted during the light portion of the cycle.

Apparatus

The unrestrained rats were placed in a 22 × 30 × 35 cm chamber with a grid floor made of 2 mm dia. steel rods spaced 12.5 mm apart through which the foot-shock US was delivered. The chamber was located in an Industrial Acoustics Corporation sound-isolation box equipped with an exhaust fan and a 40-W house light that provided continuous illumination. Further masking of extraneous sounds was provided by white noise (75 dB sound pressure level on the C scale of an Ivie Electronics, Inc., audio spectrum analyzer) presented through a 7.5-cm speaker attached to the ceiling of the chamber. A second 7.5-cm speaker on the ceiling was used for delivery of the CS. Also mounted on the ceiling was a mercury wetted swivel commutator for recording the electrocardiogram (ECG) and a sealed swivel connector for recording BP.

The restrained rats were placed in an inverted-U-shaped, plastic small-animal holder manufactured by Narco Biosystems. The holder was equipped with guillotine-type inserts that were adjusted to fit snugly in front of and behind the animals. The floor of the restrainer had 2 mm dia. steel rods spaced 12.5 mm apart for delivery of the foot-shock US. The restrainer was located within the same test chamber used for unrestrained rats. Two rats were tested concurrently in separate, identical chambers, with trials alternating between the rats.

The ECG was recorded on a Grass Model 5 polygraph from small steel washers sutured under the skin dorsal and ventral to the rats' thoracic cavity. Heart beats occurring in selected time intervals within each trial were automatically counted by means of an on-line system described elsewhere (Fitzgerald, Vardaris & Teyler, 1968). Briefly, the system consisted of a lever-type Microswitch mounted directly above the ECG polygraph pen and adjusted so that the R wave of the QRS complex activated the switch. Heart-beat totals were accumulated in an electronic-counting network and the numbers punched on paper tape using a Tally high-speed, paper-tape perforator.

Arterial BP was recorded from the abdominal aorta on a second channel of the polygraph using a Statham P-23-Db pressure transducer feeding a Grass 5P1 preamplifier. Blood-pressure measures during each trial were obtained from an on-line system that continuously converted the analogue BP signal to a digital representation. The system operated by feeding the output of the Grass 5P1 amplifier to a Tektronix AM 502 differential amplifier which in turn was connected to

a Tektronix DC 501 function generator that served as a voltage to frequency converter. The function generator was adjusted to produce a 100 Hz train of output pulses when the bridge circuit in the BP preamplifier was balanced at zero. The frequencies of output pulses from the function generator were increased and decreased linearly by the positive (above baseline BP increases) and negative (below baseline BP decreases) voltages produced by the preamplifier. The pulses were detected by a Schmitt trigger, totaled electronically, and the numbers punched along with HR on paper tape. The resolution of the BP recording system was such that a change in BP of 1 mm Hg was equivalent to a frequency count of 3.

The CS was an 8.5-sec, 85-dB sound pressure level (measured in the same way as the white noise), 1-kHz tone. The US was a 0.5-sec, .6-mA, 60-Hz ac shock delivered to the footpads of the rats through the grid floor. A relay was used to switch the ECG signal out of the recording circuit during the time that shock was delivered. Trials were initiated automatically by a film-tape programmer with stimulus events occurring within a trial controlled by transistorized logic modules.

Procedure

Surgery. Surgery was performed under general anesthesia provided by an i.p. injection of 50 mg/kg of body weight of sodium pentobarbital. A 3.0-cm midline incision was made in the abdominal wall exposing the abdominal cavity. Fascia were separated to a depth of the aorta at the branching of the left renal vein. A catheter,

consisting of a section of PE-90 tubing joined to a section of PE-10 tubing was passed subcutaneously down the back of the neck, through the left body wall and anchored to a major back muscle approximately 3 mm lateral to the aorta. The catheter was filled with heparinized saline and approximately 7 mm of the PE-10 section was inserted into the aorta in a downstream position. No ties were taken around the catheter, permitting free circulation of blood to the extremities. The abdominal wound was closed and the free end of the catheter was anchored with sutures to the base of the neck. A 1.0-cm cutaneous incision was made ventral to the chest cavity exposing the muscle layer. A small steel washer soldered to 25-ga stranded, hermetically sealed copper wire was sutured to the muscle and the wire passed subcutaneously to exit with the catheter at the back of the neck. Another washer was sutured to the muscles dorsal to the scapulae. The chest and neck incisions were closed and the electrode wires and catheter were coated with silicone rubber for protection. The animals were allowed a minimum of 3 days to recover from the surgery before they were trained and tested. On each of the recovery days, the catheter was flushed with a .2 ml of a 500 U/ml heparin solution.

Design. The experiment may be viewed as a 2 by 2 by 2 factorial design with the factors being conditioning versus unpaired control, restraint versus no restraint, and changed versus constant restraint. Generally, a restrained and an unrestrained experimental group (n=20) each received paired conditioning trials and corresponding conditioning control groups (n=10) received explicitly-unpaired trials with the CS

and US alone. The experiment was carried out in five phases over a period of 4 days. During the first phase, all animals were given 15 min to adapt to the test situation followed by 10 trials with the CS alone. The second phase, Conditioning, followed immediately. During Phase 2, the experimental groups received 30 conditioning trials in which the CS was paired with the US at an interstimulus interval of 8 sec with the US overlapping the final 0.5 sec of the CS. The conditioning control groups received 30 CS and 30 US explicitly-unpaired trials in a semi-random order with the CS occurring no less than 60 sec ($\bar{x}$ = 75 sec) before or after the US. During the first two phases, one-half of the animals in each of the experimental and the control groups were placed in the restrainers and positioned inside of the conditioning chamber. The remaining animals in each group were allowed to move about freely inside of the conditioning chamber.

Twenty-four h later, during the third and fourth phases, (Testing and Reconditioning), the conditioning groups and the control groups from each of the original restraint conditions were divided in half. Within each group, one-half of the animals were tested under the opposite restraint condition and the remaining animals were tested under the original condition. This provided a total of eight subgroups. Following 15 min adaptation to the test chamber, Phase 3 testing consisted of 10 unreinforced CS-alone trials for all groups. The purpose of the Test Trials was to determine whether the originally established response complex was modified by changing the restraint condition in the absence of further training. This was followed in

Phase 4 by 20 reinforced reconditioning trials for the conditioning groups, and 20 CS plus 20 US explicitly-unpaired trials for the control groups on each of two days. The first reconditioning session immediately followed the CS-alone test trials, while the second reconditioning session occurred 48 h later and was preceded by 15 min adaptation to the test situation. The reconditioning trials provided information on the nature of the HR and BP CRs that became established with training under new restraint conditions. The use of conditioning control groups allowed assessment of the extent to which restraint affected all forms of responding, learned or unlearned.

The fifth and final phase was concerned with the effects of parasympathetic and sympathetic blocking agents on HR and BP. Each of the eight sub-groups received an i.p. injection of 10 mg/kg of body weight of methyl atropine to block parasympathetic activity and of 2 mg/kg of phentolamine combined with 2 mg/kg of propranolol to eliminate sympathetic activity. Methyl atropine does not readily enter the CNS, enabling interpretation of vagal blockade to be uncomplicated by central influences. The dose of methyl atropine employed in the current study has been shown previously to block conditioned HR decelerations in SHRs. Similarly, the doses of phentolamine and propranolol employed here have been shown previously to block conditioned pressor responses and HR increases, respectively, in SHRs (Hatton et al., 1981). Only one type of autonomic blockade was given each day, with 48 h between test days to allow for the elimination of the drugs. A semi-random sequence of drug testing was employed, such that each drug was given

first to approximately one-half of the rats within each group. The first drug test immediately followed the 20 Day-1 reconditioning trials in Phase 4. The second drug-test followed the 20 Day-2 reconditioning trials. For both drug tests, the rats were removed from the sound isolation chamber, given an i.p. injection of the appropriate blocking agent and placed back in the chamber. Subsequent to a 15-min drug absorption period, the rats were given 8 additional conditioning trials. The time between conditioning trials during Phases 1, 2, 3, 4, and 5 varied among 120, 150, and 180 sec intervals ($\bar{x}$ = 150 sec). The average time between presentations of the US was 150 sec for both experimental and control groups. The procedures and events of each day and phase of the experiment are shown in Table 2.

Heart rate and BP were recorded in seven successive measurement intervals within each trial. The first period was 8 sec long and was located immediately prior to the beginning of the CS. The next four periods were 2 sec long and occurred in sequence during the CS. The final two periods were 2 sec long and occurred beginning .05 sec after the offset of the US. Heart rate in beats per min (bpm) during the 8-sec pre-CS baseline period was subtracted from the bpm rates during the 2-sec periods to form difference score measures of the HR responses to the CS and US. An identical computational procedure was used to obtain difference scores in mm Hg for BP.

Table 2. Summary of procedures and events during each day of the study.

DAY	PHASE	TREATMENT
Day 1		Implant catheter & ECG electrodes
Day 2		Recovery
Day 3		Recovery
Day 4	CS Alone	15-min adaptation to test chamber 10 CS-alone trials
	Conditioning	30 CS-US trials*
Day 5	Test Phase	15-min adaptation to test chamber 10 CS-alone trials
	Reconditioning 1	20 CS-US trials*
	Drug Test	Drug injection, 15-min absorption period 8 CS-US trials*
Day 6		Drug elimination
Day 7	Reconditioning 2	15-min adaptation to test chamber 20 CS-US trials*
	Drug Test	Drug injection, 15-min absorption period 8 CS-US trials*

*Conditioning control groups received equal numbers of CS- and US-alone trials during these periods.

RESULTS

The results of this study were analyzed with several separate analyses of variance. These analyses generally consisted of between-group factors pertaining to the effects of restraint, changed restraint, or conditioning, and within-group comparisons of response changes over trials and over counting periods. Three-way analyses of variance were used for the results of the Habituation and Conditioning Phases. In these analyses, between-group comparisons included the restraint conditions only during Habituation and were expanded to include the experimental and control factors for Conditioning. Conditioning groups were compared within each type of restraint, followed by separate comparisons across restraint conditions for the experimental and then the control groups.

Five-way analyses of variance, including between-group comparisons of experimental vs control by previous restraint by current restraint, were used for the CR results of the Extinction Test Phase and Day 1 of the Reconditioning Phase. The use of these analyses was justified because it was deemed important to compare across all three between-group factors at periods when the CRs should have been either maximal or undergoing maximum change.

Four-way analyses of variance were used for the remainder of the results of the Reconditioning Phase. These included between-group comparisons of experimental vs control by current restraint (for each

of the original restraint conditions) followed by comparisons of previous restraint by current restraint for the experimental and then the control groups. This allowed comparison of the effects of constant and changed restraint within each original restraint condition and across the original restraint conditions within each experimental and and control group. Within-group factors on all of these analyses included trials and counting periods.

The same between-group comparisons were made for the results of the Drug Test Phase. However, pre-drug and post-drug responses were used as a within-group factor, rather than trial blocks.

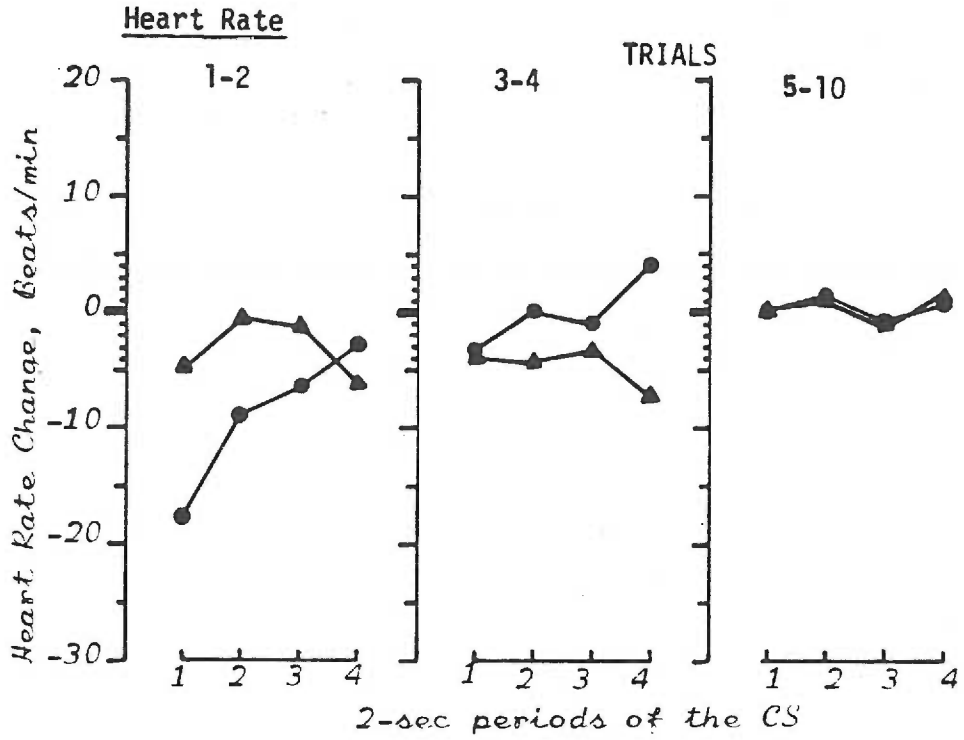
In several cases, unequal group sizes entered into the analyses. With the exception of the Reconditioning Phase CR data, least squares solutions were used uniformly for those analyses. Unweighted means solutions were used for the CR results of reconditioning.

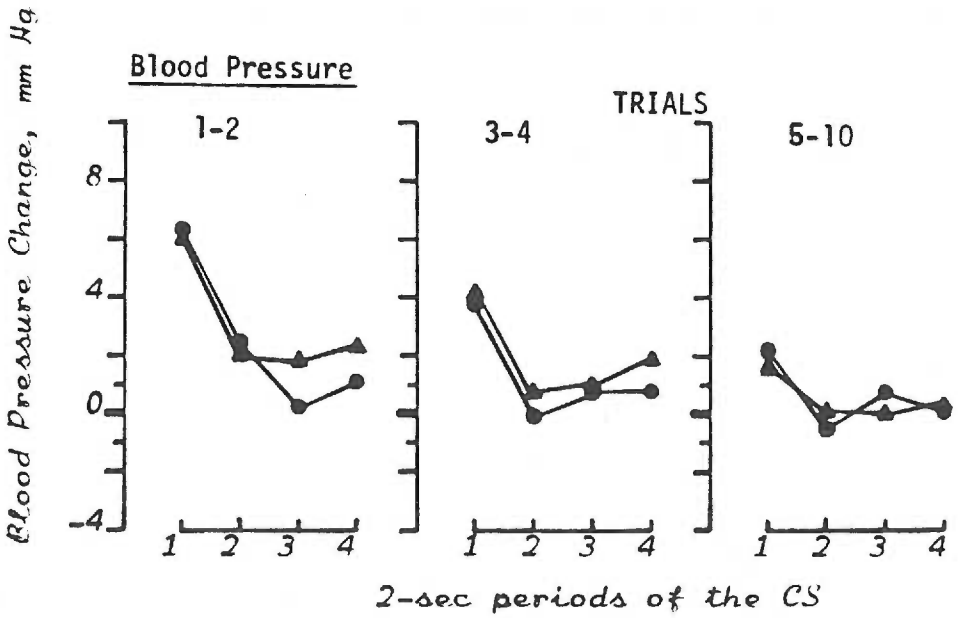
A complete listing of the results of all analyses will be presented in table form in Appendix A following the main body of the paper. Reference to the particular analyses that were carried out in each section will be given in parentheses next to the title of the section or in the text. Only the most relevant outcomes of the statistical tests will be included in the text.

Phase 1 - Preconditioning CS-alone

Figure 1 depicts the HR and BP orienting responses (ORs) of the restrained and unrestrained groups on the CS-alone trials given prior to conditioning. The data were averaged over two 2-trial blocks and then over the remaining six trials. Each point represents a 2-sec

Figure 1. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained groups as a function of intervals during the CS and two-trial or four-trial blocks during the CS-alone trials.


Heart Rate
TRIALS
1-2
3-4
5-10
20
10
0
-10
-20
-30
Heart Rate Change, beats/min
1 2 3 4
2-sec periods of the CS
Restrained
Unrestrained


Blood Pressure
TRIALS
1-2
3-4
5-10
8
4
0
-4
Blood Pressure Change, mm Hg
1 2 3 4
2-sec periods of the CS

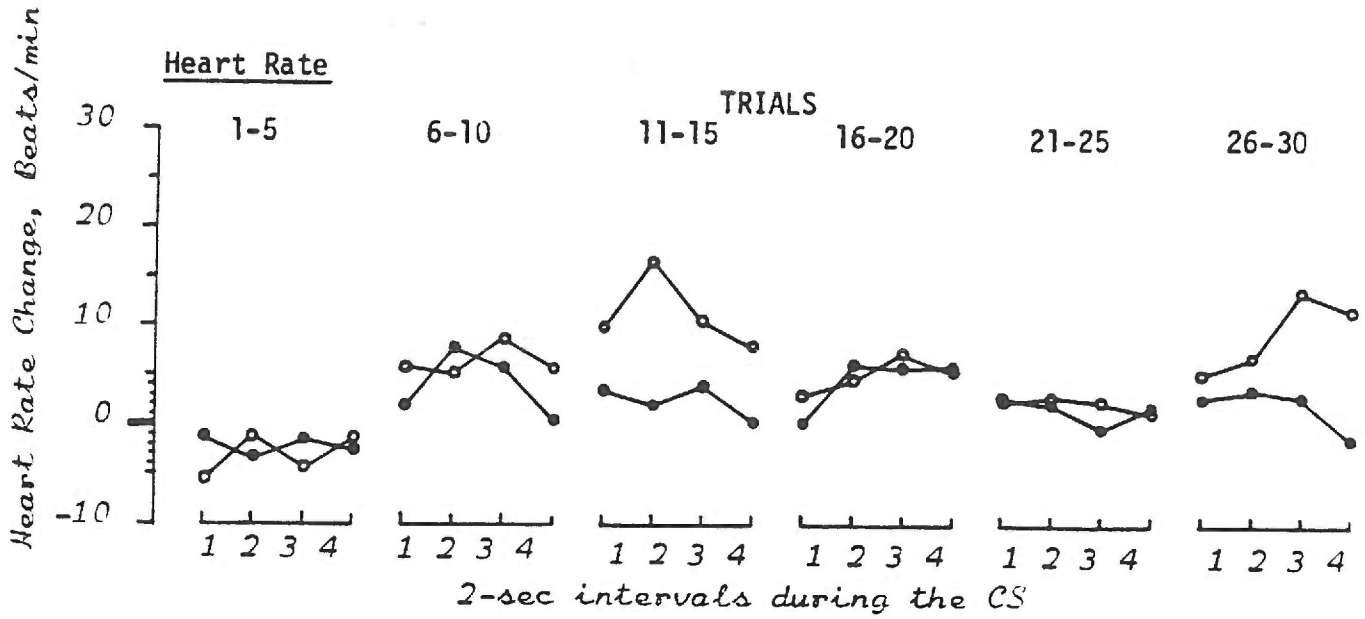
interval during the presentation of the tone CS. (HR analysis Table A-1, BP Table A-2) In general, the top half of the figure shows that the initial HR ORs of both groups to the CS were decelerations. Initially, the magnitude of the HR response of the unrestrained group appeared to have been somewhat smaller than that of the restrained group, but statistical analysis provided no significant group differences. The HR responses of both groups decreased reliably over trials ($p < .01$).

The lower panel of Figure 1 shows that the BP ORs of the groups were similar and consisted of pressor changes that were most prominent during the first 2-sec period of the CS. The magnitudes of the responses decreased significantly within the CS ($p < .01$) and over trial blocks ($p < .01$). A reliable change of response form over trial blocks ($p < .01$) left only a small pressor peak during the first 2-sec period on the final trial block.

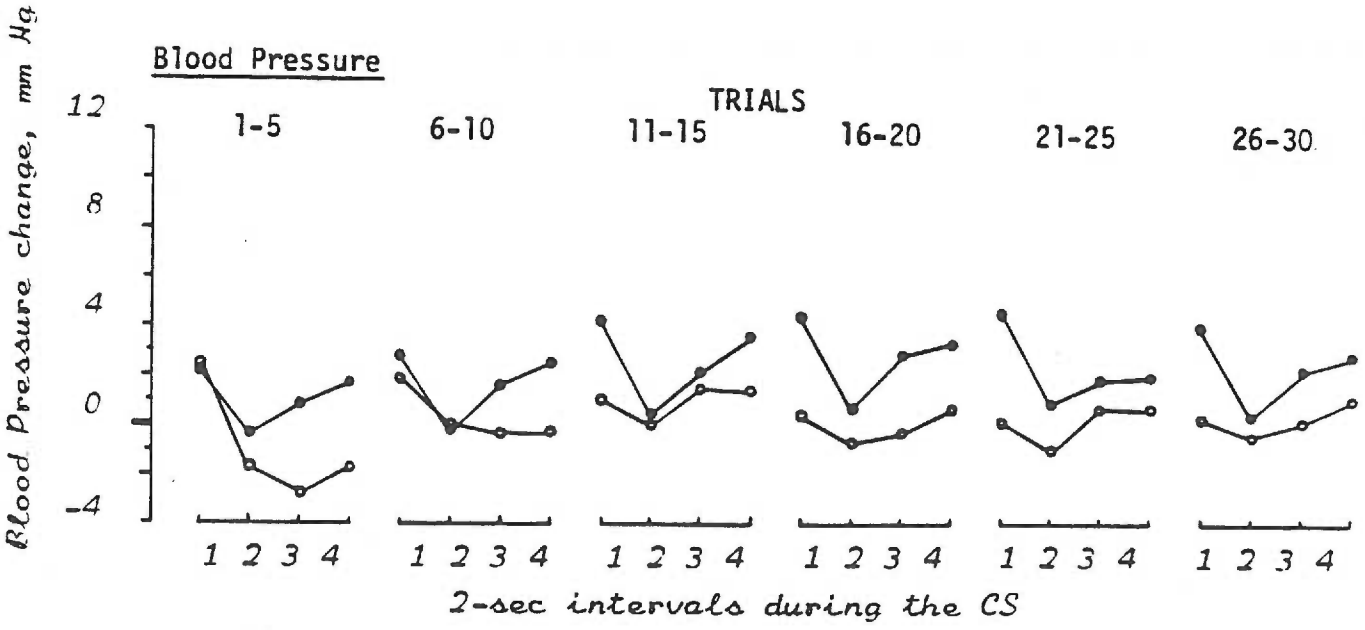
Phase 2 - Original Conditioning

Restrained CRs. (HR analysis Table A-3, BP Table A-4) Figure 2 displays the HR and BP responses of the restrained experimental and control groups to the CS during the Conditioning Phase. Each panel represents averages of successive 5-trial blocks and the points within a panel represent successive 2-sec periods during the CS. Comparative evidence of HR conditioning is not provided in the top half of the figure as the responses of both experimental and control groups changed similarly from a small deceleration to a small acceleration over trials ($p < .05$). An examination of individual rats within the experimental

Figure 2. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained experimental and control groups as a function of intervals during the CS and five-trial blocks during conditioning.



Experimental ●
Control ○

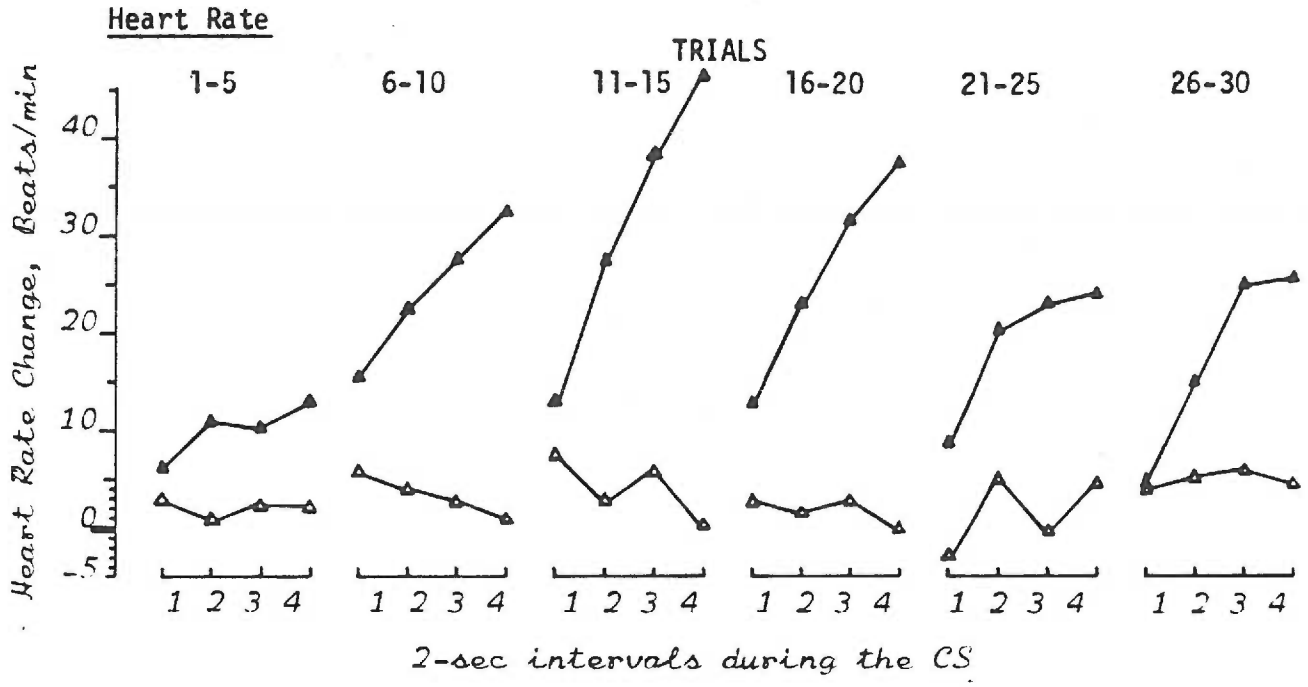


group revealed that only eight rats showed consistent deceleration, with five showing accelerations and the rest mixed HR changes.

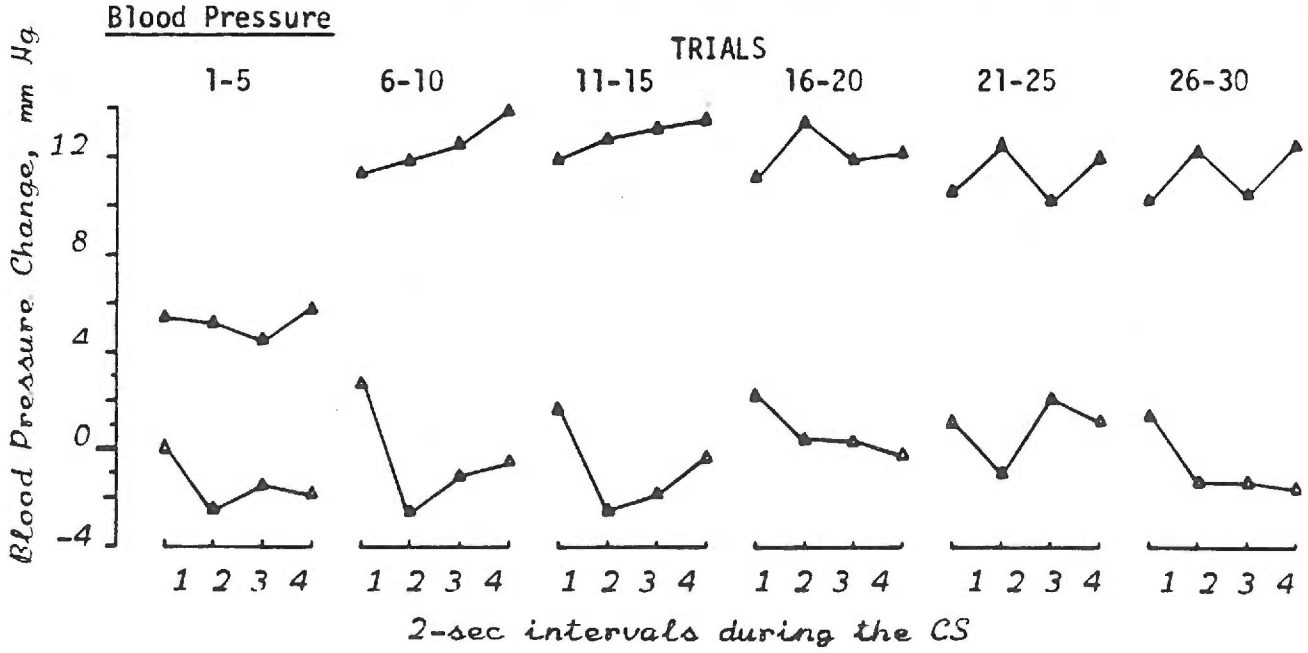
In contrast to HR, the bottom of Figure 2 shows that the experimental group developed a BP CR consisting of two pressor peaks, one near the beginning of the CS and one near the end. Following the first peak there was a marked fall in pressure to near control levels. Statistical analysis demonstrated that there was significant change in the BP responses within the CS ($p < .01$) and over trials ($p < .05$). There was also a significant conditioning vs control groups by CS periods by trials interaction ($p < .05$), indicating the presence of conditioning.

Unrestrained CRs. (HR analysis Table A-5, BP Table A-6) The HR and BP responses of the unrestrained experimental and control groups are depicted in Figure 3. This figure shows that the HR CR of the experimental group was an acceleration that reached a peak toward the end of the CS. The overall magnitude of the CR increased over the first half of the trials and then decreased slightly over the second half of the trials. Responding in the control group was near baseline throughout the Conditioning Phase. Significant outcomes involving conditioning included an overall effect of conditioning, i.e., conditioning vs control group ($p < .01$), two-way interactions between conditioning and trials ($p < .01$) and between conditioning and CS periods ($p < .01$), and a three-way interaction among conditioning, CS periods and trials ($p < .01$).

Figure 3. Mean heart rate in beats per min and blood pressure in mm Hg of the unrestrained experimental and control groups as a function of the intervals during the CS and five-trial blocks during conditioning.



Experimental ▲
Control △



The lower half of Figure 3 shows that the BP CR of the experimental group was a pressor change that grew rapidly over trials. The BP elevation showed a slight tendency to be higher at the end than at the beginning of the CS. The control group generally displayed a small pressor peak in the first CS period, followed by a fall in pressure below baseline. Significant conditioning effects were obtained for the overall groups factor ($p < .01$) and for the groups by trials ($p < .01$) and groups by CS periods ($p < .01$) interactions.

Restrained versus unrestrained CRs. (HR analysis Table A-7, BP Table A-8) A comparison of the CRs of the restrained and unrestrained experimental groups indicated that the overall effect of restraint was significant for HR ($p < .01$) (larger acceleration in unrestrained than in restrained) as were several of the interactions involving restraint ($p < .01$). For the BP CRs, it was found that the overall magnitude of the pressor change in the unrestrained group was significantly different (i.e., larger) from that of the restrained group ($p < .01$). Here too, there were several significant interactions involving restraint, trials, and measurement intervals ($p < .01$).

Similar comparison of the restrained and unrestrained control groups provided no significant between-group differences for HR and a significant three-way interaction among restraint, CS periods and trials for BP ($p < .05$), which can be attributed to more reactivity on the part of the unrestrained control group than the restrained control group.

Restrained URs. (HR analysis Table A-11, BP Table A-12) Figure 4 shows the HR and BP unconditioned responses (URs) to the US of the restrained experimental and control groups in six successive 5-trial blocks. Each point within a section represents a 2-sec interval beginning .5 sec after the offset of the US. This figure shows that the HR URs of the groups consisted of tachycardia in both intervals. The URs of the experimental group were generally smaller in the first post-US period than those of the control group. Significant outcomes were obtained for measurement intervals ($p < .01$) and for the groups by measurement intervals interaction ($p < .05$).

The BP URs of the restrained groups consisted of increases in pressure that decreased in magnitude over trials ($p < .01$). The loss over trials was more pronounced in the first interval for the control group than for the experimental group ($p < .05$).

Unrestrained URs. (HR analysis Table A-13, BP Table A-14) Figure 5 depicts the HR and BP URs of the unrestrained experimental and control groups during conditioning. As with the restrained groups, the HR URs of the unrestrained groups consisted of tachycardia, reaching a maximum of approximately 80 bpm on the third trial block. Thereafter, the HR URs of both groups became smaller. The changes over trials and measurement intervals were significant ($p < .01$ in each case) as was the three-way interaction among groups, trials, and intervals ($p < .01$).

The BP URs of the unrestrained groups, shown in the lower panel of Figure 5, consisted of pressor responses that peaked in the first

Figure 4. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained experimental and control groups as a function of intervals after the US and five-trial blocks during conditioning.

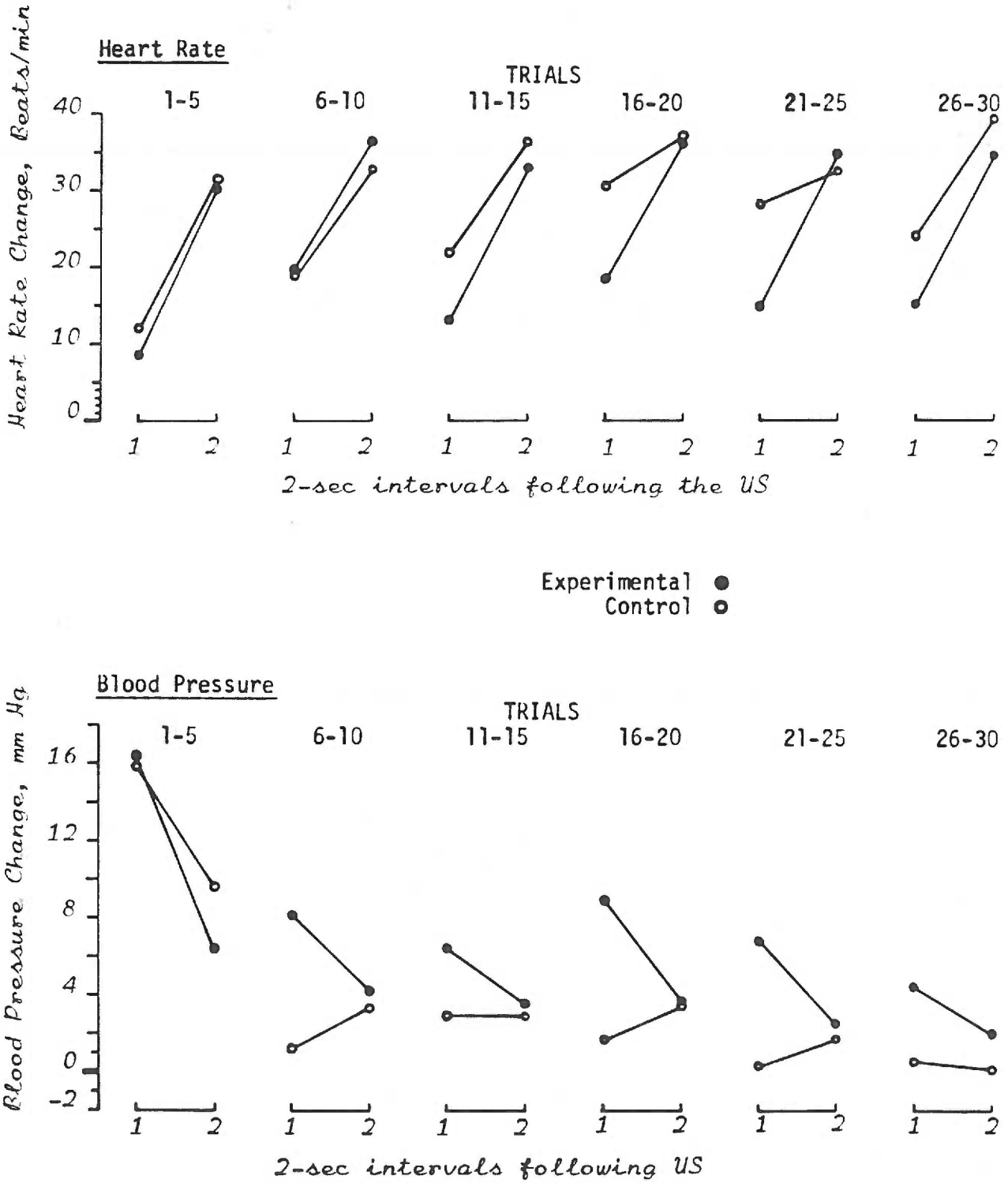
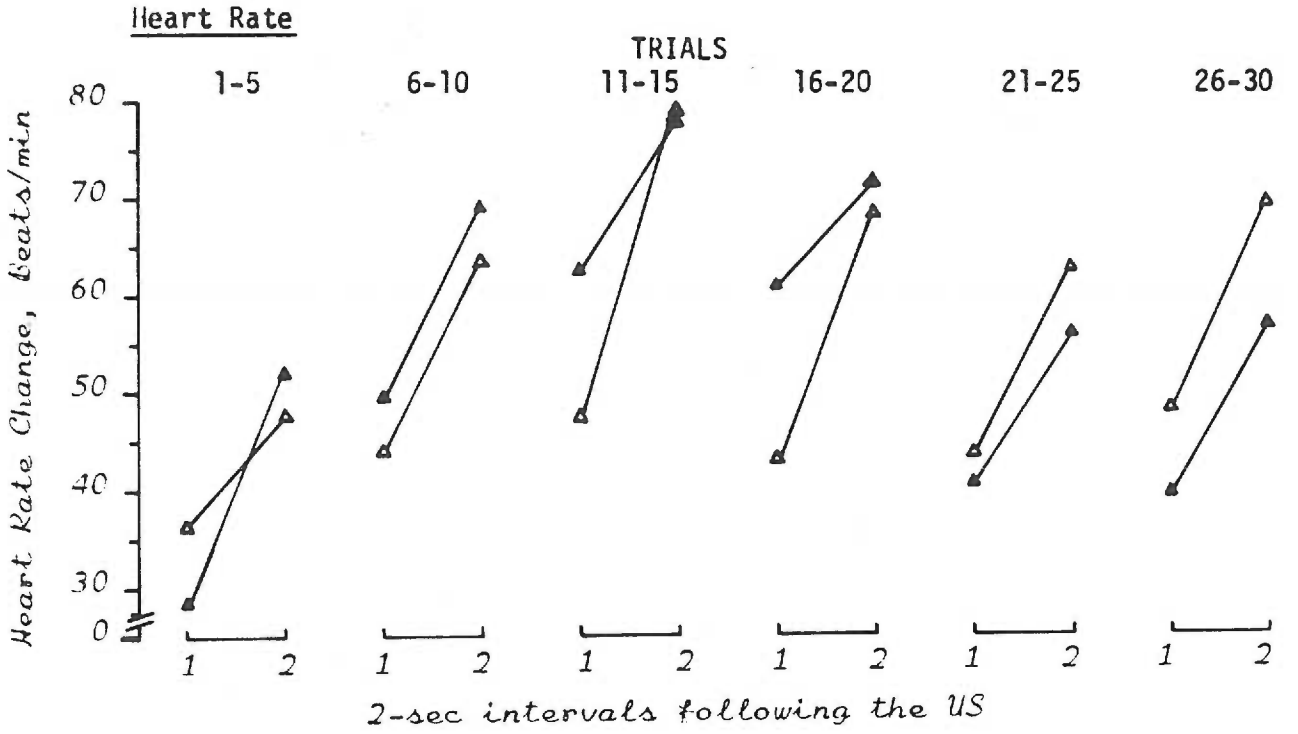
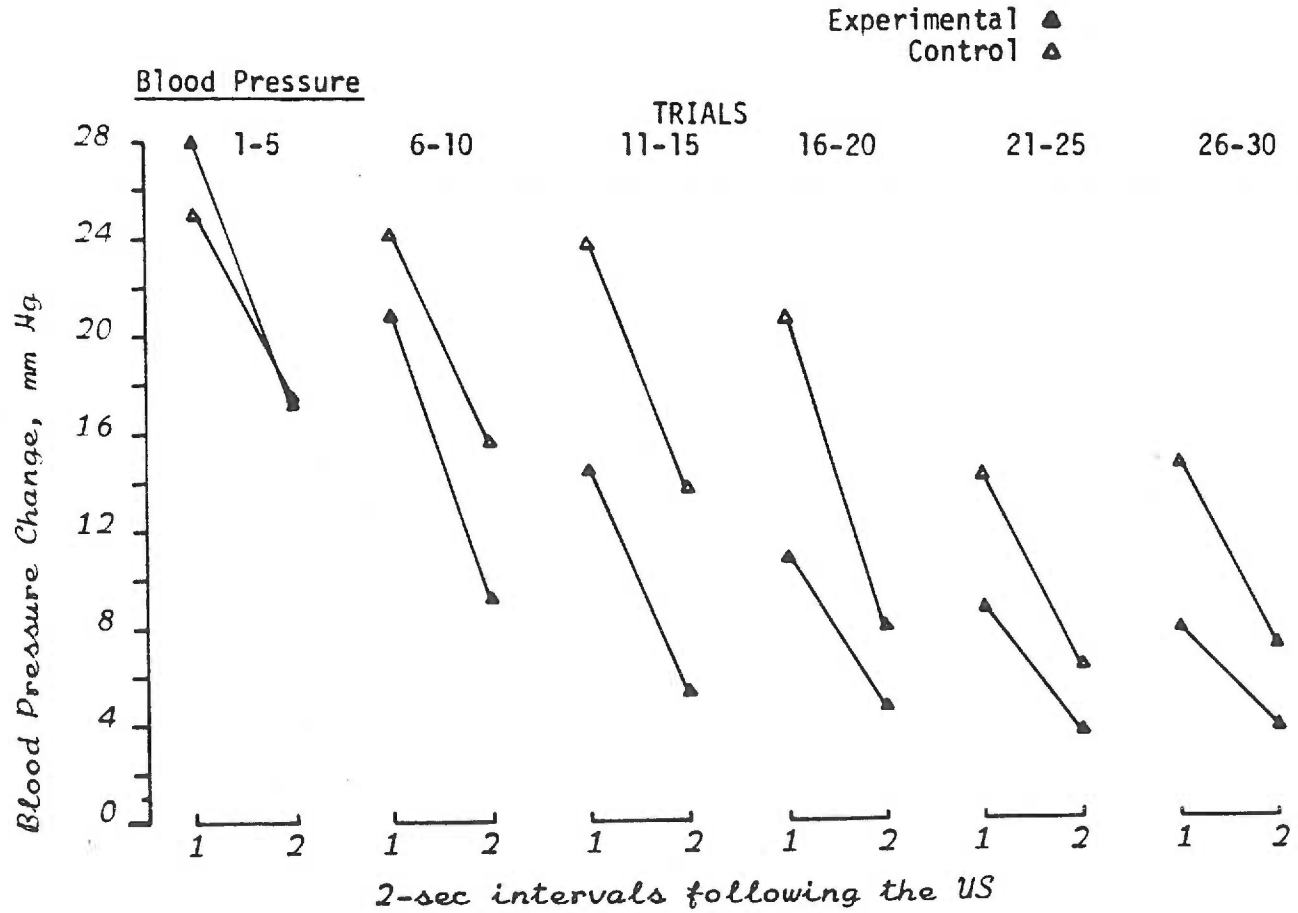

Heart Rate
TRIALS
1-5
6-10
11-15
16-20
21-25
26-30
Heart Rate Change, Beats/min
40
30
20
10
0
1
2
2-sec intervals following the US
Experimental
Control
Blood Pressure
TRIALS
1-5
6-10
11-15
16-20
21-25
26-30
Blood Pressure Change, mm Hg
16
12
8
4
0
-2
1
2
2-sec intervals following US

Figure 5. Mean heart rate in beats per min and blood pressure in mm Hg of the unrestrained experimental and control groups as a function of intervals after the US and five-trial blocks during conditioning.


Heart Rate
TRIALS
1-5
6-10
11-15
16-20
21-25
26-30
Heart Rate Change, beats/min
80
70
60
50
40
30
0
1
2
2-sec intervals following the US


Experimental
Control
Blood Pressure
TRIALS
1-5
6-10
11-15
16-20
21-25
26-30
Blood Pressure Change, mm Hg
28
24
20
16
12
8
4
0
1
2
2-sec intervals following the US

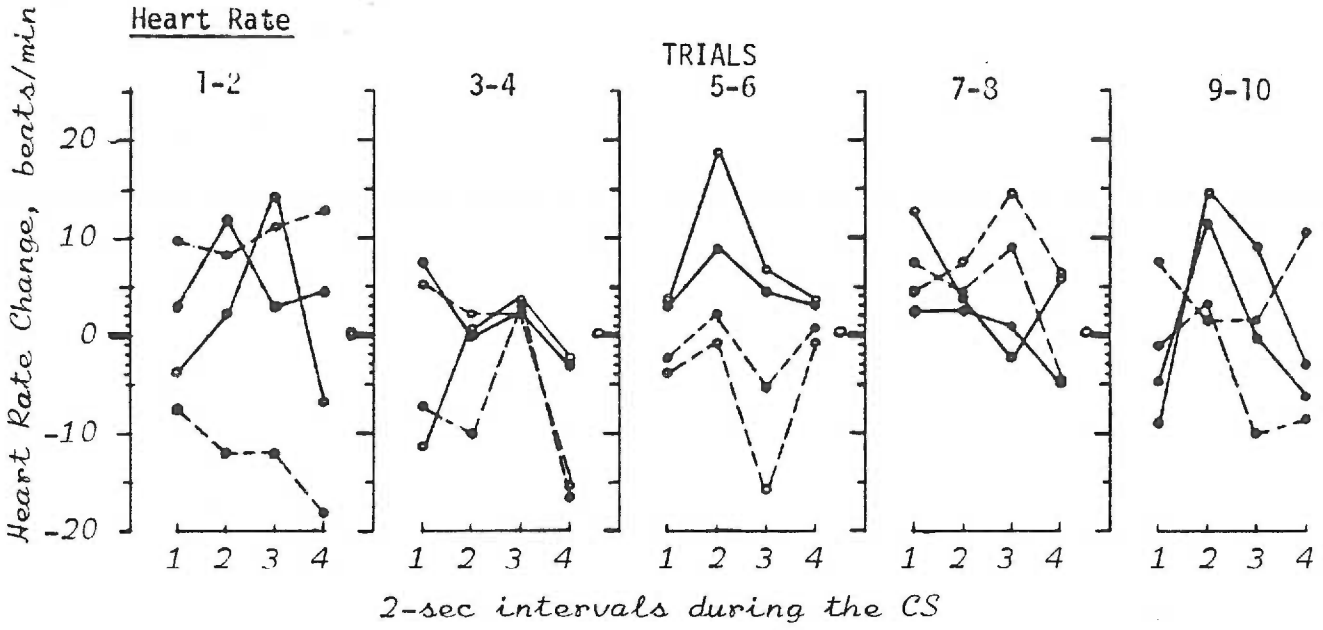
post-US period. The largest change occurred on the first trial block and averaged 25-28 mm Hg. The magnitude of the URs decreased over trials in both groups ($p < .01$), but more so in the experimental group than in the control group ($p < .05$).

Restrained versus unrestrained URs. (HR analysis Tables A-15, A-17, BP Tables A-16, A-18) Comparing Figures 4 and 5 reveals that the overall HR and BP URs of the unrestrained groups were larger than those of the restrained groups ($p < .05$ for both HR and BP). Although the decrease in the magnitude of the BP URs over trials was less rapid in the unrestrained groups than in the restrained groups ($p < .01$), the unrestrained groups started at a considerably higher level.

Phase 3 - Changed Restraint Test

Figures 6 and 7 depict the HR and BP responses of the restrained and unrestrained groups to the CS during the Test Phase when restraint conditions were manipulated. It will be recalled that each restrained group and each unrestrained group was divided into two subgroups following the Conditioning Phase; one subgroup continued under the same restraint condition and the other was changed to the opposite condition. Each subgroup is identified with a double abbreviation using R and U to designate previous restraint (first letter) and current condition (second letter). Though a single, comprehensive analysis was performed for HR (Table A-19) and for BP (Table A-20), the results are presented in an order consistent with other results sections. All statistical comparisons refer to Tables A-19 and A-20.

Figure 6. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained experimental and control groups that were previously restrained as a function of intervals during the CS and two-trial blocks during the changed restraint test.



Experimental R-R ●- - -● R-U ●——●
Control R-R ○- - -○ R-U ○——○

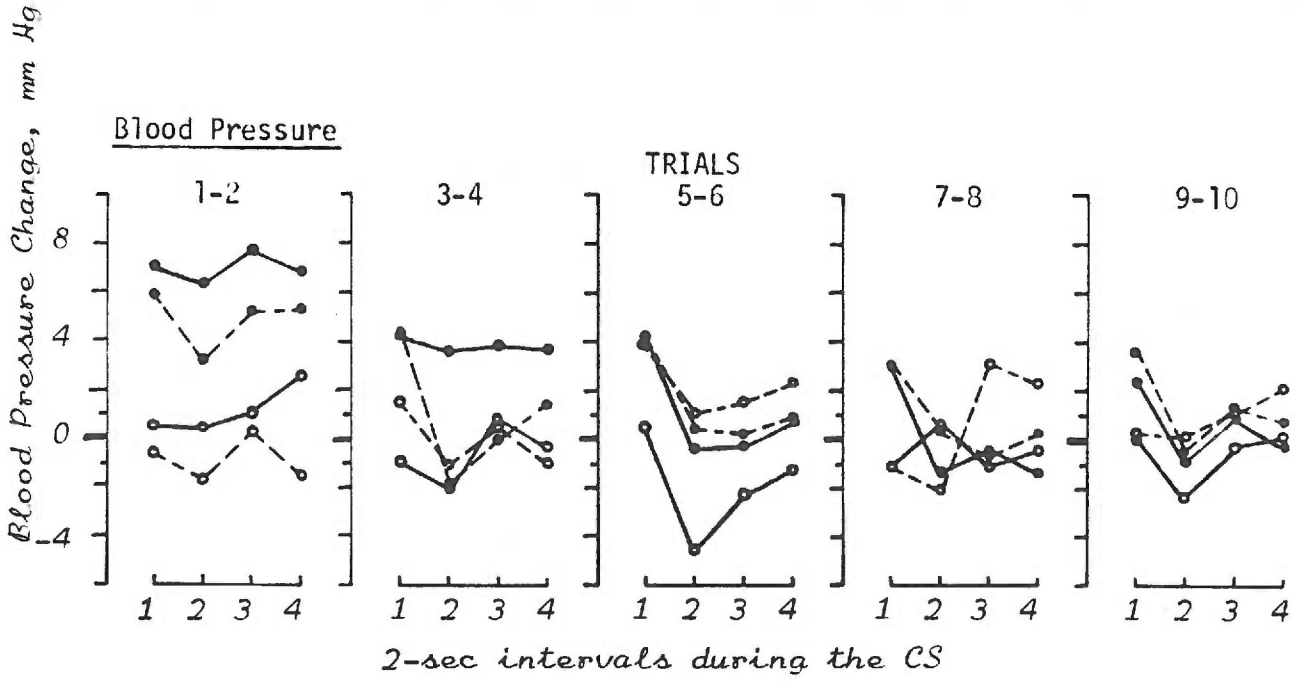
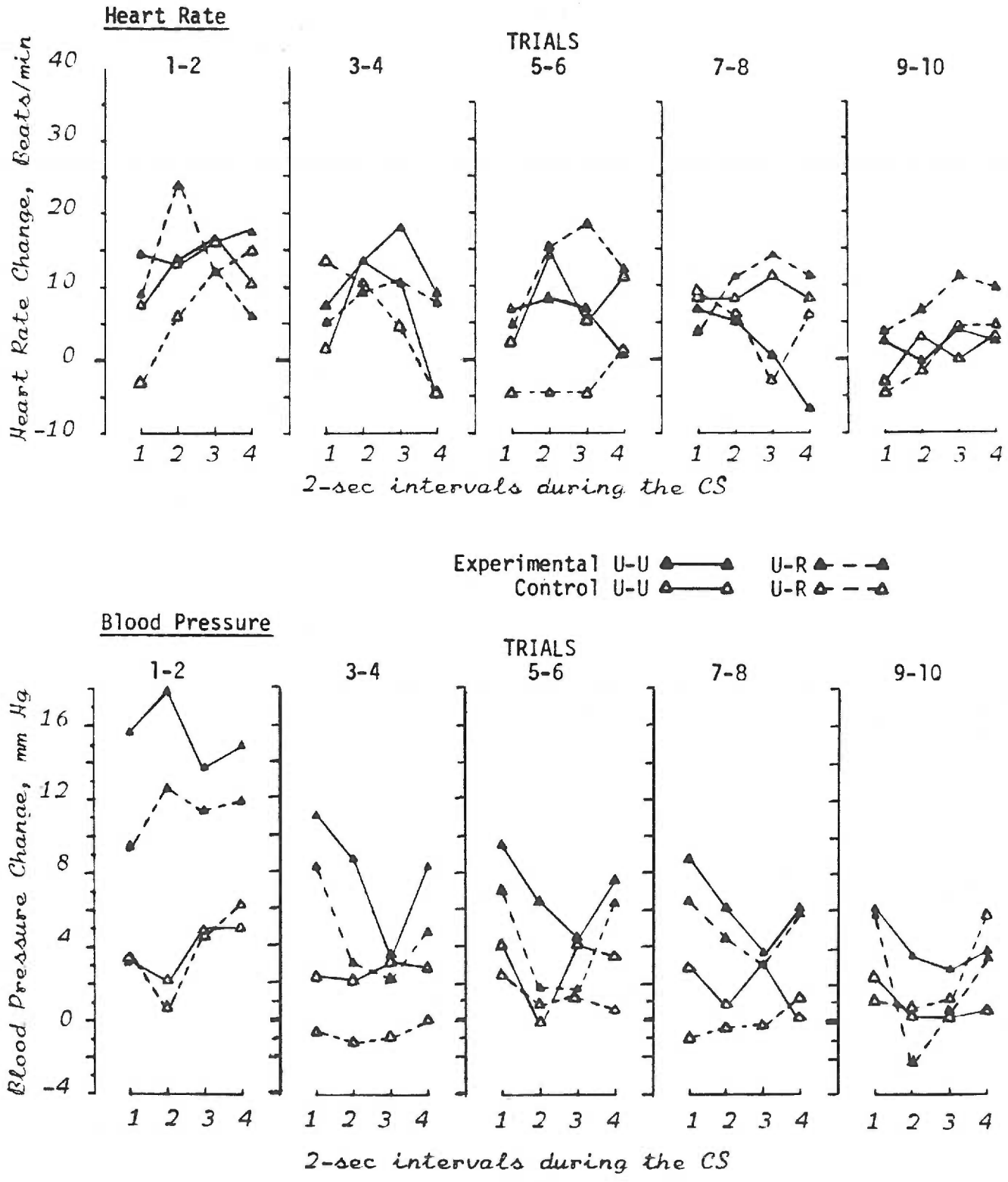


Figure 7. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained experimental and control groups that were previously unrestrained as a function of intervals during the CS and two-trial blocks during the changed restraint test.


Heart Rate
TRIALS
1-2
3-4
5-6
7-8
9-10
Heart Rate Change, Beats/min
40
30
20
10
0
-10
1 2 3 4
2-sec intervals during the CS
Experimental U-U
U-R
Control U-U
U-R
Blood Pressure
TRIALS
1-2
3-4
5-6
7-8
9-10
Blood Pressure Change, mm Hg
16
12
8
4
0
-4
1 2 3 4
2-sec intervals during the CS

Previously restrained groups. Figure 6 depicts the test trial HR and BP responses of the experimental and control groups having a previous history of restraint during conditioning. The responses were averaged over 2-trial blocks, and each point represents successive 2-sec periods during the CS. The top of the figure shows that there were no consistent differences between these experimental and control groups or between currently restrained and unrestrained groups. On the first trial block, experimental Group R-R showed a decelerative HR change while the other three groups showed mainly accelerative HR responses. This difference did not persist, however. All groups displayed reliable responding within each trial, as indicated by an overall effect of measurement intervals ($p < .01$). The general change of response form over trials was reflected in a significant trials by measurement intervals interaction ($p < .05$).

The lower half of Figure 6 shows the test trial BP responses of the four previously restrained groups. This figure indicates that both experimental groups exhibited similar pressor BP CRs on the first trial block, that were also similar to those shown during the previous Conditioning Phase. Both CRs were quickly extinguished on subsequent nonreinforced test trials. Although the initial BP CR of the experimental R-U group was slightly larger than that of the R-R group, no significant effects involving changed restraint were found in this test. There was, however, a significant effect of conditioning ($p < .01$), as well as significant conditioning by trials ($p < .01$) and conditioning by measurement periods ($p < .05$) interactions. There

were also overall effects of trials ($p < .01$) and measurement periods ($p < .01$).

Previously unrestrained groups. Figure 7 shows the test-phase HR and BP responses of the experimental and control groups with a prior history of being unrestrained, plotted as in Figure 6. The top of Figure 7 shows that, in general, the HR responses of all four groups were accelerative and similar in magnitude. There was no indication that restraining the previously unrestrained experimental group (U-R) generated consistent change in the HR CR from the established accelerative CR. On the first trial block, experimental Group U-R showed a smaller HR acceleration than Group U-U, but this difference did not persist. Moreover, no conditioning is immediately evident due to the fact that both control groups also demonstrated major accelerative HR changes. Again, a significant trials by measurement intervals interaction ($p < .05$) reflected the decline of HR response form over the course of test trials.

The bottom of Figure 7 indicates that the previously established BP CR of the unrestrained group was retained on the initial test trials, with both the U-U and U-R experimental groups exhibiting pressor BP changes comparable in magnitude to those occurring during conditioning. Although the BP CR of the U-R group was generally smaller than that of the U-U group, no significant outcomes concerning current restraint were found. As mentioned earlier, there was a significant overall conditioning effect ($p < .01$), as well as significant conditioning by trials ($p < .01$) and conditioning by measurement intervals

($p < .05$) interactions. These outcomes reflect the initial divergence of response forms and the convergence of the responses of the experimental and control groups over trials.

Comparison of previously restrained/unrestrained groups. While overall reliable HR CRs did not occur on the test trials in comparison to the control groups, it was found that the overall accelerative responses of the previously unrestrained U-U and U-R groups were significantly larger than the responses of the previously restrained R-R and R-U groups ($p < .05$). There was also a significant conditioning by current restraint by trials interaction ($p < .01$) due to the fact that the currently unrestrained R-U and U-U experimental groups were more accelerative than the currently restrained U-R and R-R experimental groups on early trials, but not on later trials.

As was true of HR, the BP responses of experimental Groups R-R and R-U were significantly smaller than those of Groups U-U and U-R ($p < .01$). This difference was more evident on early as opposed to later trials, contributing to a significant previous restraint by trials interaction ($p < .05$).

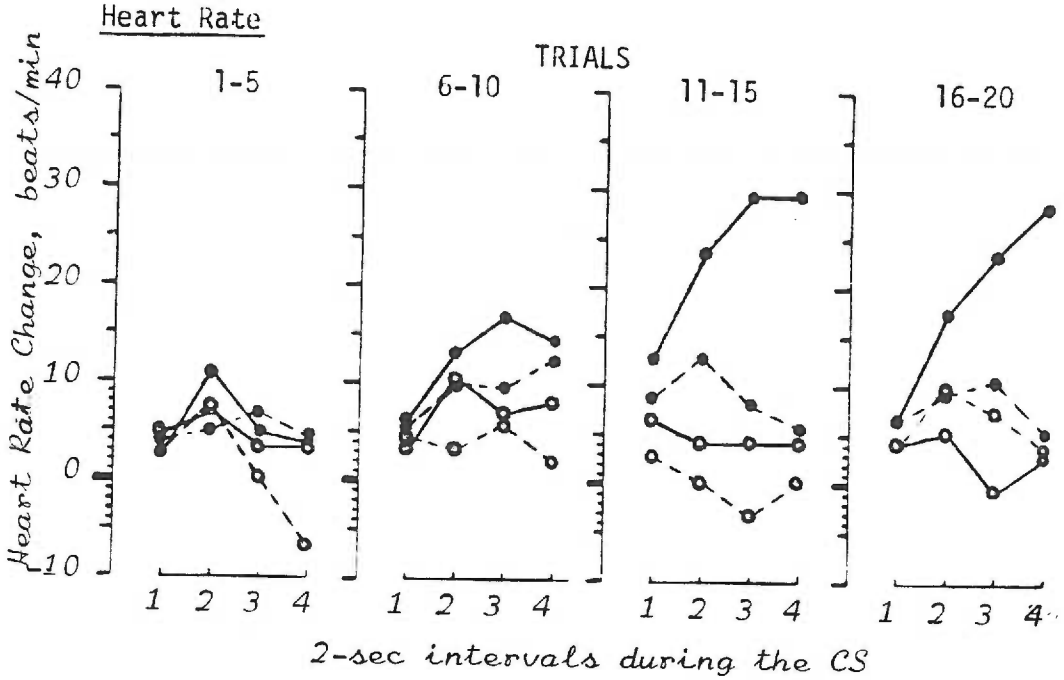
Phase 4 - Reconditioning

A comprehensive 5-way analysis was performed for the HR CR (Table A-21) and for the BP CR (Table A-22) data of Reconditioning Day 1. Once again, the outcomes of these analyses have been presented in an order that is consistent with other sections. All Reconditioning Day 1 CR statistical comparisons refer to Tables A-21 and A-22, consisting of unweighted means analysis.

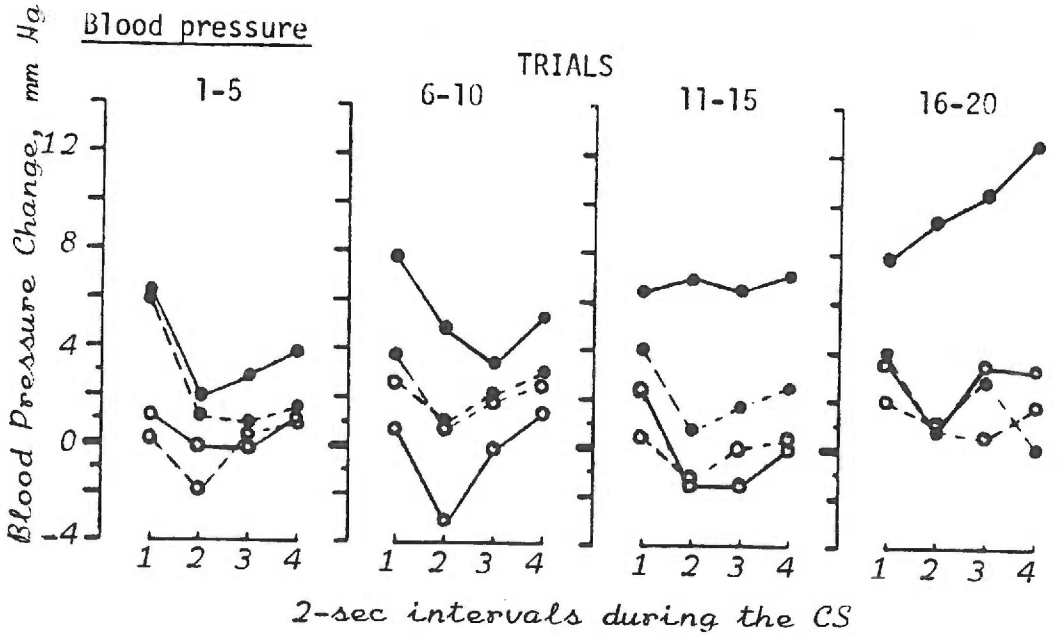
CRs of previously restrained groups. Figure 8 depicts the mean HR and BP responses of the four previously restrained groups on the first reconditioning day in 2-sec periods of the CS averaged over successive blocks of five trials. This figure shows that only the experimental R-U group displayed major evidence of the development of a HR CR. The CR was accelerative and reached a peak toward the end of the CS, as did the unrestrained HR CRs during original conditioning. Although less pronounced, the difference between the experimental and control R-R groups indicates the presence of some conditioning in the experimental R-R group. These observations were supported by a significant overall effect of conditioning ($p < .05$) and a conditioning by measurement intervals interaction ($p < .01$). The divergence of the experimental R-U group from the rest of the groups over trials, especially during the last half of the CS, was reliable as demonstrated by a significant conditioning by current restraint by trials by measurement intervals interaction ($p < .05$).

Considering the bottom of Figure 8, it is clear that the experimental R-U group that was switched from restraint to no restraint exhibited appropriately changed BP CR, which was a pressor response like that occurring earlier for the unrestrained group. In this case, the R-U BP CR initially had a form characteristic of restrained BP CRs (i.e. early BP peak) with the form gradually changing to the typical unrestrained shape (i.e. more sustained or gradual increases). The experimental R-R group, for whom restraint was maintained, showed a BP CR much like that shown earlier by the restrained group. However,

Figure 8. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained experimental and control groups that were previously restrained as a function of intervals during the CS and five-trial blocks during the Reconditioning Day 1 trials.



Experimental R-R ●– –● R-U ●——●
Control R-R ○– –○ R-U ○——○

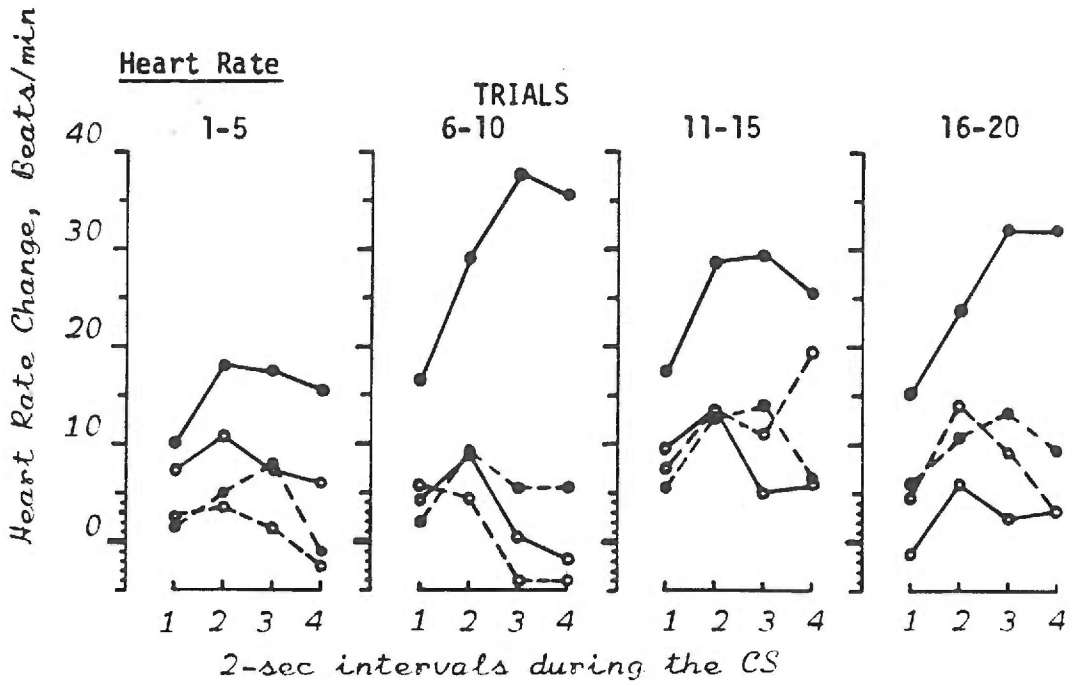


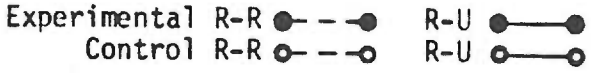
here the BP responses of the control R-R group were enhanced and at times matched those of the experimental R-R group, making conditions difficult to see. In the data analysis there was an overall effect of conditioning ($p < .01$) and an interaction of conditioning and current restraint ($p < .05$), the latter being due to smaller BP responses in the restrained as opposed to the unrestrained experimental groups. Conditioning and current restraint interacted with trials and measurement periods in a four-way interaction ($p < .05$).

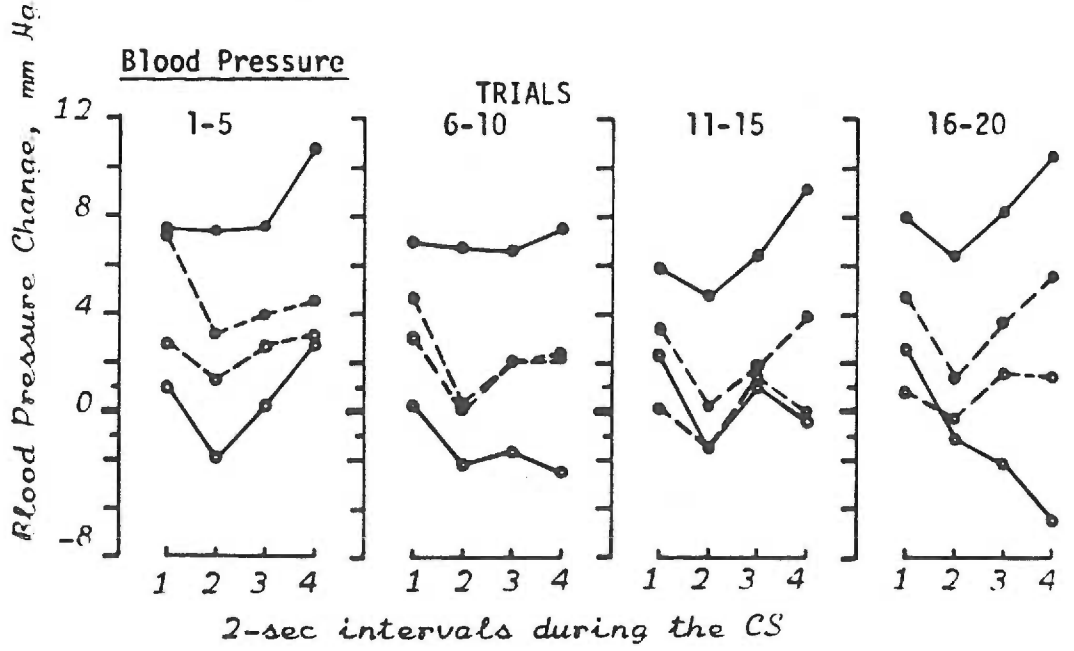
Figure 9 shows the Reconditioning Day 2 HR and BP responses of the previously restrained groups. (HR analysis Table A-23, BP Table A-24) This figure shows that experimental group R-U continued to show accelerative HR CRs as during the first reconditioning day. As was true of the first reconditioning day, the continuously restrained experimental R-R group displayed accelerative HR responses that were slightly larger than those of the R-R control group, but smaller than those of experimental R-U group. The overall effect of current restraint was not significant. The reliability of the divergence of the HR responses of the experimental and control groups was indicated by significant interactions of conditioning and trials ($p < .05$), of conditioning and measurement intervals ($p < .01$) and of conditioning, trials and measurement intervals ($p < .05$).

The lower part of Figure 9 shows that the BP CRs of the previously restrained experimental groups were pressor responses as in earlier phases. The overall effect of conditioning was significant ($p < .01$). The CRs of the unrestrained group, R-U, appear to be larger than those

Figure 9. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained experimental and control groups that were previously restrained as a function of intervals during the CS and five-trial blocks during the Reconditioning Day 2 trials.


Heart Rate
TRIALS
1-5
6-10
11-15
16-20
40
30
20
10
0
Heart Rate Change, Beats/min
1 2 3 4
2-sec intervals during the CS


Experimental R-R
R-U
Control R-R
R-U

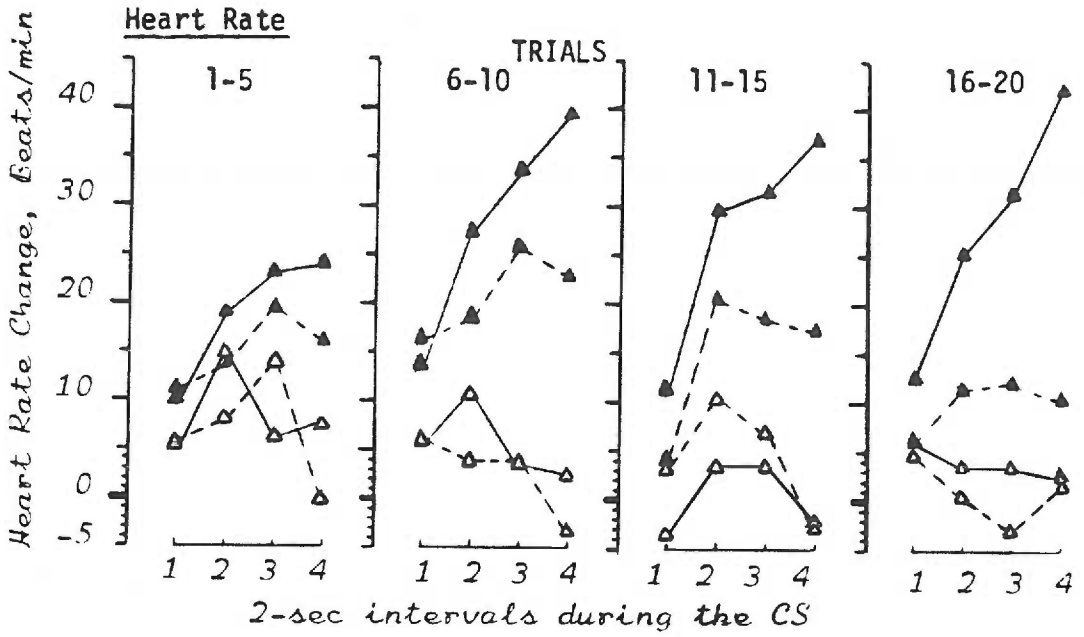

Blood Pressure
TRIALS
1-5
6-10
11-15
16-20
12
8
4
0
-8
Blood Pressure Change, mm Hg
1 2 3 4
2-sec intervals during the CS

of the restrained group, R-R, but the difference was not significant. Toward the end of reconditioning, both previously restrained experimental groups displayed response forms that were highly similar and contained early and late pressor peaks. A significant effect of measurement intervals ($p < .01$) supported the reliability of the BP changes within each trial.

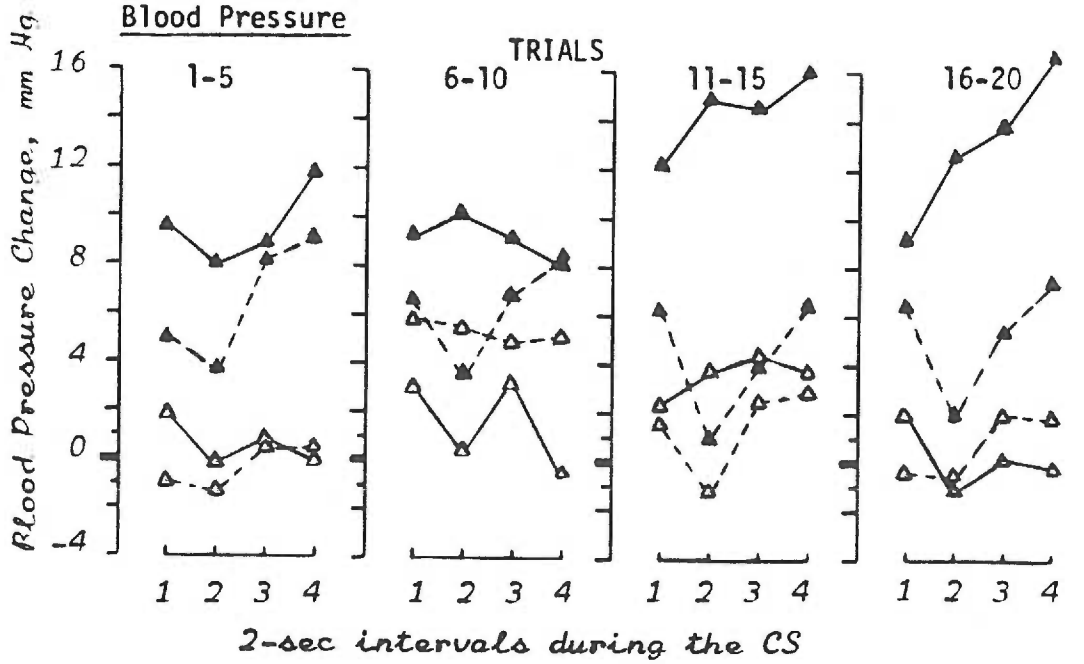
CRs of previously unrestrained groups. (HR analysis Table A-21, BP Table A-22) Figure 10 shows the reconditioning HR and BP responses of the four previously unrestrained groups. Here it may be seen that the experimental U-U group showed the redevelopment of an accelerative HR CR following the previous non-reinforced test trials. Even though now restrained, the experimental U-R group also displayed an accelerative CR, albeit somewhat smaller than that of the U-U group. After first growing, the HR CR of the experimental U-R group became progressively smaller over trials. The overall effect of conditioning was significant for the HR CRs ($p < .05$). The restraint-magnitude difference was reflected by interactions of current restraint with measurement intervals ($p < .01$) and of conditioning, current restraint, trials and measurement intervals ($p < .05$).

The BP data in Figure 10 indicate the presence of pressor BP CRs in the two experimental groups, the relative magnitudes and forms of which matched what was found during the previous Conditioning Phase. Thus, the pressor changes in the restrained experimental U-R group were smaller than those of the experimental U-U group and contained two distinct peaks as opposed to a sustained elevation. Statistical

Figure 10. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained experimental and control groups that were previously unrestrained as a function of intervals during the CS and five-trial blocks during the Reconditioning Day 1 trials.



Experimental U-U ——▲—— U-R - - ▲ - -
Control U-U ——△—— U-R - - △ - -



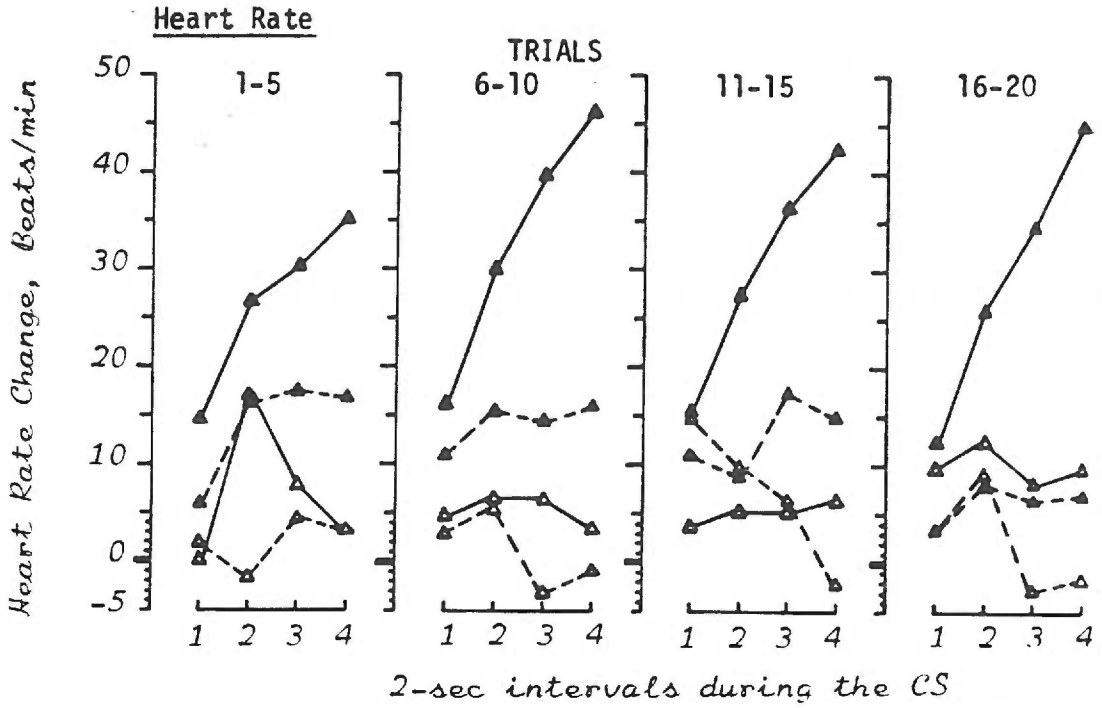
analysis showed a significant conditioning effect ($p < .01$), conditioning by current restraint interaction ($p < .05$) and conditioning by current restraint by trials by measurement intervals interaction ($p < .05$).

Figure 11 shows the HR and BP CRs of the previously unrestrained groups on the second reconditioning day (HR analysis Table A-25, BP Table A-26). The difference between the responses of experimental Groups U-U and U-R continued, as at the end of the first day of reconditioning. There appeared to be some tendency for the restrained experimental group U-R to display larger HR responses to the CS on the first trial block than on later trial blocks. This tendency was not reliable, however. The overall effects of conditioning and of restraint were significant ($p < .01$, $p < .05$, respectively). Statistical analysis also included significant interactions of conditioning by measurement intervals ($p < .01$) and of current restraint by measurement intervals ($p < .01$).

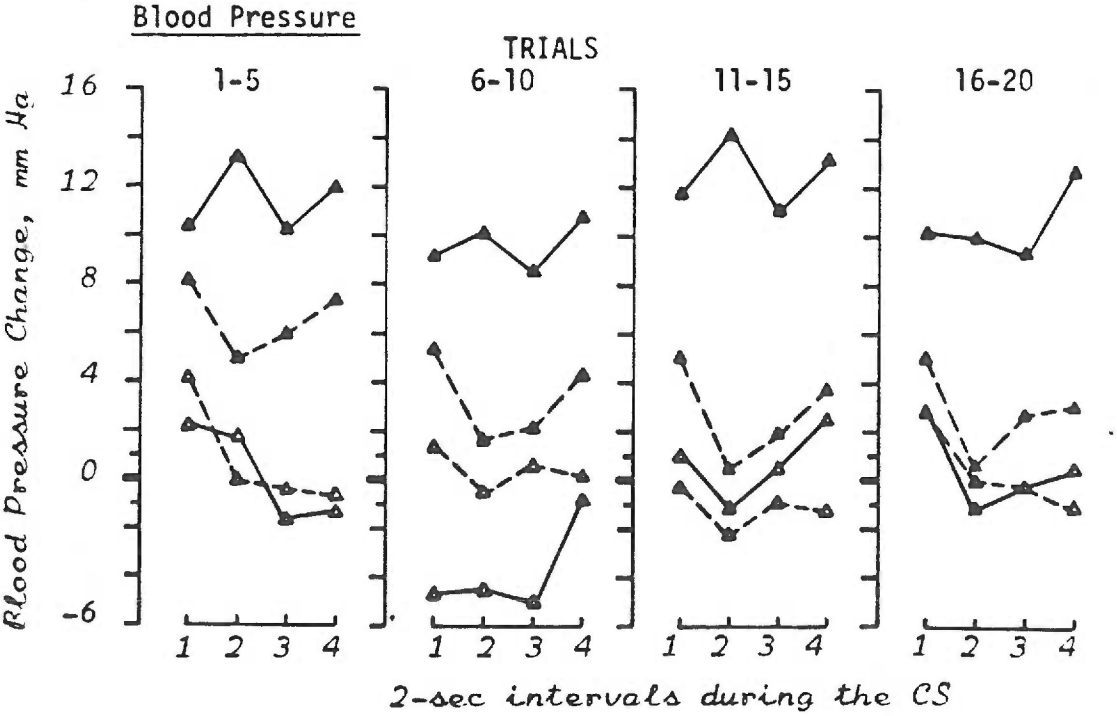
The lower part of Figure 11 shows that the BP CRs of the previously unrestrained groups continued on the second day of reconditioning just as on the first day. Statistical analysis included significant effects of conditioning ($p < .01$) and a current restraint by trials interaction ($p < .05$).

Reconditioning HR and BP CRs as a function of restraint history. (HR analyses Tables A-21, 27, 29, BP Tables A-22, 28, 30) Comparison of the experimental groups in Figures 8 and 10 reveals that throughout the first day of reconditioning, the HR and BP CRs of the two

Figure 11. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained experimental and control groups that were previously unrestrained as a function of intervals during the CS and five-trial blocks during the Reconditioning Day 2 trials.



Experimental U-U —▲— U-R - -▲- -
Control U-U —△— U-R - -△- -



experimental groups that were previously unrestrained (groups U-U and U-R in Figure 10) were slightly larger than those of the two experimental groups that were previously restrained (groups R-R and R-U in Figure 8). These differences were reliable only for BP ($p < .05$), however. As stated previously, there were significant interactions involving conditioning, current restraint and trials or measurement intervals for both HR and BP due to the increasing levels of responding in the U-U and R-U groups compared to the R-R and U-R groups. Interactions between previous and current restraint conditions were not found.

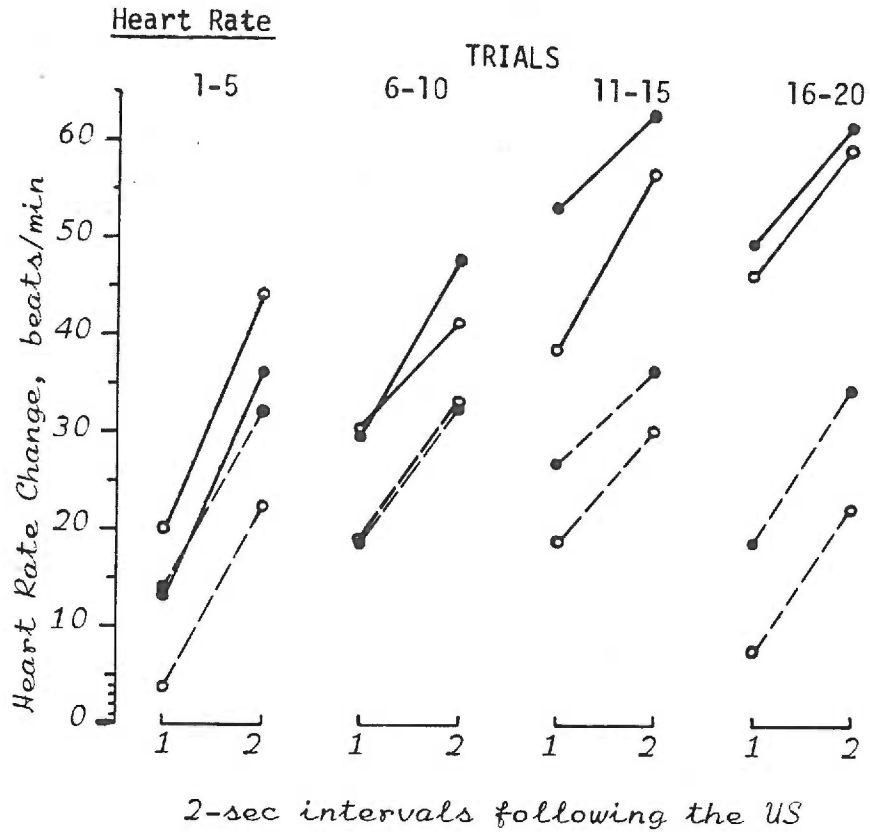
Comparison of the experimental groups in Figures 9 and 11 revealed that on the second reconditioning day the HR and BP CRs of the two unrestrained groups, U-U and R-U, were consistently larger than those of the two restrained groups, R-R and U-R (HR $p < .01$, BP $p < .01$). These differences were more pronounced at the end than at the beginning of the CS for HR, and were more pronounced during the middle of the CS for BP as indicated by significant restraint by measurement intervals interactions ($p < .01$ in each case). Previous restraint did not exert any overall significant effects on the HR or BP responses of the experimental groups during the second day of reconditioning. However, there was a reliable tendency for the HR responses of the experimental groups to diverge towards the end of the CS according to previous restraint, as indicated by a significant interaction of previous restraint and measurement intervals ($p < .01$).

URs of previously restrained groups. (HR analysis Table A-31, BP Table A-32) Figure 12 shows the Reconditioning Day 1 HR and BP URs of the previously restrained experimental and control groups in 2-sec post-US periods averaged over 5-trial blocks. Consistent with what was observed during original conditioning, the unrestrained experimental and control groups, R-U, showed larger HR accelerations than did the two restrained groups, R-R, ($p < .01$). This difference increased in size over trials significantly ($p < .01$), due to the increase in the magnitude of the URs of both R-U groups. For BP, the URs of the unrestrained R-U groups were larger than those of the restrained R-R groups in the first measurement period, which produced a significant restraint by measurement intervals interaction ($p < .01$).

Figure 13 shows the HR and BP URs of the previously restrained groups during the second day of reconditioning. (HR analysis Table A-33, BP Table A-34) As on the first reconditioning day, the unrestrained groups, R-U, showed larger HR URs than the restrained groups, R-R, ($p < .01$). This difference was relatively constant over trials. The BP URs did not differ between any of the previously restrained groups on this day.

URs of previously unrestrained groups. (HR analysis Table A-35, BP Table A-36) As was seen in the previous comparisons, Figure 14 indicates that both unrestrained U-U groups showed larger accelerative HR URs than did the restrained U-R groups ($p < .01$) on the first reconditioning day. Here, however, the differences varied as a function of conditioning treatment, trials and measurement intervals as shown

Figure 12. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained experimental and control groups that were previously restrained as a function of intervals following the US and five-trial blocks during the Reconditioning Day 1 trials.



Experimental R-R ●- - -● R-U ●——●
Control R-R ○- - -○ R-U ○——○

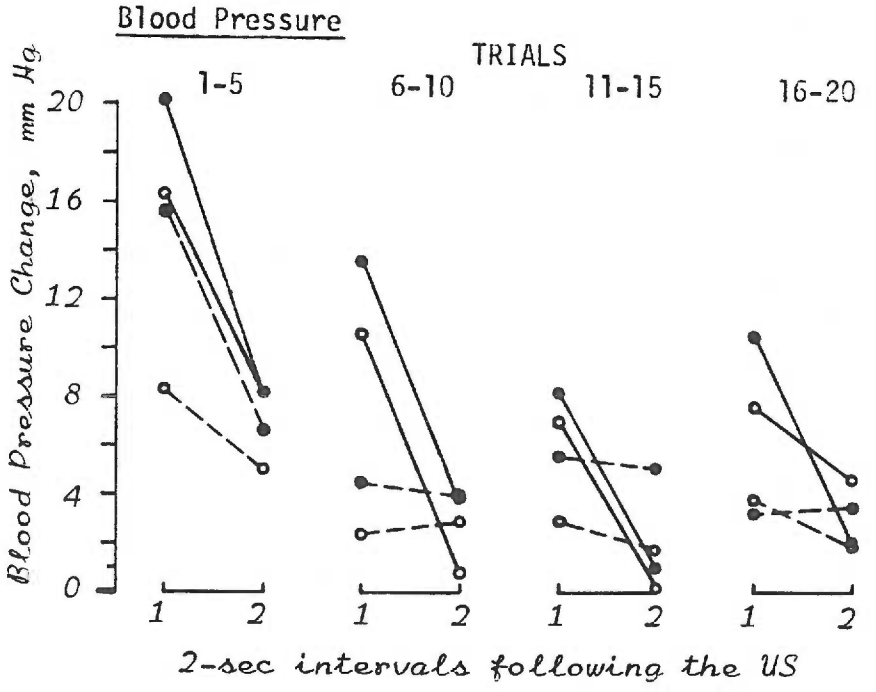
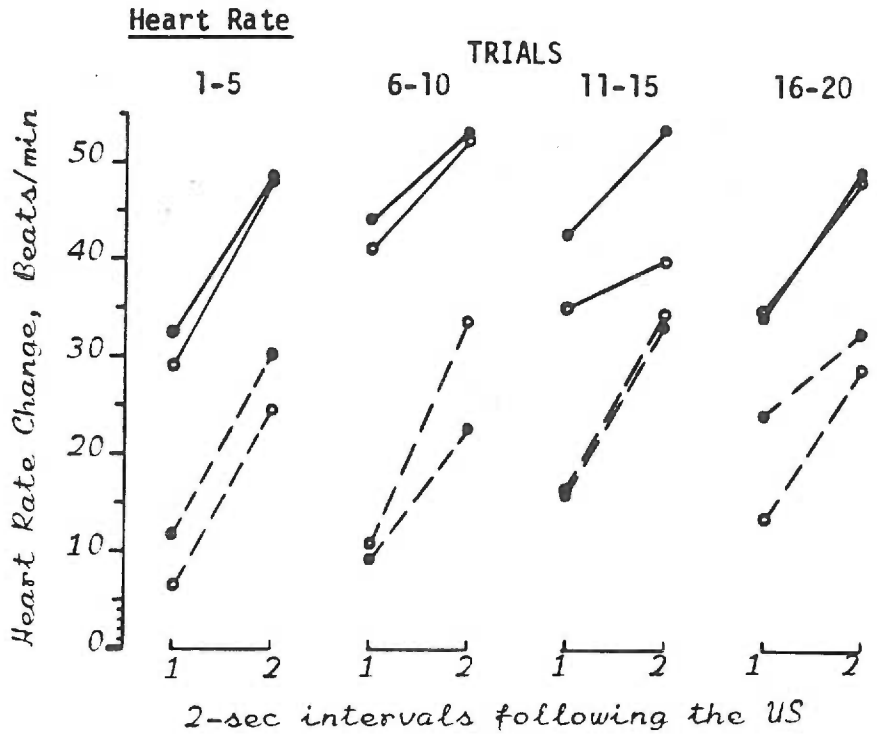


Figure 13. Mean heart rate in beats per min and blood pressure in mm Hg in the restrained and unrestrained experimental and control groups that were previously restrained as a function of intervals following the US and five-trial blocks during the Reconditioning Day 2 trials.



Experimental R-R ●- - -● R-U ●——●
Control R-R ○- - -○ R-U ○——○

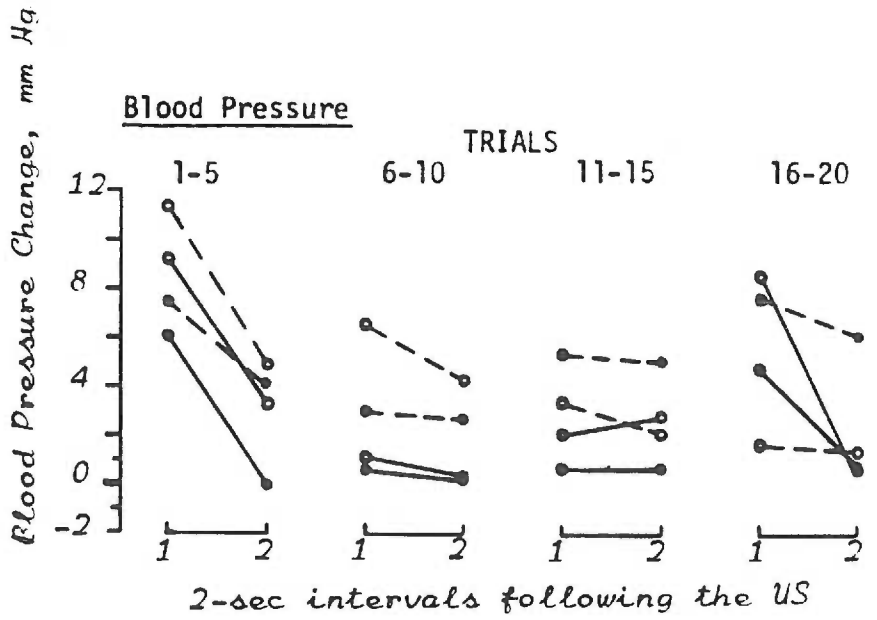
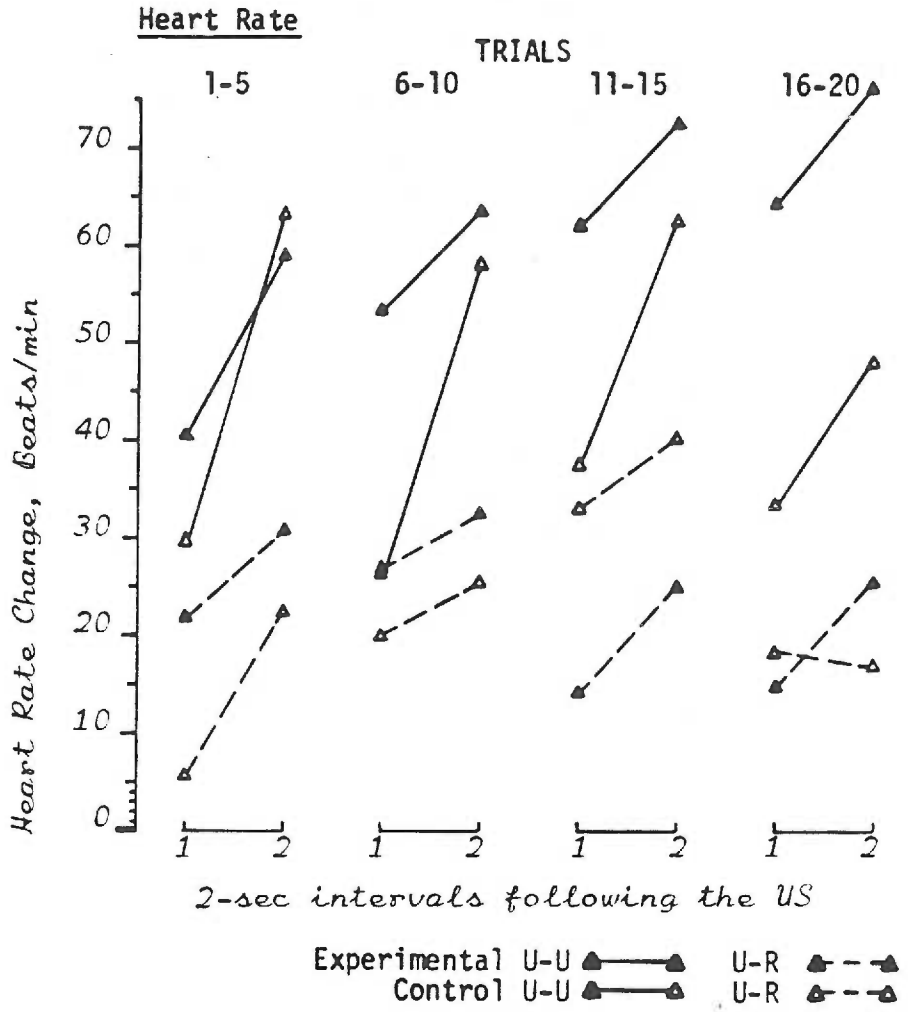
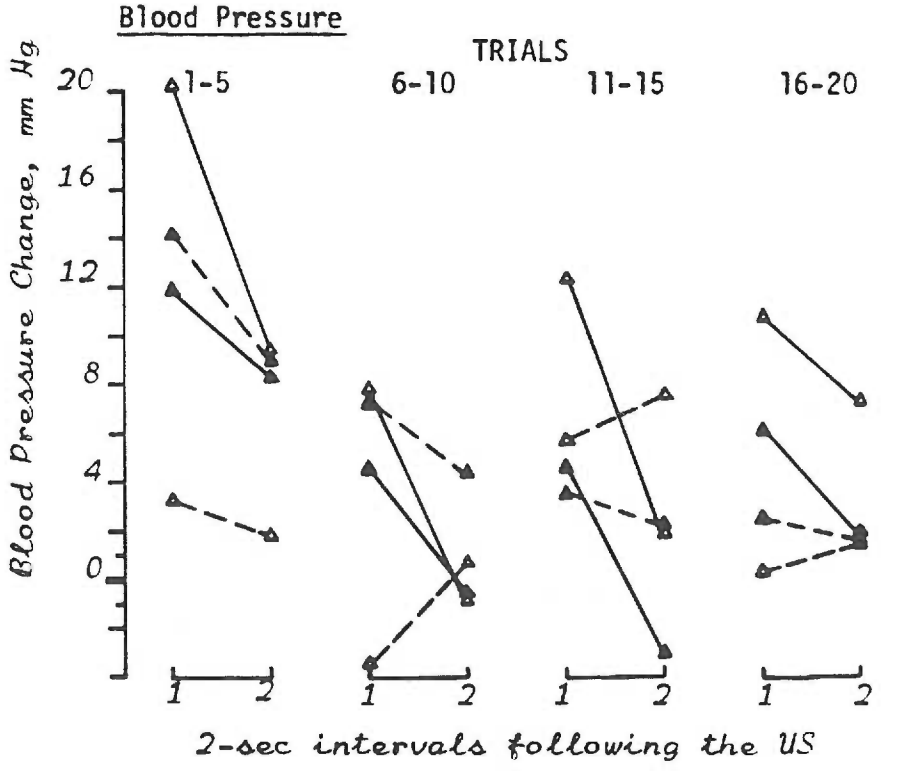


Figure 14. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained experimental and control groups that were previously unrestrained as a function of intervals following the US and five-trial blocks during the Reconditioning Day 1 trials.


Heart Rate
TRIALS
1-5
6-10
11-15
16-20
70
60
50
40
30
20
10
0
Heart Rate Change, Beats/min
1
2
2-sec intervals following the US
Experimental U-U
U-R
Control U-U
U-R

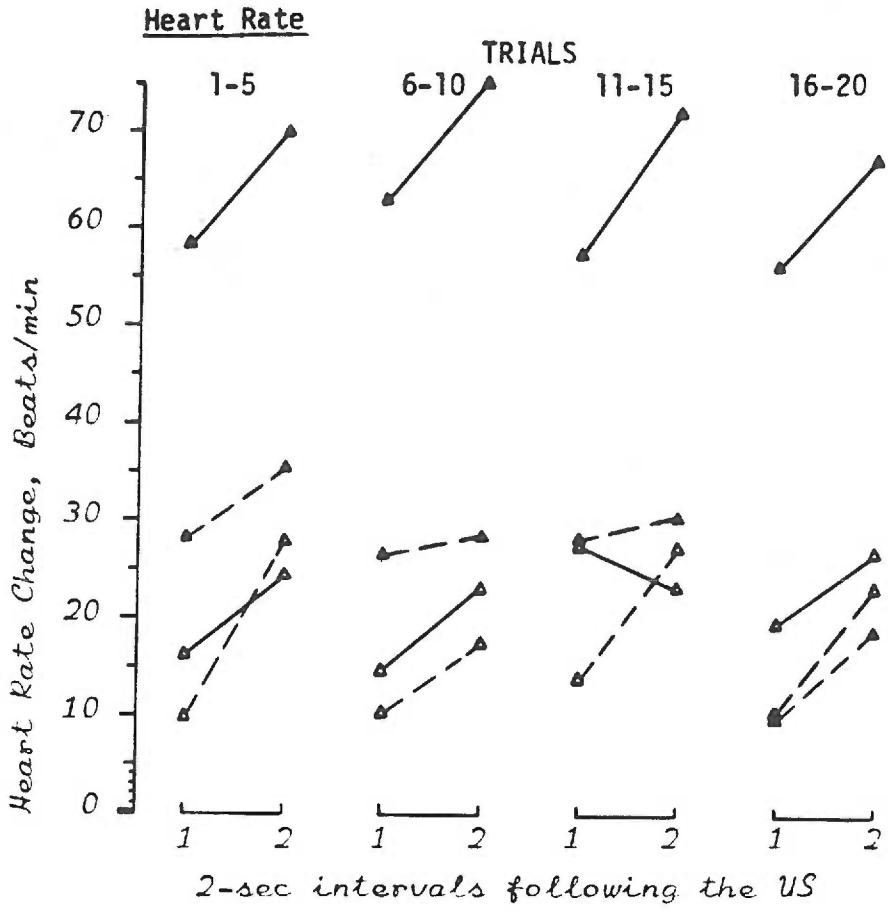

Blood Pressure
TRIALS
1-5
6-10
11-15
16-20
20
16
12
8
4
0
Blood Pressure Change, mm Hg
1
2
2-sec intervals following the US

by a significant three-way interaction involving these factors ($p < .05$). For the BP URs plotted in the bottom half of Figure 14, there were no consistent overall differences between the restrained and unrestrained groups. A significant restraint by measurement intervals interaction ($p < .05$) was found due to the fact that the enhanced pressor changes in the unrestrained U-U groups were more pronounced in the first interval than in the second interval.

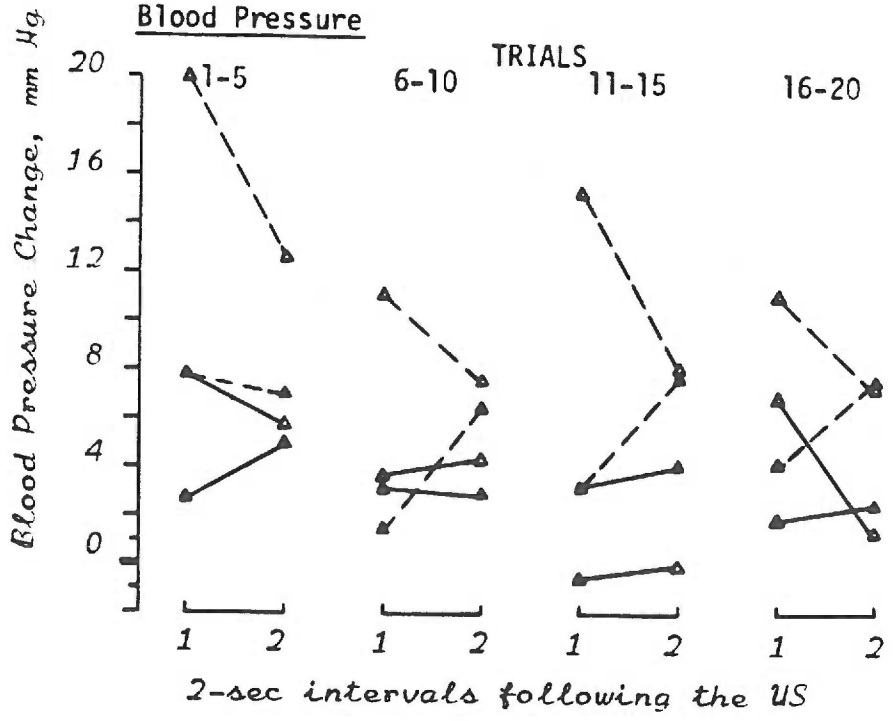
In Figure 15 it can be seen that the Reconditioning Day 2 HR URs of the unrestrained experimental U-U group were larger than those of any other group, including the control U-U group (HR analysis Table A-37, BP Table A-38.) The experimental U-R group displayed somewhat larger HR changes than the control U-R group but the difference was not as large as that occurring in the two unrestrained groups. The contrasting responses were shown to be reliable by a significant conditioning by restraint interaction ($p < .05$). The BP URs in the lower half of Figure 15 appear to indicate that the control group responses were larger than those of the experimental groups on most trials. There were no significant outcomes involving conditioning, however, nor were there any involving restraint as a factor.

Reconditioning HR and BP URs as a function of previous restraint. (HR analysis Tables A-39, A-40, BP Tables A-41, A-42) In contrast to the conditioned HR and BP responses during reconditioning, neither HR nor BP URs of the experimental groups were significantly affected by previous restraint conditions on Reconditioning Day 1. Thus, those experimental groups switched to a new restraint situation showed URs

Figure 15. Mean heart rate in beats per min and blood pressure in mm Hg of the restrained and unrestrained experimental and control groups that were previously unrestrained as a function of intervals following the US and five-trial blocks during the Reconditioning Day 2 trials.



Experimental U-U ——— U-R – – –
Control U-U ——— U-R – – –



that were comparable to those shown by the unswitched experimental groups, regardless of their earlier restraint circumstance.

On Reconditioning Day 2, however, there was a significant effect of previous restraint on the experimental groups. The HR URs of the previously unrestrained groups were larger than those of the previously restrained groups ($p < .05$), which may reflect the influence of the larger HR CRs of the previously unrestrained groups. The BP URs of the experimental groups did not reflect any influences of previous restraint. There were no effects of previous restraint for the HR or BP URs of the control groups on either the first or second day of reconditioning. (HR analysis Tables A-43, A-44; BP Tables A-45, A-46)

Baseline HR and BP

Baseline HR and BP during the Conditioning Phase are shown in Table 3. (HR analysis Table A-47, BP Table A-48) This table shows that baselevel HR was higher for the restrained groups than for the unrestrained groups during the Conditioning Phase. Baselevel HR was also higher for the control groups within each restraint condition. Statistically, the effects of both restraint and conditioning were significant ($p < .01$ in each case). For BP, there were only small and insignificant differences between any of the groups.

Table 4 shows baselevel HR and BP during the Reconditioning Phase. (HR analysis Tables A-49, A-50, BP analysis Tables A-51, A-52) Table 4 shows that the HR differences between the restrained and unrestrained groups and between the experimental and control groups continued into the Reconditioning Phase. Both restraint and conditioning exerted

Table 3. Mean baselevel HR (in beats per min) and BP (in mm Hg) of the restrained and unrestrained experimental and control groups averaged over all trials of the Conditioning Phase.

	Restrained		Unrestrained	
GROUP	HR	BP	HR	BP
Experimental	431	161.2	372	157.4
Control	451	166.6	413	158.6

Table 4. Mean baselevel HR (in beats per min) and BP (in mm Hg) of the restrained and unrestrained experimental and control groups averaged over all trials of the Reconditioning Phase.

GROUP		HR	BP
Experimental	R-R	417	154.4
	R-U	399	137.7
Control	R-R	440	165.1
	R-U	426	173.3
Experimental	U-R	414	155.9
	U-U	390	153.5
Control	U-R	439	169.1
	U-U	409	172.6

significant effects on baselevel HR ($p < .05$ in each case) for the previously unrestrained groups, but these effects fell short of significance for the previously restrained groups. Baselevel BP was still largely unaffected by restraint during the Reconditioning Phase. It appears that baselevel BP of experimental Group R-U was lower than that of the other groups, but this difference fell short of statistical significance. This table shows that baselevel BP of the experimental groups was lower than that of the control groups during reconditioning. Analysis indicated that this difference was significant ($p < .05$).

Phase 5 - Pharmacological Blockade

The Drug Test Phase dealt with blockade of the sympathetic and parasympathetic portions of the ANS. Comparisons were made between the last 8 reconditioning trials on each of the two reconditioning days and the 8 trials that were given following the drug treatments. For one-half of the animals in each drug test, the pre-drug trials consisted of the final trials of Reconditioning Day 1, while for the remaining animals in each drug test, the pre-drug trials occurred on Reconditioning Day 2. Separate analyses of HR and BP were conducted to determine whether pre-drug responses on the first and second reconditioning days were equivalent. The data showed that there were no significant differences between the days for the experimental groups. The control groups showed a small but significant decrease of BP responses between the first and second day ($p < .05$, table not included).

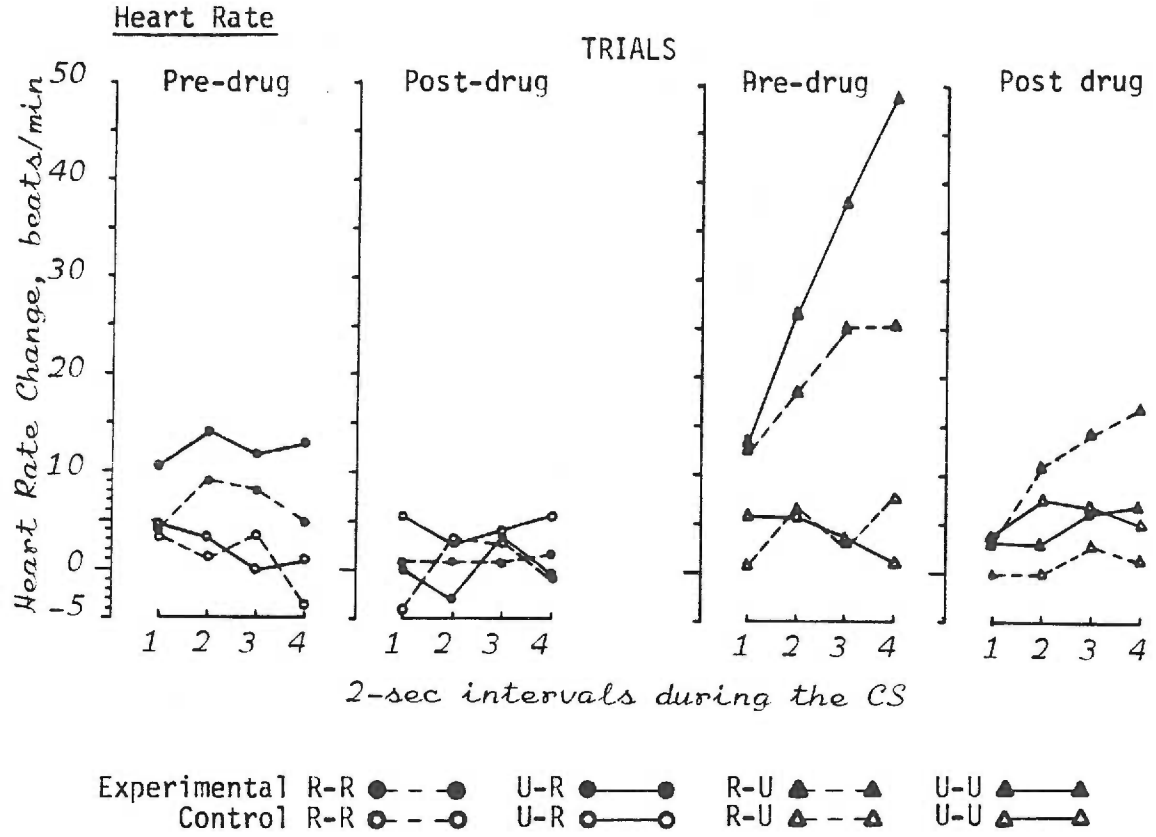
The effects of the drugs were evaluated by combining the experimental and control groups according to the type of restraint that was imposed during the Drug Test Phase. Restraint history was still considered as a factor in the analyses, but the major comparisons were between the groups that were either restrained or unrestrained during the drug tests.

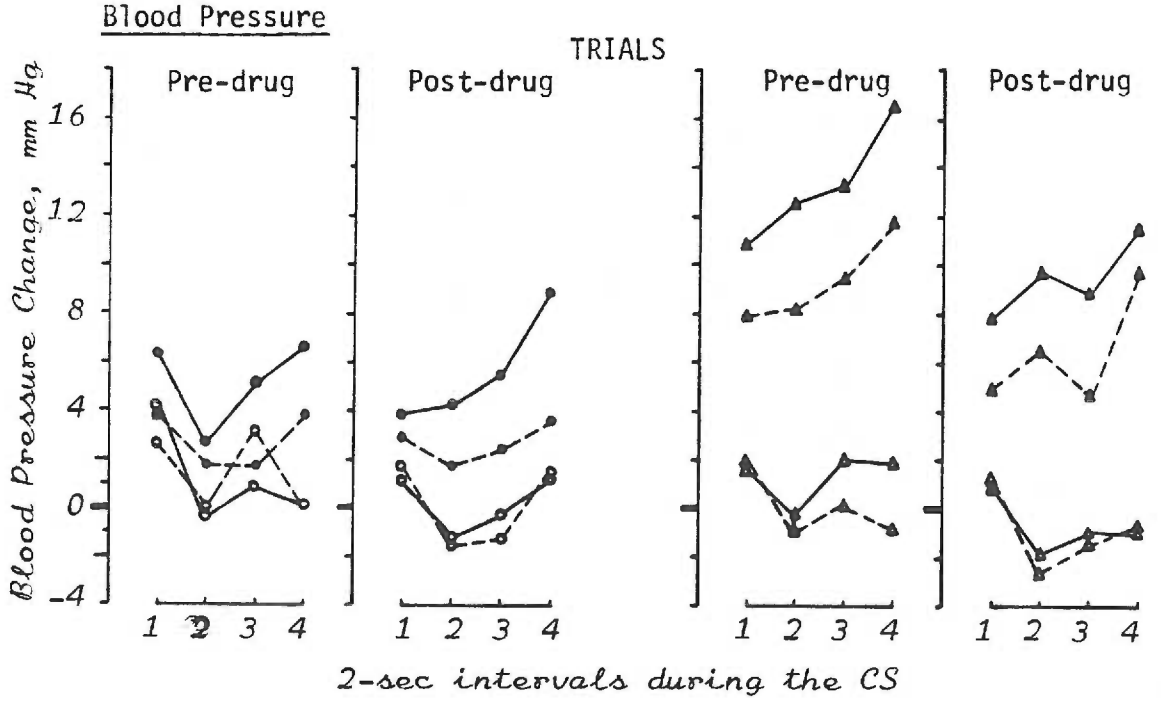
Sympathetic blockade, CRs of restrained groups. (HR analysis Table A-53, BP Table A-54) The left side of Figure 16 depicts the HR and BP responses of the restrained groups receiving sympathetic blockade in 2-sec periods of the CS averaged over the 8 pre-drug trials and over the 8 post-drug trials. The upper left of the figure shows that sympathetic blockade abolished the accelerative HR responses of both experimental groups. Statistical analysis provided a significant overall drug effect ($p < .01$) and a significant conditioning by drug interaction ($p < .05$).

The lower left panel of Figure 16 shows that sympathetic blockade had little effect on the pressor BP responses of the restrained experimental groups. In general, the responses of the two experimental groups remained largely unchanged, while those of the two control groups decreased slightly in size, especially during the middle of the CS. Analysis of these results yielded significant interactions of drug by measurement intervals ($p < .01$) and conditioning by drug by measurement intervals ($p < .05$).

Sympathetic blockade, CRs of unrestrained groups. (HR analysis Table A-55, BP Table A-56) The two panels on the right of Figure 16

Figure 16. Mean heart rate in beats per min and blood pressure in mm Hg of all restrained and unrestrained experimental and control groups as a function of intervals during the CS and eight-trial blocks immediately before and after drug administration during sympathetic blockade.


Heart Rate
TRIALS
Pre-drug
Post-drug
Pre-drug
Post drug
Heart Rate Change, beats/min
50
40
30
20
10
0
-5
1 2 3 4
2-sec intervals during the CS
Experimental R-R
Control R-R
U-R
U-R
R-U
R-U
U-U
U-U

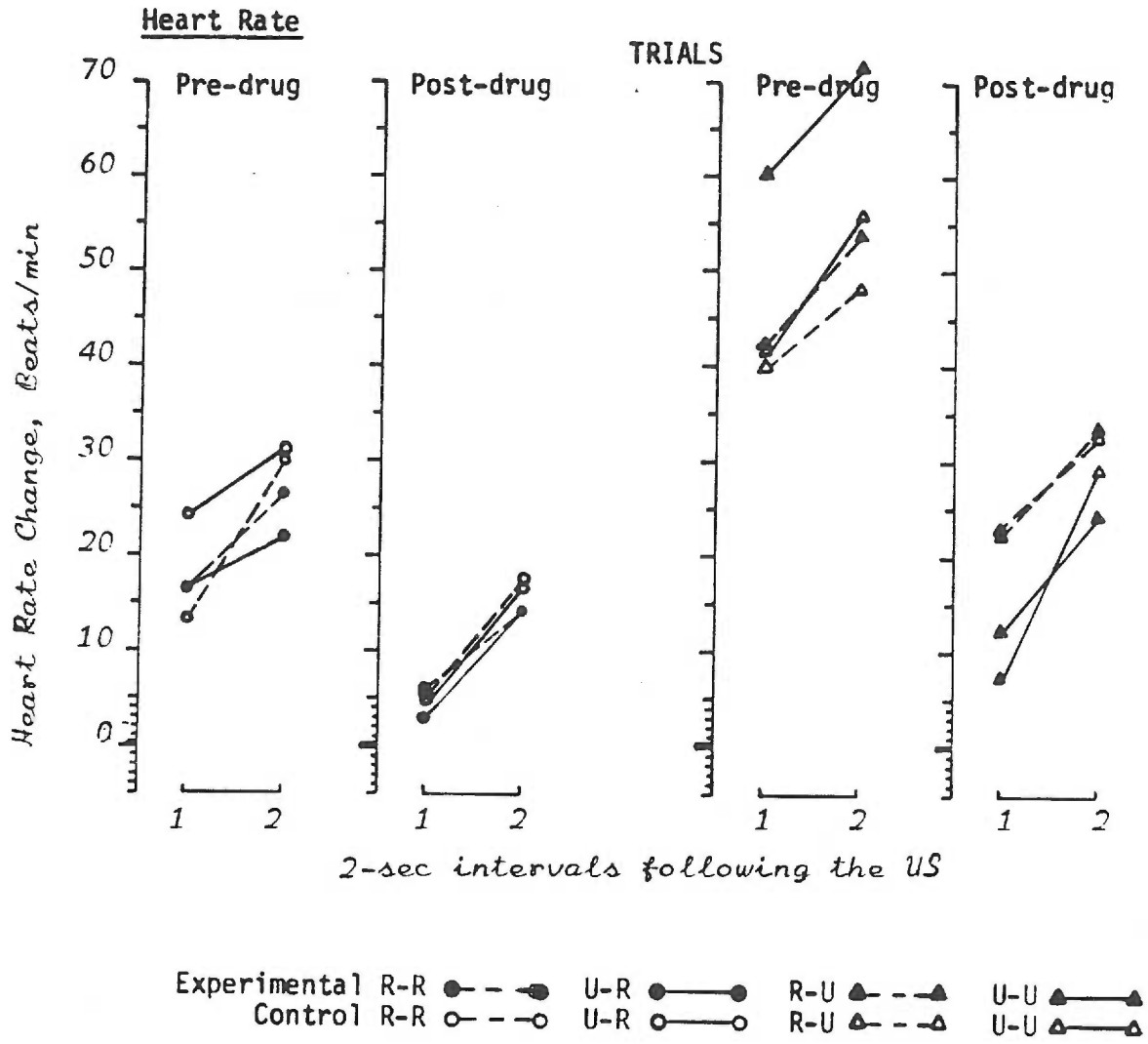

Blood Pressure
TRIALS
Pre-drug
Post-drug
Pre-drug
Post-drug
Blood Pressure Change, mm Hg
16
12
8
4
0
-4
1 2 3 4
2-sec intervals during the CS

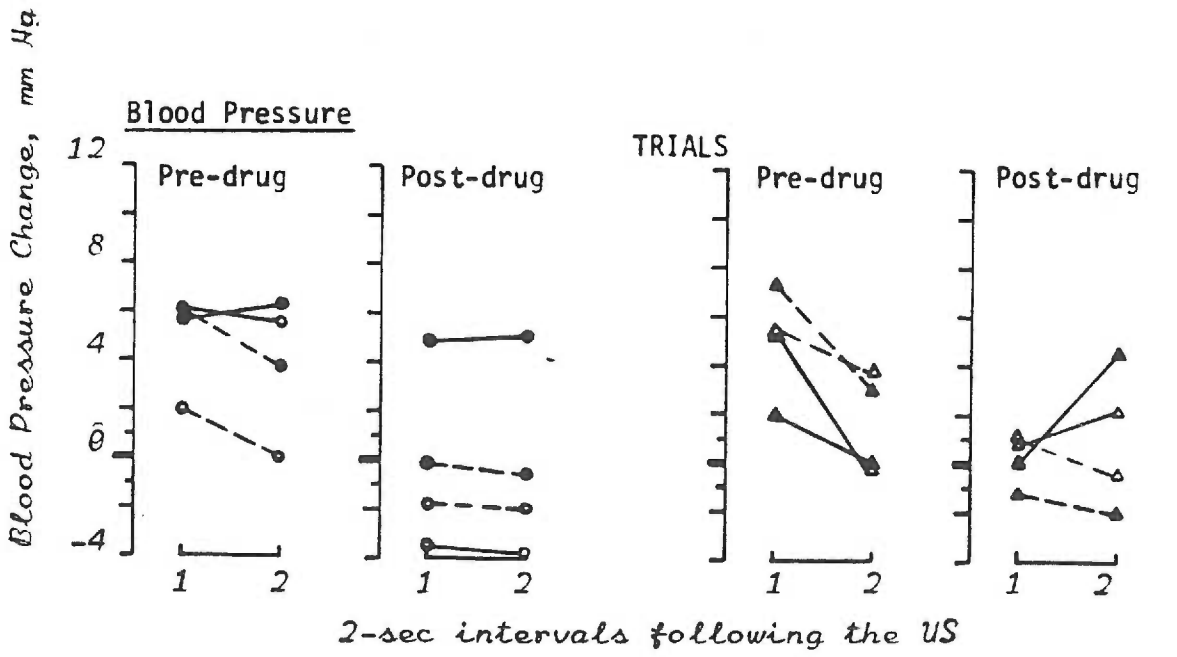
show the effects of sympathetic blockade on the HR and BP responses of the unrestrained groups. The top right of the figure reveals that sympathetic blockade attenuated the accelerative HR CRs of both unrestrained experimental groups. The response of the experimental U-U group was reduced to control levels, while some acceleration remained for the R-U group. Analysis of these results provided a significant conditioning by drug ($p < .01$) interaction and a significant conditioning by previous restraint by drug by counting periods ($p < .05$) interaction.

The lower right of Figure 16 shows that blockade of the sympathetic system attenuated the pressor BP responses of both unrestrained experimental groups, but did not completely eliminate the responses. Both control groups also showed a response decrement. An analysis provided a significant overall drug effect ($p < .05$), as well as conditioning ($p < .01$).

Sympathetic blockade, URs of restrained groups. (HR analysis Table A-57, BP Table A-58) The left side of Figure 17 shows the HR and BP responses of the restrained groups in 2-sec periods after the US, averaged over 8-trial blocks prior to and following drug administration. The upper left panel shows that sympathetic blockade decreased the HR accelerations of all groups ($p < .01$). For the BP URs, sympathetic blockade decreased the pressor changes in all of the restrained groups except the experimental U-R group. This produced a significant conditioning by previous restraint by drug interaction ($p < .05$).

Figure 17. Mean heart rate in beats per min and blood pressure in mm Hg of all restrained and unrestrained experimental and control groups as a function of intervals following the US and eight-trial blocks immediately before and after drug administration during sympathetic blockade.


Heart Rate
TRIALS
Pre-drug
Post-drug
Pre-drug
Post-drug
Heart Rate Change, Beats/min
70
60
50
40
30
20
10
0
1
2
2-sec intervals following the US
Experimental R-R
Control R-R
U-R
U-R
R-U
R-U
U-U
U-U


Blood Pressure
TRIALS
Pre-drug
Post-drug
Pre-drug
Post-drug
Blood Pressure Change, mm Hg
12
8
4
0
-4
1
2
2-sec intervals following the US

Sympathetic blockade, URs of unrestrained groups. (HR analysis Table A-59, BP Table A-60) The upper right panels of Figure 17 show that, for the unrestrained groups, sympathetic blockade attenuated the accelerative HR URs of all groups, as shown by a significant overall drug effect ($p < .01$). There was also an interaction of previous restraint with drug administration ($p < .05$), due to the fact that the U-U group displayed accelerations on the pre-drug trials that were larger than those of the other groups.

Sympathetic blockade did not exert an overall effect on the BP URs of the unrestrained groups. All groups did show a significant decrement in the first post-US measurement interval, however, as shown in a significant drug effect by intervals interaction ($p < .05$).

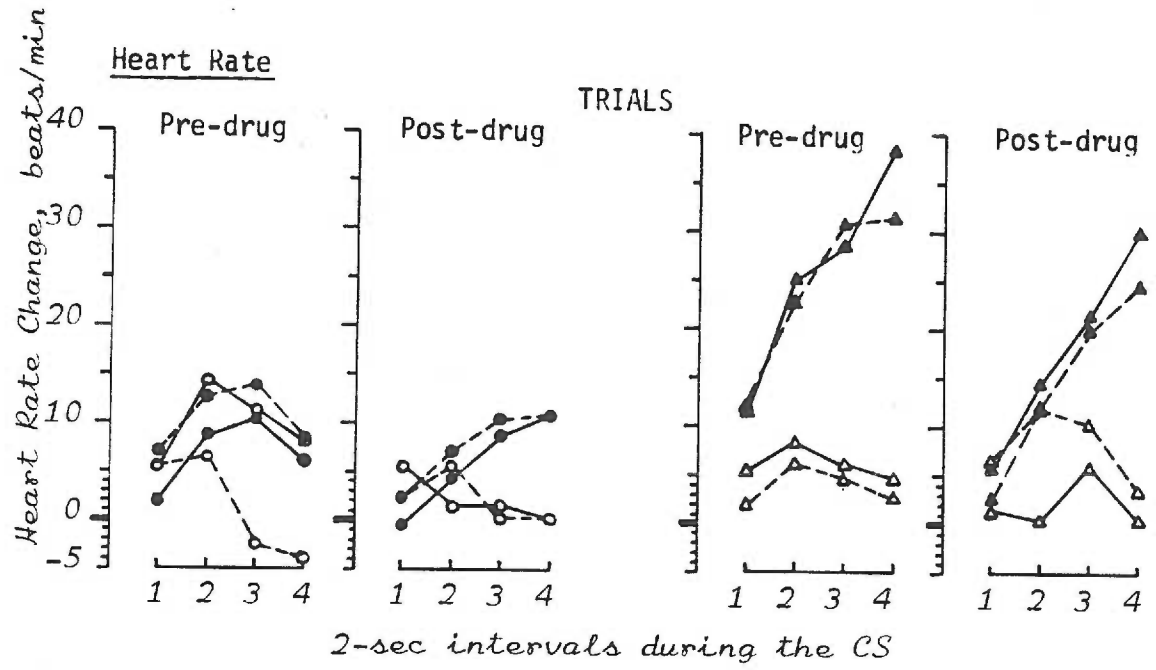
Sympathetic blockade, baselevel HR and BP. (HR analysis Tables A-61, A-62, BP Tables A-63, A-64) The effects of sympathetic blockade on baselevel HR and BP of all experimental and control groups as shown in Table 5. It can be seen that drug administration lowered baselevel HR by approximately 35 bpm in all groups. Baselevel BP was reduced by approximately 13 mm Hg in all groups. The effects of drug administration on both HR and BP were significant ($p < .01$).

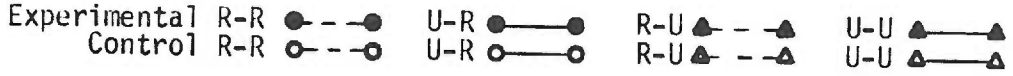
Parasympathetic blockade, CRs of restrained groups. (HR analysis Table A-65, BP Table A-66) The left side of Figure 18 displays the HR and BP responses of the restrained groups during the parasympathetic Drug Test in 2-sec periods of the CS averaged over 8-trial blocks prior to and following drug administration. The top panels on the left show that vagal blockade exerted little effect on the overall magnitude of

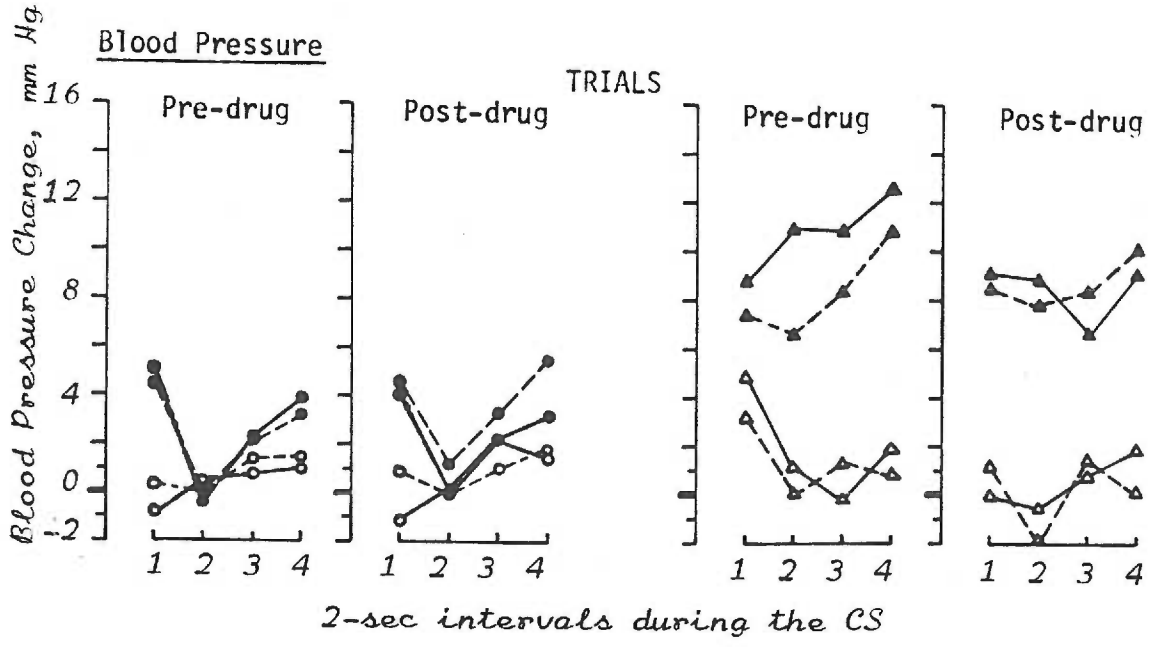
Table 5. Mean baselevel HR (in beats per min) and BP (in mm Hg) of the restrained and unrestrained experimental and control groups averaged over 8-trial blocks immediately prior to and following drug administration during the Sympathetic Drug Test.

GROUP		Pre-drug HR	Pre-drug BP	Post-drug HR	Post-drug BP
Experimental	R-R	414	157.8	367	144.0
	U-R	389	155.3	360	143.5
	R-U	395	139.3	372	128.8
	U-U	394	150.9	357	135.5
Control	R-R	433	164.9	373	158.9
	U-R	431	152.3	366	139.7
	R-U	435	177.7	444	173.4
	U-U	398	164.2	367	154.8

Figure 18. Mean heart rate in beats per min and blood pressure in mm Hg of all restrained and unrestrained experimental and control groups as a function of intervals during the CS and eight-trial blocks immediately before and after drug administration during parasympathetic blockade.


Heart Rate
TRIALS
Pre-drug
Post-drug
Pre-drug
Post-drug
Heart Rate Change, beats/min
40
30
20
10
0
-5
1 2 3 4
2-sec intervals during the CS


Experimental R-R
Control R-R
U-R
U-R
R-U
R-U
U-U
U-U

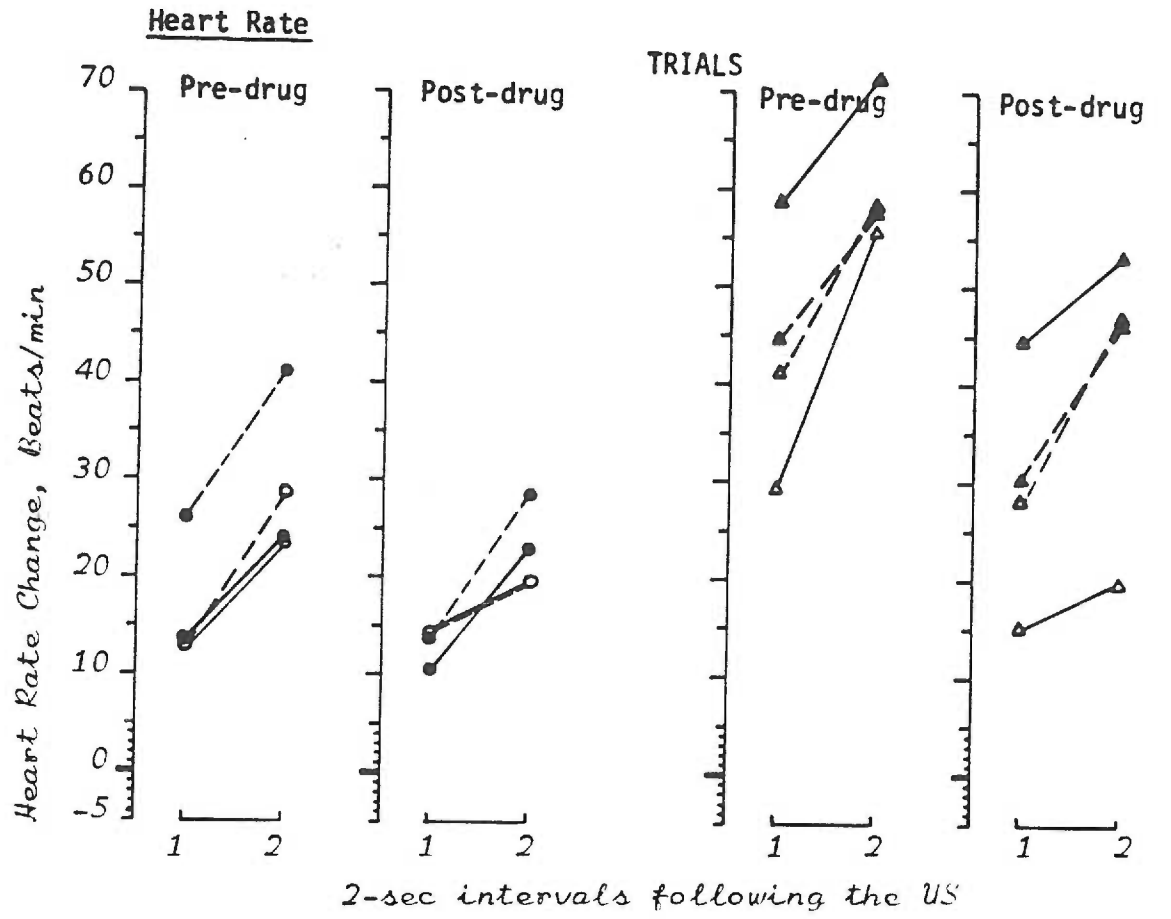

Blood Pressure
TRIALS
Pre-drug
Post-drug
Pre-drug
Post-drug
Blood Pressure Change, mm Hg
16
12
8
4
0
-2
1 2 3 4
2-sec intervals during the CS

the accelerative HR responses of the restrained groups. The only significant outcome was a drug by measurement intervals interaction ($p < .05$), which indicates that the pattern of HR changes was different in the pre- and post-drug trial blocks. The lower left of the figure shows that the elimination of vagal input to the heart left BP responding in the restrained groups virtually unchanged. There were no reliable drug-related statistical outcomes from the analysis of these findings.

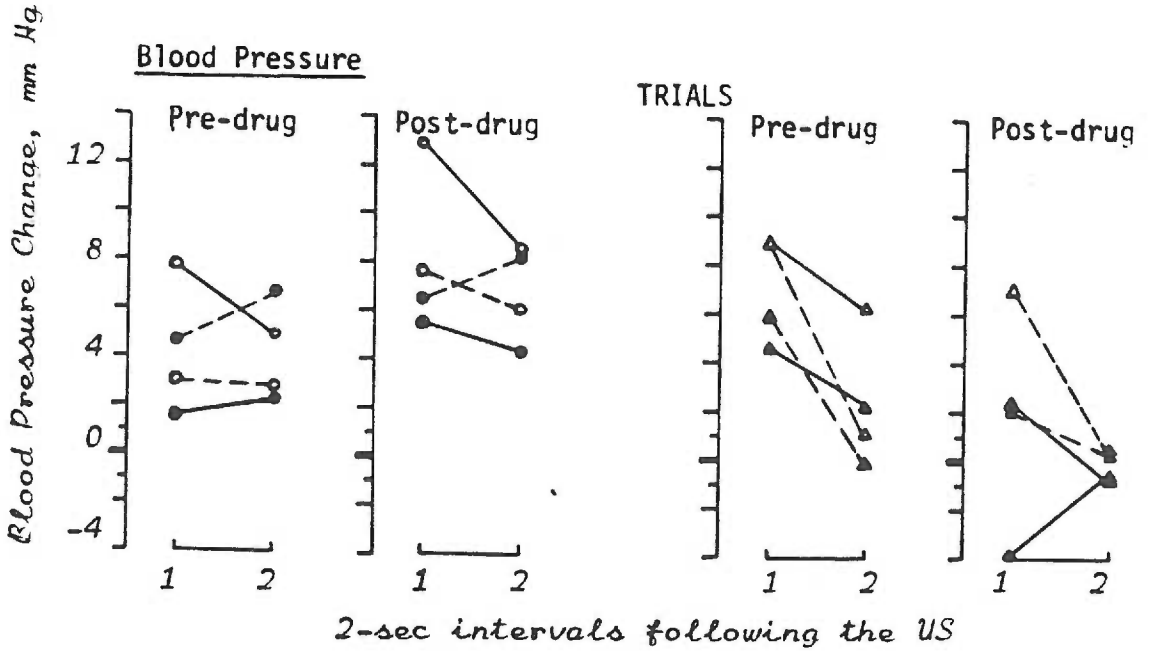
Parasympathetic blockade, CRs of unrestrained groups. (HR analysis Table A-67, BP Table A-68). The upper panels on the right of Figure 18 show that following parasympathetic blockade there was an overall decrease in the accelerative HR responses of the unrestrained experimental groups. However, the decrease was not significant. The lower right panel shows that the absence of vagal activity altered the forms of the BP responses of both the experimental and the control groups, but in different ways. For the experimental groups there was a reduction in the pressor reactions late in the CS whereas for the control groups there was a reduction early in the CS. The reliability of this difference was provided by a significant conditioning by drug by measurement intervals interaction ($p < .05$).

Parasympathetic blockade, URs of restrained groups. (HR analysis Table A-69, BP Table A-70) The left side of Figure 19 depicts the mean HR and BP responses of the restrained groups receiving parasympathetic blockade in 2-sec periods beginning .5 sec after the US averaged over 8-trial blocks prior to and following drug administration.

Figure 19. Mean heart rate in beats per min and blood pressure in mm Hg of all restrained and unrestrained experimental and control groups as a function of intervals following the US and eight-trial blocks immediately before and after drug administration during parasympathetic blockade.



Experimental R-R U-R R-U U-U
Control R-R U-R R-U U-U



The upper left panel shows that vagal blockade exerted almost no effects on the HR URs of these groups. In the lower panel it appears that this drug administration caused a slight increment in the BP URs of the restrained groups. There were no significant drug-effect outcomes in the analysis of these results, however.

Parasympathetic blockade, URs of unrestrained groups. (HR analysis Table A-71, BP Table A-72) The upper right panel of Figure 19 shows that the accelerative HR URs of the unrestrained groups were decremented by parasympathetic blockade. The amount of the loss varied, however, as indicated by significant conditioning by drug ($p < .05$) and conditioning by previous restraint by drug ($p < .05$) interactions. The lower panel shows that parasympathetic blockade also exerted a decremental effect on the BP URs of several groups. This effect was more pronounced in the first interval, especially for the experimental U-U group. Analysis of these results provided significant drug by measurement intervals ($p < .01$) and conditioning by drug by intervals ($p < .05$) interactions.

Parasympathetic blockade, baselevel HR and BP. (HR analysis Table A-73, A-74, BP Table A-75, A-76) Table 6 shows the effects of parasympathetic blockade on baselevel HR and BP for all experimental and control groups. This table shows that drug administration resulted in an increase of baselevel HR by 50-60 bpm in nearly all groups ($p < .01$). Baselevel BP, on the other hand, was virtually unaffected by parasympathetic blockade.

Table 6. Mean baselevel HR (in beats per min) and BP (in mm Hg) of the restrained and unrestrained experimental and control groups averaged over 8-trial blocks immediately prior to and following drug administration during the Parasympathetic Drug Test.

GROUP		HR	BP	HR	BP
Experimental	R-R	410	157.3	470	157.0
	U-R	429	153.5	474	148.6
	R-U	393	133.8	427	136.0
	U-U	380	153.9	422	152.9
Control	R-R	413	166.8	483	168.1
	U-R	414	176.9	464	174.6
	R-U	418	167.1	459	170.5
	U-U	424	174.8	424	166.5

DISCUSSION

The principal findings of the present study were that: (a) restraint did not exert a significant effect on HR or BP orienting responses. Both groups initially displayed similar decelerative HR and pressor BP ORs that rapidly habituated to near baseline; (b) restraint exerted a profound attenuating effect on conditioned HR and BP responses. HR responses to the CS were not seen in the restrained experimental groups, while large-magnitude accelerative HR CRs were seen in the unrestrained experimental groups. The BP CRs of the restrained groups consisted of small pressor responses, while those of the unrestrained groups consisted of very large pressor responses. Restrained and unrestrained URs were similarly affected; (c) several reinforced trials under a new restraint condition were required for the effects of changed restraint on conditioned responding to become apparent. These effects consisted of gradual changes in the HR and BP CRs until they were similar in magnitude to those of the groups that had been consistently maintained under the new restraint condition; (d) restraint caused a major upward shift in baselevel HR, but did not significantly affect baselevel BP; (e) autonomic blockade indicated that the HR and BP CRs of both restrained and unrestrained groups were mainly sympathetically mediated, but that there may have been some contributions of parasympathetic control.

Orienting Responses

It is worth noting that the cardiac orienting responses of both the restrained and unrestrained rats in the present study were decelerative in direction. However, the response magnitudes appeared to be smaller for the unrestrained group than for the restrained group. Though unreliable, this difference suggests that restraint may have exerted a potentiating effect on vagal control of the orienting response.

For the restrained group, the direction and magnitude of the HR ORs agree with previous findings in SHRs (Hatton et al., 1979, 1981) and in normal rats (Fitzgerald, Martin & O'Brien, 1973; Teyler, 1971). Hatton et al. (1981), however, reported that the HR ORs of the SHR rats in their study did not completely habituate by the end of 10 trials, while the results of the present study and that of Hatton et al. (1979) showed very rapid habituation of the OR during the first few trials. A possible explanation for this discrepancy is that the rats used by Hatton et al. (1981) were very young and were probably in the labile phase of hypertension, while the rats used in the present study and in the earlier study of Hatton et al. (1979) were older. This age difference and the accompanying secondary structural changes of the vasculature may have attenuated cardiovascular reactivity in the older rats (Folkow, 1975).

The direction of the HR OR in unrestrained rats in the present experiment was not consistent with results reported by Hallback and Folkow (1974), in which accelerative HR ORs were seen. However, the tone stimulus used in the present study was less intense than that

used by Hallback and Folkow. Hallback and Folkow (1974) described the reactions to intense stimulus presentations in their experiments as "defense" reactions. This suggests that the responses evoked by initial presentation of the rather mild tone CS in the present study were of a different nature than those reported by Hallback and Folkow (1974).

The BP ORs in the present study were identical pressor responses in both the restrained and unrestrained groups. Moreover, the responses of both groups habituated at the same rate over trials. The direction, magnitude, and rate of habituation of these responses agree with previous findings in both restrained and unrestrained SHRs (Hallback & Folkow, 1974; Hatton et al., 1981).

Conditioned Responses

In the present study, conditioned HR decelerations were not seen in the restrained animals. This outcome is not consistent with previous findings using restrained SHR rats in this laboratory (Hatton et al., 1979, 1981). Previous findings have included conditioned HR decelerations of approximately 30 bpm, while the HR responses of restrained SHR rats in the present study consisted of slight accelerations that were not different from the unpaired controls. Although the averaged group HR response was not decelerative, 8 out of 20 restrained rats in the present study showed decelerative HR responses to the CS. The remaining animals showed either mixed changes or slight accelerative HR responses to the CS. These outcomes indicate that there was a tendency for the development of decelerative HR CRs in at least some of the restrained animals in the present study.

The reasons for the lack of observable conditioned HR decelerations in the remaining animals may relate to differences between the

present study and previous studies by Hatton et al. (1979, 1981). The ages of the animals used in the present study was an unlikely factor, as the ages of animals used by Hatton et al. (1979, 1981) were both younger and older than those in the current study. The only other major difference between the present study and those of Hatton et al. (1979, 1981) pertains to the location of the delivery of the shock US, Electric footshock through the grid floor was used as the US in the present study, while electric chest-shock through ECG electrodes was used as the US by Hatton et al. (1979, 1981).

A previous study by Teyler (1971) compared the effects of different locations of delivery of electric shock USs on normotensive rats. Results of that study were partly consistent with the outcomes of the present study. In the Teyler (1971) study, normal restrained rats receiving footshock USs developed only small conditioned HR decelerations compared to restrained rats receiving chest-shock as the US. Another, and perhaps more important finding of the Teyler (1971) study was that rats receiving footshock as the US displayed larger magnitude accelerative HR URs than chest-shock animals. The extent of conditioned HR deceleration was negatively correlated with the magnitude of the HR UR. Thus, animals showing the largest magnitude of accelerative HR URs showed the smallest magnitudes of decelerative HR CRs. Teyler suggested that, due to shocking the densely innervated feet, the footshock animals reacted as if they were receiving a very intense shock, which would cause attenuation of cardiac CRs (Fitzgerald & Teyler, 1970; Schwartzbaum, 1965).

It has, of course, been demonstrated that SHR rats display

exaggerated defense reactions to noxious stimuli (Hallback & Folkow, 1974; Folkow, 1975). The possibility seems strong, therefore, that electric footshock in these animals may have produced a level of arousal, or sympathetic activation, that would have interfered with the development of vagally mediated conditioned cardiodecelerations. Evidence which indicates that footshock produced a very high level of arousal comes from the UR magnitudes, which were much larger overall than those reported by Hatton et al. (1979, 1981). This will be discussed in more detail later. Further investigations into the nature of the effects of different US locations on the development of cardiovascular conditioning in SHR rats seem to be indicated.

The conditioned HR accelerations seen in the unrestrained SHR rats in the present study were consistent with the direction and magnitude of conditioned HR responses previously reported for unrestrained SHR rats (McCarty, Chiueh & Kopin, 1978b) and for unrestrained normotensive rats (Black & Black, 1967). These conditioned cardioaccelerations developed rapidly to asymptotic levels of 45-50 bpm and then stabilized near 35 bpm. Though opposite in direction, the magnitudes of the HR CRs of unrestrained SHRs in the present study were similar to the magnitudes of decelerative HR CRs reported for restrained SHRs (Hatton et al., 1979, 1981).

The conditioned BP responses of both restrained and unrestrained SHRs in the present study consisted of pressor responses. These were consistent with previous findings in restrained SHRs (Hatton et al., 1981), but not in unrestrained SHRs (McCarty et al., 1978b). Both the magnitude and the form of the BP CRs of the restrained rats in the

present study agree closely with the findings of Hatton et al. (1981), consisting of bimodal pressure peaks near 4-5 mm Hg.

McCarty et al. (1978b), on the other hand, did not report the presence of any conditioned BP reactions in their study of unrestrained SHRs. The large magnitude BP CRs of unrestrained SHRs in the present study seem to be at odds with the findings of McCarty et al. (1978b). In that study, the presence of conditioned anticipatory reactions was assessed after only 4 CS-US pairings, while 30 CS-US pairings were given in the present study. However, conditioned BP reactions were very prominent in the present study after only 5 CS-US pairings. It is unlikely, therefore, that the difference in the number of CS-US pairings can account for the discrepancy between the results of the present study and those found by McCarty et al. (1978b).

Perhaps a more important difference between the two experiments is the length of the inter-stimulus interval (ISI), or the time between the onset of the CS and the delivery of the US. In the McCarty et al. (1978b) study, the CS consisted of placement of the rats into a distinctive environment in which shock had been delivered several times in the past. The ISI in that study was 5 min, while the ISI used in the present study was 8 sec. Owing to the phasic nature of BP responses, it seems unlikely that a conditioned increase in BP, especially of the magnitude found in the present study, would persist over a 5-min measurement interval. Blood pressure responses, even to an intense stimulus like electric shock, seldom last more than a few seconds in either SHRs (Hatton et al., 1981; Hallback & Folkow, 1974) or normotensive rats (Hatton et al., 1981; Hoffman, 1977).

Moreover, the onset of the CS in the McCarty et al. (1978b) study, i.e., placement of the rat into the shock environment, was not as discrete as the onset of the tone CS in the present study. These and other unknown factors may have contributed to the failure to observe conditioned BP responses by McCarty et al. (1978b).

The effects of restraint on the development of conditioned HR and BP reactions were very apparent in the present study. Although it cannot be concluded that restraint totally shifted the direction of conditioned HR responses from acceleration to deceleration, restraint reliably prevented the development of large magnitude conditioned HR accelerations such as were seen in unrestrainted rats. A similar effect was seen on conditioned BP responses; restraint prevented the development of large magnitude conditioned pressor responses and allowed only the presence of small BP responses. Taken together, the HR and BP results indicate that restraint caused a major shift in the autonomic discharge pattern controlling conditioned cardiovascular activity. Although the results of this experiment do not imply a total shift from sympathetic to parasympathetic dominance, it can be implied that restraint produced pronounced inhibition of the magnitude of sympathetic outflow in conditioned responding. These findings are consistent with what has been found in normal rats (Martin & Fitzgerald, 1980).

The attenuation of conditioned sympathetic outflow in restrained SHR rats might be attributed to several possible mechanisms. The first and most immediate consideration is that related to the "law of initial values" (Wilder, 1957). According to this argument, the

presence of high background HR activity in the restrained rats would block further increases of HR. However, as stated in the introduction, the results of several investigations (Fitzgerald & Martin, 1971, 1971; Fitzgerald, Martin & O'Brien, 1973; Fitzgerald & Teyler, 1971) have indicated that the magnitudes of HR CRs in normal restrained rats were independent of major fluctuations in baselevel HR. In light of the consistency between SHRs and normal rats, it seems unlikely that the law of initial values would account for the response differences in the present study.

Observations of baseline HR on individual trial blocks in the present study also indicated that background sympathetic activity did not interact with HR CRs in the manner that would be predicted by the law of initial values. The highest level of baseline HR for the unrestrained group occurred on the third trial block of the Conditioning Phase, precisely when the HR CRs of this group were the largest. This positive relationship between baseline HR and CR magnitude suggests that both of these measures may reflect the same underlying process, namely sympathetic arousal level or reactivity.

Another possible mechanism underlying the attenuating effects of restraint relates to the physiological impact of high circulating levels of catecholamines induced by the stress of restraint (Chiueh & Kopin, 1978). It has been physiologically demonstrated in intact (Bevan, 1978; Langer, 1974) and isolated vascular (Dixon, Mosimann & Weiner, 1979) preparations, that activation of alpha-adrenergic receptors located on presynaptic nerve endings can cause inhibition of sympathetic outflow from the affected nerve terminals (Langer, 1976;

Starke & Docherty, 1980). Chiueh and Kopin (1978) reported that plasma NE levels of restrained SHRs increased by 438 pg/ml, or by 69%. This is within the range required to effectively activate presynaptic alpha-adrenoceptors and attenuate further catecholamine release from sympathetic nerve terminals (Dixon et al. 1979). This hypothesis might be tested by the use of exogenously applied norepinephrine in unrestrained SHR rats or by the use of selected pharmacological blockade of presynaptic alpha-adrenergic receptors in restrained SHR rats.

Martin and Fitzgerald (1980) suggested another possible explanation for the effect of restraint on cardiovascular CRs. They suggested that cardiovascular CRs may be linked to alternative patterns of naturally occurring defense reactions such as freezing or attack behaviors. According to this conception, restraint may lead to motor inhibition and cause an aversive CS to activate a septo-hippocampal inhibitory system accompanied by sympathetic inhibition. Freedom to move, on the other hand, may cause the CS to activate an amygdala-hypothalamic-aggression system associated with sympathetic outflow.

Unconditioned Responses

The unconditioned responses to electric footshock consisted of HR and BP increases for all of the animals in the present study. These responses are consistent with the types of unconditioned responses that have been reported previously for SHR rats subjected to electric shock (Hatton et al., 1979, 1981; McCarty et al., 1978a, 1978b) as well as other forms of intense stimulation (Hallback & Folkow, 1974). The magnitudes of the HR URs of restrained SHR rats in the present study differed from those seen by Hatton et al. (1981), however. The

HR URs found by Hatton et al. (1981) reached only 20 bpm and rapidly attenuated over 30 trials of conditioning.

On the other hand, the magnitudes of the HR URs in the present study reached over 35 bpm and showed no attenuation over 30 conditioning trials. This discrepancy appeared despite the fact that the shock intensity in the present study was less than one-half that used by Hatton et al. (1981). This finding lends support to the notion that electric footshock produced more intense effects and a higher level of arousal than electric chest-shock in restrained SHR rats. The HR UR magnitudes of unrestrained SHR rats in the present study were not as large as those reported in studies by McCarty et al. (1978a, 1978b). However, 2.5 mA footshock was used in those studies, while .6 mA footshock was used in the present study.

It is clear that restraint exerted large effects on HR and BP URs in the present experiment. The HR URs of restrained rats were 35-45 bpm less than those of unrestrained rats and the BP URs of restrained rats. It seems possible that the same physiological mechanisms responsible for the attenuation of HR and BP CRs may have also been responsible for the attenuation of HR and BP URs. Again, further pharmacological investigation is indicated in order to ascertain the contributions of circulating catecholamines and presynaptic inhibition of sympathetic outflow to cardiovascular URs of restrained SHR rats.

Effects of changed restraint

Changing the type of restraint that was imposed on SHR rats in this experiment resulted in a corresponding change in the magnitudes

and forms of conditioned HR and BP responses. A corresponding change also occurred in the magnitudes of HR and BP URs that were seen. However, these changes were not all immediate. There was little effect of changed restraint during the Extinction Test Phase. The type of restraint that had been present during the Conditioning Phase continued to be the dominant influence on both HR and BP conditioned responding during extinction. That is to say, responses learned under one type of restraint continued to be displayed when restraint was changed during extinction. Changes in the nature of HR and BP CRs were not seen until after several trials of the Reconditioning Phase that followed. The CRs of both "changed" experimental groups (R-U, U-R) appeared to become altered at about the same rate during reconditioning. This indicates that changed restraint, per se, did not alter the forms of the observed CRs, but forced the learning of new responses.

As reconditioning continued, the restraint condition in effect during this phase became the major influence on cardiovascular CRs. However, some effects of original restraint persisted throughout reconditioning. This was seen mainly on the forms of the HR CRs, which continued to show a slight resemblance to orginally learned response forms. Though insignificant, the magnitude differences also reflected previous restraint history, i.e., the HR CRs of Group R-U were slightly smaller than those of Group U-U and the HR CRs of Group U-R were slightly larger than those of Group R-R.

Taken together, the results of the changed restraint test and reconditioning indicate that restraint exerted effects mainly on the

learning processes underlying cardiovascular response patterns rather than on the expression of the CRs. The HR and BP CRs remained fairly stable for some time after restraint conditions were changed. This observation negates explanations for restraint effects that are based on peripheral physiological factors. Such explanations would predict immediate response changes following changed restraint. This includes explanations based on peripheral catecholamines and high sympathetic background activity. Alternative explanations must be favored that are based on central states associated with restraint, as this is what appeared to be learned. The explanation suggested by Martin and Fitzgerald (1980) based on the learning of alternative patterns of defense reactions triggered by restraint is consistent with this latter view.

The CRs were not the only responses that changed after the change in restraint. The URs were also affected by restraint changes in either direction. For both the experimental and control groups that were changed from being restrained to unrestrained (R-U), the HR URs did not change immediately but grew steadily over reconditioning trials until they were almost as large as the HR URs of the consistently unrestrained groups. For the experimental group, the gradual growth of the HR UR paralleled the growth of the HR and BP CRs. It is not immediately obvious why the HR URs of Groups R-U did not change as soon as the inhibitary influence of restraint was removed. It appears that previous restraint interfered with subsequent UR magnitudes, perhaps by the imposition of a competing response. As unconditioned HR responses are strongly linked to somatomotor activation (Obrist,

Howard, Lawler, Galosy & Meyers, 1974), this outcome suggests that the HR URs may have reflected an inhibitory motor response carryover from the previous state. The persistence of this competing response following the removal of restraint suggests that the response learned during restraint consisted of a complete pattern of cardiovascular as well as motor response inhibition.

The growth of the BP URs of Groups R-U, on the other hand, was much more rapid. Following the change to the unrestrained condition, these groups immediately displayed BP URs of the same magnitude and form as those of the unrestrained groups during the Conditioning Phase.

For the experimental and control groups that were changed from unrestrained to restrained (U-R), changes in both HR and BP UR magnitudes were immediate. On the first trial block of reconditioning, these groups displayed URs that were comparable to those of the restrained groups during the Conditioning Phase. The HR and BP URs of Groups U-R then continued to decline slightly over trials. The immediate nature of these changes, especially for BP URs, is consistent with the hypothesis that high plasma levels of NE may have resulted in feedback inhibition and response attenuation (Langer, 1976).

The outcomes of the changed restraint portions of the present study indicate that HR and BP CRs and URs may be relatively independent of each other in SHRs. Although there was little evidence for the presistence of HR CRs in any group during the non-reinforced test trials, BP CRs remained prominently intact during the initial trials of this phase. Also, in this and other phases, HR changes did not appear to be reflexive to BP changes as both HR and BP changed in the

same direction. Additionally, changed restraint resulted in relatively immediate changes in the magnitudes of BP URs, while HR and BP CRs as well as the HR URs of Groups R-U did not change until the occurrence of several reinforced trials. These findings are consistent with previous findings in normal rats (Hoffman, 1977).

Baselevel Heart Rate and Blood Pressure

The baselevel HR of restrained SHRs in the present study was significantly higher than that of the unrestrained animals. This difference was largest during the initial Conditioning Phase on the first day and became smaller with subsequent exposures to the restraint situation, but still remained significant on the last day. Initially, baselevel HR of the restrained groups was 40-60 bpm higher than that of the unrestrained groups. This finding is consistent with the findings reported by Chiueh and Kopin (1978) for the effects of restraint in SHRs, although the magnitude of increased HR in that study was somewhat larger. The finding of habituation to the effect of restraint on baselevel HR in the present study is consistent with the habituation to immobilization induced HR increases reported by Kvetnansky et al. (1979).

The baselevel BP of restrained and unrestrained SHRs in the present study was not significantly affected by restraint. This is not consistent with the findings of Chiueh and Kopin (1978), but is consistent with the findings of Kvetnansky et al. (1979) for initial exposure of SHRs to immobilization. The reasons for this discrepancy are not clear.

An interesting finding in the present study pertains to the

change of baselevel BP in the experimental group that was changed from restrained to unrestrained. Baselevel BP in this group decreased by about 15 mm Hg and remained depressed throughout the remainder of the experiment. Though this decrease largely fell short of significance, it parallelled findings reported by Kvetnansky et al. (1979). In that study, the resting BP of SHRs declined by about 25 mm Hg following exposure to immobilization. Kvetnansky et al. (1979) suggested that struggling during immobilization may have exerted effects similar to exercise training which has been found to reduce BP in SHRs.

Pharmacological Blockade of the Autonomic Nervous System

Sympathetic blockade. That there was a strong contribution of the sympathetic system to the control of HR CRs was demonstrated by the results of sympathetic pharmacological blockade. This blockade almost completely suppressed the HR CRs of both the restrained and unrestrained groups. An interesting feature of this drug test is that even though the HR responses of the restrained experimental groups were not reliably different from those of the control groups, the responses of the experimental groups were decremented significantly more than the responses of the control groups. This indicated that the autonomic balance mediating HR responses to the CS was reliably different between these groups, even though the response magnitudes were not significantly different.

Pharmacological blockade of the sympathetic system in the absence of restraint differentiated between the groups that were conditioned either originally restrained or originally unrestrained. The R-U experimental group that was restrained during the original Conditioning

Phase showed smaller HR CR and UR decrements in response to drug administration than the U-U experimental group that was originally unrestrained. There is some evidence in Figures 16 and 17 that this effect may have been due to originally larger pre-drug responses in the U-U group. However, following drug administration, the CRs and URs of Group U-U were smaller than those of Group R-U. This seems to indicate that the sympathetic system was somewhat less instrumental in mediating the accelerative responses of the previously restrained R-U group.

While sympathetic blockade resulted in significant attenuation of BP CRs in both restrained and unrestrained SHRs, substantial BP response magnitudes remained after drug administration. This result is not consistent with the previous findings of Hatton et al. (1981), in which sympathetic blockade with phentolamine effectively inhibited all BP conditioned responding of SHRs. Propranolol in that study also caused much more inhibition of the BP CRs of restrained SHRs than in the present study.

In the study by Hatton et al. (1981), sympathetic blockade was accomplished in two different stages. Propranolol was administered on one day to block beta-adrenergic receptors and phentolamine was administered on a separate test day to block alpha-adrenergic receptors. However, difficulties in maintaining patent BP recording catheters made it necessary to drop some animals from the study of Hatton et al (1981) before all drug tests could be administered. Therefore, sympathetic blockade was carried out on a single test day in the present experiment in order to eliminate one drug-test day. Propranolol and

phentolamine were given in a regimen of combined drug administration in order to simultaneously block both alpha- and beta- adrenergic receptors.

Since the advent of this study, new findings have come to light that indicate potential problems with a regimen of combined propranolol and phentolamine. Although these two drugs have been thought of traditionally as acting at two completely separate populations of receptor sites in the nervous system, recent evidence has indicated that each drug may attenuate the effects of the other.

In a study of the effects of combined administration of phentolamine and propranolol, Oates and Stoker (1980) found that propranolol administration attenuated the magnitude of BP decrease produced by phentolamine. This effect was observed whether propranolol administration preceeded or followed phentolamine. Another study by Mottram and Hickman (1979) demonstrated that propranolol reversed the alpha-adrenergic receptor blockade produced by phentolamine at postsynaptic sites. Additionally, Richards, Prichard and Hernandez (1979) showed that HR and BP responses to exogenously applied E and NE were attenuated, but not abolished by combined blockade of alpha- and beta-adrenergic receptors in vivo.

Together, the studies just mentioned indicate that combined phentolamine and propranolol administration produces less than optimal blockade of the alpha-adrenergic sympathetic system. It is unfortunate that these findings were not uncovered prior to the design of the present study. Both HR and BP CRs were attenuated by the combined drug treatment of the present study, but it is difficult to make strong

conclusions about the nature of underlying autonomic nervous activity from the amount of BP attenuation that was produced. Ideally, complete response attenuation would have been desirable in order to conclude that the sympathetic portion of the ANS was totally responsible for both HR and BP CRs. The pharmacological data gathered in the present study warrant a conclusion that sympathetic activity was primarily responsible for the HR CRs of both restrained and unrestrained SHRs, but statements about the extent of sympathetic involvement in BP CRs must be limited. However, direct parasympathetic innervation of the arterial vasculature has not been demonstrated in either SHRs or normal rats. Therefore a conclusion that activity mediated the pressor BP CRs is fairly secure.

Parasympathetic blockade. Blockade of the parasympathetic portion of the ANS by methyl-atropine resulted in small, but largely insignificant attenuation of the HR responses to the CS of both the restrained and unrestrained experimental groups. Parasympathetic blockade also resulted in a diminution of the magnitude of the HR URs of both the restrained and unrestrained groups. A significant increase in baselevel HR accompanied the other effects of drug administration in all groups. Additionally, this drug test affected the BP CRs and URs of the unrestrained groups, U-U and R-U. The effect on BP CRs was an attenuation of the rate of BP increase over measurement intervals such that the pressor peak was decremented by 2-3 mm Hg at the end of the CS.

No other studies have been located in which parasympathetic blockade was administered during the performance of accelerative HR

CRs in SHR or normotensive rats. Earlier pharmacological studies with either SHRs or normal rats in this laboratory have dealt with decelerative HR CRs (Hatton et al., 1981; Fitzgerald, Martin & O'Brien, 1973). Conditioned HR decelerations in these studies were found to be mainly under parasympathetic influence. However, the implications of those findings for the results of the present study are uncertain.

The findings of the present study are consistent with the findings for defense reactions of SHRs reported by Hallback and Folkow (1974). In that study, defense reactions to mild intense alerting stimuli were partially attenuated following atropine administration. It was concluded that the defense reactions of SHRs were partially mediated by suppression of vagal discharge.

The slight attenuation of HR CRs by atropine in the present study suggests that there were some parasympathetic influences contributing to conditioned reactions, similar to the defense reactions reported by Hallback and Folkow (1974). The fact that the responses became smaller following drug administration suggests that the nature of the parasympathetic contribution was a suppression of vagal discharge during the tone CS which contributed to HR acceleration. This effect was seen in restrained and unrestrained SHRs about equally, indicating that restraint did not have an effect on vagal suppression in this study.

The effects of atropine administration on the BP CRs of the unrestrained group were peculiar, as BP is not under the direct influence of the parasympathetic system in rats. The lack of effect on baselevel BP is further evidence that parasympathetic blockade did not

affect BP CRs directly. A probable explanation lies in the fact that sympathetic outflow can be attenuated through the baroreflex system when cardiac output is high (Guyton, 1980). Increased baselevel HR and cardiac output associated with administration of atropine may have activated the baroreflex enough to exert the slight suppressive effects that were seen on the BP CRs of the unrestrained groups.

SUMMARY AND CONCLUSIONS

The purpose of the present investigation was to provide information on the direction and magnitude and autonomic control of classically conditioned changes in heart rate and blood pressure in restrained and unrestrained spontaneously hypertensive rats. A 2 x 2 x 2 factorial design was employed in which one dimension was the conditioning procedure (paired conditioning trials vs explictly unpaired presentations of the CS and US). Another dimension was the factor of restraint (tightly restrained vs freely moving) and the third dimension was the factor of changing restraint (changed vs constant). Sixty SHR rats were randomly assigned to the four (restrained and unrestrained, conditioning and control) groups making up this design. All animals received 10 CS-alone trials with the tone CS. Animals in the conditioning groups then received 30 paired conditioning trials with the tone and a .6 mA footshock US. Animals in the control groups received 30 unpaired presentations of the CS and US. Following conditioning, one half of each group was changed to the opposite restraint condition and the remaining animals were maintained for 10 non-reinforced test trials, 40 reconditioning trials, and selective pharmacological autonomic blockade of the sympathetic and parasympathetic systems.

The principal findings were that restraint influenced the magnitude and form of the conditioned HR and the conditioned BP responses that were learned. The restrained and unrestrained group displayed similar decelerative HR and pressor BP ORs to the CS prior to

conditioning. Throughout the study, the unrestrained groups showed accelerative HR CRs and pressor BP CRs while the restrained groups showed slight evidence of these HR and BP CRs that were much smaller than those of the unrestrained groups. The HR responses of all experimental groups were not different from those of the control groups during the nonreinforced test trials, but the pressor BP CRs were initially retained. Those experimental groups that were reconditioned under a changed restraint condition came to display HR and BP CRs consistent with the new restraint, but this change was gradual. The HR and BP URs of all groups consisted of HR acceleration and pressor BP responses, with the magnitudes of both responses being larger in the unrestrained than in the restrained groups. Selective autonomic blockade indicated that sympathetic activity was primarily responsible for the HR CRs and at least partially responsible for the BP CRs.

It was suggested that the results indicate that restraint affected the pattern of cardiovascular responses that were learned rather than exerting an effect directly on the output of the responses. The failure to observe conditioned cardiodecelerations in restrained SHRs was discussed in terms of relative noxiousness of the footshock US.

REFERENCES

Berecek, K.H., Schwertschlag, U. and Gross, F. Alterations in renal vascular resistance and reactivity in spontaneous hypertension of rats. American J. Physiology, 1980, 238, H287-H293.

Bevan, J.A. Norepinephrine and the presynaptic control of adrenergic transmitter release. Federation Proceedings, 1978, 37, 187-190.

Black, R.W. and Black, P.E. Heart rate conditioning as a function of interstimulus interval in rats. Psychonomic Science, 1967, 8, 219-220.

Bohlen, H.G. Arteriolar closure mediated by hyperresponsiveness to norepinephrine in hypertensive rats. J. Appl. Physiol., 1979, 236, H157-H164.

Buccafusco, J.J. and Spector, S. Role of central cholinergic neurons in experimental hypertension. J. Cardiovascular Pharmacology, 1980, 3, 347-355.

Chiueh, C.C. and Kopin, I.J. Hyperresponsivity of spontaneously hypertensive rats to indirect measurement of blood pressure. American J. Physiology, 1978, 234, H690-H695.

Chiueh, C.C., McCarty, R. and Kopin, I.J. Sympathoadrenal medullary activities in spontaneously hypertensive rats and Wistar Kyoto rats following resting, handling, restraint, cold stress and foot-shock stress. Neuroscience Abstracts, 1977, 3, 18.

Cohen, D.H. and Obrist, P.A. Interactions between behavior and the cardiovascular system. Circulation Research, 1975, 37, 693-704.

Dallman, M.F. and Jones, M.T. Corticosteroid feedback control of ACTH secretion: Effect of stress-induced corticosterone secretion on subsequent stress responses in the rat. Endocrinology, 1973, 92, 1367-1375.

DeTurck, K.H. and Vogel, W.H. Factors influencing plasma catecholamine levels in rats during immobilization. Pharmacology, Biochemistry and Behavior, 1980, 13, 129-131.

Dixon, W.R., Mosimann, W.F. and Weiner, N. The role of presynaptic feedback mechanisms in regulation of norepinephrine release by nerve stimulation. J. Pharmacology and Experimental Therapeutics, 1979, 209, 196-204.

Dykman, R.A. On the nature of classical conditioning. In C.C. Brown (ed.), Methods in Psychophysiology. Williams & Wilkins, Baltimore, 1967.

Fitzgerald, R.D. and Martin, G.K. Heart rate conditioning in rats as a function of interstimulus interval. Psychological Reports, 1971, 29, 1103-1110.

Fitzgerald, R.D., Martin, G.K. and O'Brien, J.H. Influence of vagal activity on classically conditioned heart rate in rats. Journal of Comparative and Physiological Psychology, 1973, 83, 485-491.

Fitzgerald, R.D. and Teyler, T.J. Trace and delayed heart-rate conditioning in rats as a function of US intensity. Journal of Comp. & Physiol. Psychol., 1970, 70, 242-253.

Fitzgerald, R.D., Vardaris, R.M. and Teyler, T.J. An on-line method for measuring heart rate in conditioning experiments. Psychophysiology, 1968, 4, 352-353.

Folkow, B. Haemodynamic responses to cortical and hypothalamic stimulation. In: The Pathogenesis of Essential hypertension, Proceedings of the WHO-Czekoslavakian Cardiology Symposium, Prague. State Medical Publishing House, Prague, 1960.

Folkow, B. Central neuro-hormonal mechanisms in spontaneously hypertensive rats compared with human essential hypertension. Clinical Science and Molecular Medicine, 1975, 48 (Suppl. 2), 205s-229s.

Folkow, B. Cardiovascular structural adaptation; its role in the initiation and maintenance of primary hypertension. Clinical Science and Molecular Medicine, 1978, 55, 3s-22s.

Fowler, M.E. Restraint and Handling of Wild and Domestic Animals. Iowa State Univ. Press, Ames, Iowa, 1978.

Gantt, W.H. Cardiovascular components of the conditioned reflex to pain, food, and other stimuli. Physiological Review, 1960, 40, 266-291.

Grobecker, H., Saavedra, J.M., Roizen, M.F., Weise, V., Kopin, I.J. and Axelrod, J. Peripheral and central catecholaminergic neurons in genetic and experimental hypertension in rats. Clinical Science and Molecular Medicine, 1976, 51, 377s-380s.

Grollman, A. The spontaneously hypertensive rat: An experimental analogue of essential hypertension in the human being. In K. Okamoto (ed.) Spontaneous Hypertension, Its Pathogenesis and Complications. Springer-Verlag, NY, 1972.

Gutman, M.C. and Benson, H. Interaction of environmental factors and systemic arterial blood pressure. Medicine, 1971, 50, 543-553.

Guyton, A.C. Circulatory Physiology III, Arterial Pressure and Hypertension. W.B. Saunders Co., Philadelphia, 1980.

Hallbäck, M. and Folkow, B. Cardiovascular responses to acute mental 'stress' in spontaneously hypertensive rats. Acta Physiol. Scand., 1974, 90, 684-698.

Hallbäck-Nordlander, M. and Lundin, S. Background of hyperkinetic circulatory state in young spontaneously hypertensive rats. In Meyer, P. and Schmitt, H. (eds), Nervous System and Hypertension. Wiley & Sons, N.Y., 1979.

Hansen, C.T. A genetic analysis of hypertension in the rat. In K. Okamoto (ed.) Spontaneous Hypertension, Its Pathogenesis and Complications. Springer-Verlag, NY, 1972.

Hatton, D.C., Buchholz, R.A. and Fitzgerald, R.D. Autonomic control of heart rate and blood pressure in spontaneously hypertensive rats during aversive classical conditioning. In press, 1981.

Hatton, D.C., Wilkin, L.D., Francisco, D.L., Hoffman, J.W., Buchholz, R.A. and Fitzgerald, R.D. Heart rate responses of spontaneously hypertensive rats during aversive classical conditioning. Behavioral and Neural Biology, 1979, 27, 107-114.

Hoffman, J.W. Classically conditioned changes in heart rate and blood pressure based on electric shock or ammonia-fumes reinforcement. Unpublished masters thesis, University of Oregon Health Sciences Center, 1977.

Holdstock, T.L. and Schwartzbaum, J.S. Classical conditioning of heart rate and galvanic skin response in the rat. Psychophysiology, 1965, 2, 25-38.

Iriuchijima, J. Sympathetic discharge rate in spontaneously hypertensive rats. Japanese Heart J., 1973, 14, 350-356.

Iriuchijima, J. Sympathetic discharge rate in SHR. In Julius, S. and Esler, M.D. (eds.), The Nervous System in Arterial Hypertension. Chas. C. Thomas, Springfield, Illinois, 1976.

Judy, W.V., Watanabe, A.M., Henry, D.P., Besch, H.R., Murphy, W.R. and Hockel, G.M. Sympathetic nerve activity: Role in regulation of blood pressure in the spontaneously hypertensive rat. Circulation Research, 1976, 38 (Suppl. II), 21-29.

Kvetnansky, R., McCarty, R., Thoa, N.B., Lake, C.R. and Kopin, I.J. Sympatho-adrenal responses of spontaneously hypertensive rats to immobilization stress. Amer. J. Physiol, 1979, 236, H457-462.

Kvetnansky, R., Sun, C.L., Torda, T. and Kopin, I.J. Plasma epinephrine and norepinephrine levels in stressed rats-effect of adrenalectomy. Pharmacologist, 1977, 19, 241.

Kvetnansky, R., Weise, V.K. and Kopin, I.J. Elevation of adrenal tyrosine hydroxylase and phenylethanolamine-N-methyl transferase by repeated immobilization of rats. Endocrinology, 1970, 87, 744-749.

Lamprecht, F., Williams, R.B. and Kopin, I.J. Serum dopamine-beta-hydroxylase during development of immobilization-induced hypertension. Endocrinology, 1973, 92, 953-956.

Langer, S.Z. Presynaptic regulation of catecholamine release. Biochemical Pharmacology, 1974, 23, 1793-1800.

Langer, S.Z. The role of α- and β-presynaptic receptors in the regulation of noradrenaline release elicited by nerve stimulation. Clinical Science and Molecular Medicine, 1976, 51, 423s-426s.

Langer, S.Z. Presynaptic receptors and the regulation of transmitter release in the peripheral and central nervous system: Physiological and pharmacological significance. In Usdin, E., Kopin, I.J., and Barchas, J. (eds.) Catecholamines: Basic and Clinical Frontiers, Vol. 1, Pergamon Press, NY, 1979.

Limas, C., Westrum, B. and Limas, C.J. The evolution of vascular changes in the spontaneously hypertensive rat. Am. J. Pathology, 1980, 98, 357-376.

Mackintosh, N.J. The Psychology of Animal Learning. New York: Academic Press, 1974.

Martin, G.K. and Fitzgerald, R.D. Heart rate and somatomotor activity in rats during signalled escape and yoked classical conditioning. Physiology and Behavior, 1980, 25, 519-526.

McCarty, R., Chiueh, C.C. and Kopin, I.J. Behavioral and cardiovascular responses of spontaneously hypertensive and normotensive rats to inescapable footshock. Behavioral Biology, 1978, 22, 405-410.

McCarty, R., Chiueh, C.C. and Kopin, I.J. Spontaneously hypertensive rats: Adrenergic hyperresponsivity to anticipation of electric shock. Behavioral Biology, 1978, 23, 180-188.

McCarty, R. and Kopin, I.J. Changes in plasma catecholamines and behavior of rats during the anticipation of footshock. Hormones and Behavior, 1978, 11, 248-257.

McCarty, R. and Kopin, I.J. Alterations in plasma catecholamines and behavior during acute stress in spontaneously hypertensive and Wistar-Kyoto normotensive rats. Life Sciences, 1978, 22, 997-1006.

Mottram, D.R. and Hickman, J.A. On the relationship between uptake inhibition and reversal of alpha receptor blockade by proprandol. Pharmacological Research Communications, 1979, 11, 795-808.

Oates, H.F. and Stoker, L.M. Haemodynamic interactions between α- and β-adrenoceptor antagonists in conscious or anesthetized rats. Clinical and Experimental Pharmacology and Physiology, 1980, 7, 231-236.

Obrist, P.A., Howard, J.L., Lawler, J.E., Galosy, R.A., Meyers, K.A. and Gaebelein, C.J. The cardiac somatic interaction. In P.A. Obrist, A.H. Black, J. Brener and L.V. DiCara (eds.) Cardiovascular Psychophysiology: Current Issues in Response Mechanisms, Biofeedback and Methodology. Aldine Publ. Co., Chicago, 1974.

Okamoto, K. Spontaneous hypertension in rats. Int. Revue of Experimental Pathology, 1969, 7, 227-270.

Okamoto, K. (ed.) Spontaneous Hypertension, Springer-Verlag, NY, 1972.

Okamoto, K., Nosaka, S., Yamori, Y. and Matsumoto, M. Participation of neural factors in the pathogenesis of hypertension in the spontaneously hypertensive rat. Japanese Heart J., 1967, 8, 168-173.

Pfeffer, M.A., Pfeffer, J.M. and Frohlich, E.D. Autonomic inhibition in spontaneously hypertensive rats. In Julius, S. and Esler, M.D. (eds.), The Nervous System in Arterial Hypertension. Chas. C. Thomas, Springfield, Illinois, 1976.

Pickering, G.W. High Blood Pressure. J. & A., Churchill: London, 1968.

Popper, C.W., Chiueh, C.C. and Kopin, I.W. Plasma catecholamine concentrations in unanesthetized rats during sleep, wakefulness, immobilization, and after decapitation. J. Pharmacology and Experimental Therapeutics, 1977, 202, 144-148.

Richards, D.A., Prichard, B.N.C. and Hernandez, R. Circulatory effects of noradrenaline and adrenaline before and after labetalol. British J. Clinical Pharmacology, 1979, 7, 371-378.

Schneiderman, N. The relationship between learned and unlearned cardiovascular responses. In: P.A. Obrist, A.H. Black, J. Brener & L.V. DiCara (eds.) Cardiovascular Psychophysiology, Chicago, Ill.: Aldine Publ. Co., 1974.

Starke, K. and Docherty, J.R. Recent developments in α-adrenoceptor research. J. Cardiovascular Pharmacology, 1980, 2 (Suppl. 3), S269-S286.

Teyler, T.J. Effects of restraint on heart rate conditioning in rats as a function of US location. Journal of Comparative and Physiological Psychology, 1971, 77, 31-37.

Vanhoutte, P.M. The adrenergic neuroeffector interaction in the normotensive and hypertensive blood vessel wall. J. Cardiovascular Pharmacology, 1980, 2 (Suppl. 3) S253-S267.

Vetadzakoska, D., Gudeska, S., Glavas, E., Sukarova, M. and Nikodijevic, B. Endogenous level of norepinephrine and the sensitivity of adrenergic receptors in spontaneously hypertensive rats. In K. Okamoto (ed.) Spontaneous Hypertension, Its Pathogenesis and Complications, Springer Verlag, NY, 1972.

Webb, R.C. and Vanhoutte, P.M. Sensitivity to norepinephrine in isolated tail arteries from spontaneously hypertensive rats. Clinical Science, 1979, 57, 31s-33s.

Weiss, L. Aspects of the relation between functional and structural cardiovascular factors in primary hypertension. Acta Physiol. Scand., 1974, 86 (Suppl. 409), 1-51.

Wilder, J. The law of initial values in neurology and psychiatry. Facts and problems. J. Nervous and Mental Disabilities, 1957, 125, 73-86.

Wolf, S. Emotions and the autonomic nervous system. Archives of Internal Medicine, 1970, 126, 1024-1030.

Yamaguchi, I. and Kopin, I.J. Blood pressure, plasma catecholamines, and sympathetic outflow in pithed SHR and WKY rats. American J. Physiology, 1980, 238, H365-H372.

Yamori, J., Matsumoto, M., Yamabe, H. and Okamoto, K. Augmentation of spontaneous hypertension by chronic stress in rats. Jap. Circul. (En.) J., 1969, 33, 399-409.

Yen, T.T., Pearson, D.V., Powell, C.E. and Kirschner, G.L. Thermal stress elevates the systolic blood pressure of spontaneously hypertensive rats. Life Sciences, 1978, 22, 359-362.

Table A-1. A 2 by 5 by 4 (restraint by trials by measurement intervals) analysis of variance summary table comparing the HR ORs of the restrained and unrestrained groups during the CS alone trials.

Between Subjects	DF	MS	F	p
A (Restraint)	1	4.68	.00	
Error	58	859.35		
Within Subjects				
B (Trials)	4	1866.84	3.84	.01
A×B	4	1090.78	2.24	
C (Measurement intervals)	3	344.25	2.02	
A×C	3	334.25	1.96	
B×C	12	213.78	1.43	
A×B×C	12	273.78	1.84	
B×Error	232	485.61		
C×Error	174	170.37		
B×C×Error	696	148.77		

Table A-2. A 2 by 5 by 4 (restraint by trials by measurement intervals) analysis of variance summary table comparing the BP ORs of the restrained and unrestrained groups during the CS-alone trials.

Between Subjects	DF	MS	F	P
A (Restraint)	1	.27	.00	
Error	58	154.63		
Within Subjects				
B (Trials)	4	257.08	8.41	.01
A×B	4	18.64	.61	
C (Measurement intervals)	3	545.57	28.21	.01
A×C	3	10.66	.55	
B×C	12	33.90	4.64	.01
A×B×C	12	7.84	1.07	
B×Error	232	30.55		
C×Error	174	19.33		
B×C×Error	696	7.30		

Table A-3. A 2 by 6 by 4 (conditioning by trials by measurement intervals) analysis of variance summary table comparing the HR CRs of the restrained experimental and control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	1696.50	1.11	
Error	28	1522.65		
Within Subjects				
B (Trials)	5	1088.93	3.10	.05
A×C	5	444.33	1.26	
C (Measurement intervals)	3	160.35	1.52	
A×C	3	37.35	.35	
B×C	15	67.60	1.03	
A×B×C	15	76.46	1.16	
B×Error	140	351.23		
C×Error	84	105.38		
B×C×Error	420	65.45		

Table A-4. A 2 by 6 by 4 (conditioning by trials by measurement intervals) analysis of variance summary table comparing the BP CRs of the restrained experimental and control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	670.91	3.47	
Error	28	192.84		
Within Subjects				
B (Trials)	5	42.71	2.34	.05
A×B	5	7.08	.38	
C (Measurement intervals)	3	260.52	17.46	.01
A×C	3	22.81	1.52	
B×C	15	3.23	.75	
A×B×C	15	11.91	2.78	.01
B×Error	140	18.18		
C×Error	84	14.91		
B×C×Error	420	4.28		

Table A-5. A 2 by 6 by 4 (conditioning by trials by measurement intervals) analysis of variance summary table comparing the HR CRs of the unrestrained experimental and control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	55279.22	21.10	.01
Error	28	2619.45		
Within Subjects				
B (Trials)	5	3188.36	9.73	.01
A×B	5	1404.07	4.28	.01
D (Measurement intervals)	3	5440.61	30.54	.01
A×C	3	3143.88	17.64	.01
B×C	15	223.36	4.03	.01
A×B×C	15	185.15	3.34	.01
B×Error	140	327.52		
C×Error	84	178.13		
B×C×Error	420	55.41		

Table A-6. A 2 by 6 by 4 (conditioning by trials by measurement intervals) analysis of variance summary table comparing the BP CRs of the unrestrained experimental and control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	19939.42	36.98	.01
Error	28	539.11		
Within Subjects				
B (Trials)	5	515.04	11.94	.01
A×B	5	156.90	3.63	.01
C (Measurement intervals)	3	19.95	.59	
A×C	3	147.54	4.41	.01
B×C	15	8.99	1.30	
A×B×C	15	9.56	1.39	
B×Error	140	43.11		
C×Error	84	33.41		
B×C×Error	420	6.87		

Table A-7. A 2 by 6 by 4 (restraint by trials by measurement intervals) analysis of variance summary table comparing the HR CRs of the restrained and unrestrained experimental groups during conditioning.

Between Subjects	DF	MS	F	p
A (Restraint)	1	90850.95	33.27	.01
Error	38	2730.71		
Within Subjects				
B (Trials)	5	3607.61	9.37	.01
A×B	5	1367.96	3.55	.01
C (Measurement intervals)	3	4192.63	24.99	.01
A×C	3	4496.78	26.80	.01
B×C	15	218.02	3.43	.01
A×B×C	15	218.97	3.45	.01
B×Error	190	384.75		
C×Error	114	167.64		
B×C×Error	570	63.38		

Table A-8. A 2 by 6 by 4 (restraint by trials by measurement intervals) analysis of variance summary table comparing the BP CRs of the restrained and unrestrained experimental groups during conditioning.

Between Subjects	DF	MS	F	p
A (Restraint)	1	18103.01	28.15	.01
Error	38	642.89		
Within Subjects				
B (Trials)	5	452.05	13.18	.01
A×B	5	221.21	6.45	.01
C (Measurement intervals)	3	93.70	2.58	
A×C	3	220.23	6.08	.01
B×C	15	7.06	1.18	
A×B×C	15	6.28	1.05	
B×Error	190	34.28		
C×Error	114	36.20		
B×C×Error	570	5.95		

Table A-9. A 2 by 6 by 4 (restraint by trials by measurement intervals) analysis of variance summary table comparing the HR responses of the restrained and unrestrained control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Restraint)	1	684.01	1.16	
Error	18	587.80		
Within Subjects				
B (Trials)	5	797.20	3.30	.05
A×B	5	352.90	1.46	
C (Measurement intervals)	3	45.91	.58	
A×C	3	46.86	.59	
B×C	15	55.93	1.03	
A×B×C	15	59.64	1.10	
B×Error	90	241.29		
C×Error	54	78.75		
B×C×Error	270	54.12		

Table A-10. A 2 by 6 by 4 (restraint by trials by measurement intervals) analysis of variance summary table comparing the BP responses of the restrained and unrestrained control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Restraint)	1	22.25	.77	
Error	18	28.80		
Within Subjects				
B (Trials)	5	29.75	1.34	
A×B	5	18.72	.84	
C (Measurement intervals)	3	123.43	13.31	.01
A×C	3	13.46	1.45	
B×C	15	10.95	2.18	.01
A×B×C	15	9.42	1.88	.05
B×Error	90	22.04		
C×Error	54	9.27		
B×C×Error	270	5.00		

Table A-11. A 2 by 6 by 2 (conditioning by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the restrained experimental and control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	1398.62	.35	
Error	28	3994.92		
Within Subjects				
B (Trials)	5	592.37	1.18	
A×B	5	169.91	.34	
C (Measurement intervals)	1	25376.40	154.69	.01
A×C	1	948.75	5.78	.05
B×C	5	98.64	.67	
A×B×C	5	91.05	.62	
B×Error	140	498.84		
C×Error	28	164.03		
B×C×Error	140	146.27		

Table A-12. A 2 by 6 by 2 (conditioning by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the restrained experimental and control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	501.65	1.85	
Error	28	270.72		
Within Subjects				
B (Trials)	5	681.93	12.74	.01
A×B	5	53.11	.99	
C (Measurement intervals)	1	945.07	9.65	.01
A×C	1	414.27	4.23	.05
B×C	5	110.98	7.31	.01
A×B×C	5	12.73	.83	
B×Error	140	53.48		
C×Error	28	97.83		
B×C×Error	140	15.17		

Table A-13. A 2 by 6 by 2 (conditioning by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the unrestrained experimental and control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	86.11	.01	
Error	28	7020.86		
Within Subjects				
B (Trials)	5	5589.68	9.37	.01
A×B	5	866.32	1.45	
C (Measurement intervals)	1	29920.90	170.47	.01
A×C	1	369.80	2.10	
B×C	5	50.74	.60	
A×B×C	5	359.24	4.29	.01
B×Error	140	596.13		
C×Error	28	175.51		
B×C×Error	140	83.73		

Table A-14. A 2 by 6 by 2 (conditioning by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the unrestrained experimental and control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	1746.61	2.46	
Error	28	707.68		
Within Subjects				
B (Trials)	5	2011.56	37.90	.01
A×B	5	155.25	2.92	.05
C (Measurement intervals)	1	6048.15	105.85	.01
A×C	1	27.03	.47	
B×C	5	70.89	4.18	.01
A×B×C	5	49.17	2.89	.05
B×Error	140	53.06		
C×Error	28	57.13		
B×C×Error	140	16.95		

Table A-15. A 2 by 6 by 2 (restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the restrained and unrestrained experimental groups during conditioning.

Between Subjects	DF	MS	F	P
A (Restraint)	1	114901.87	21.88	.01
Error	38	5251.38		
Within Subjects				
B (Trials)	5	3686.11	7.28	.01
A×B	5	2158.83	4.26	.01
C (Measurement intervals)	1	38637.37	233.20	.01
A×C	1	156.97	.94	
B×C	5	143.65	1.24	
A×B×C	5	73.63	1.24	
B×Error	190	506.06		
C×Error	38	165.67		
B×C×Error	190	115.07		

Table A-16. A 2 by 6 by 2 (restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the restrained and unrestrained experimental groups during conditioning.

Between Subjects	DF	MS	F	p
A (Restraint)	1	3070.71	6.60	.05
Error	38	464.63		
Within Subjects				
B (Trials)	5	1693.30	31.75	.01
A×B	5	338.97	6.35	.01
C (Measurement intervals)	1	4738.38	75.60	.01
A×C	1	279.53	4.46	.05
B×C	5	125.42	6.62	.01
A×B×C	5	50.51	2.66	.05
B×Error	190	53.31		
C×Error	28	62.67		
B×C×Error	190	18.92		

Table A-17. A 2 by 6 by 2 (restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the restrained and unrestrained control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Restraint)	1	39706.53	6.56	.02
Error	18	6049.40		
Within Subjects				
B (Trials)	5	1107.87	1.74	
A×B	5	265.47	.41	
C (Measurement intervals)	1	16633.35	93.22	.01
A×C	1	1188.15	6.65	.02
B×C	5	139.23	1.21	
A×B×C	5	243.15	2.11	
B×Error	90	634.94		
C×Error	18	178.41		
B×C×Error	90	114.85		

Table A-18. A 2 by 6 by 2 (restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the restrained and unrestrained control groups during conditioning.

Between Subjects	DF	MS	F	p
A (Restraint)	1	8982.08	16.60	.01
Error	18	541.08		
Within Subjects				
B (Trials)	5	733.63	13.79	.01
A×B	5	135.94	2.55	.05
C (Measurement intervals)	1	1263.85	11.62	.01
A×C	1	1152.77	10.59	.01
B×C	5	21.25	2.11	
A×B×C	5	46.59	4.64	.01
B×Error	90	53.18		
C×Error	18	108.75		
B×C×Error	90	10.02		

Table A-19. A 2 by 2 by 2 by 5 by 4 (conditioning by previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR CRs of all groups during the Test Phase.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	127.88	.046	
B (Previous restraint)	1	14035.69	5.061	.05
C (Current restraint)	1	1170.19	.422	
A×B	1	2469.83	.891	
A×C	1	145.19	.052	
B×C	1	1464.22	.528	
A×B×C	1	2026.50	.731	
Error	52	2773.04		
Within Subjects				
D (Trials)	4	512.59	.964	
A×D	4	783.00	1.472	
B×D	4	1013.07	1.905	
C×D	4	1117.28	2.214	
A×B×D	4	104.76	.197	
A×C×D	4	2162.62	4.067	.01
B×C×D	4	165.88	.312	
A×B×C×D	4	41.28	.078	
E (Measurement intervals)	3	1354.91	7.07	.01
A×E	3	73.53	.384	
B×E	3	456.05	2.38	
C×E	3	141.96	.741	
A×B×E	3	192.5	1.005	
A×C×E	3	434.93	2.27	
B×C×E	3	332.66	1.736	
A×B×C×E	3	94.94	.495	

Table A-19 (cont'd.).

Within Subjects (cont'd.).	DF	MS	F	P
D×E	12	268.58	1.70	.05
A×D×E	12	172.43	1.092	
B×D×E	12	196.02	1.241	
C×D×E	12	117.68	.745	
A×B×D×E	12	99.6	.631	
A×C×D×E	12	153.78	.974	
B×C×D×E	12	237.26	1.502	
A×B×C×D×E	12	144.586	.916	
D×Error	208	531.806		
E×Error	156	191.63		
D×E×Error	624	157.918		

Table A-20. A 2 by 2 by 2 by 5 by 4 (conditioning by previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP CRs of all groups during the Test Phase.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	2629.23	9.576	.01
B (Previous restraint)	1	3522.74	12.831	.01
C (Current restraint)	1	577.55	2.104	
A×B	1	892.42	3.250	
A×C	1	43.39	.158	
B×C	1	201.35	.733	
A×B×C	1	45.76	.167	
Error	52	274.559		
Within Subjects				
D (Trials)	4	1102.065	14.211	.01
A×D	4	464.16	5.985	.01
B×D	4	187.293	2.415	.05
C×D	4	82.585	1.065	
A×B×D	4	107.53	1.387	
A×C×D	4	110.44	1.424	
B×C×D	4	41.583	.536	
A×B×C×D	4	68.285	.880	
E (Measurement intervals)	3	368.907	9.840	.01
A×E	3	141.143	3.765	.05
B×E	3	57.91	1.545	
C×E	3	24.227	.646	
A×B×E	3	13.623	.363	
A×C×E	3	15.003	.400	
B×C×E	3	19.72	.526	
A×B×C×E	3	12.613	.336	

Table A-21. A 2 by 2 by 2 by 4 by 4 (conditioning by previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR CRs of all groups during Reconditioning Day 1 (unweighted means).

Between Subjects	DF	MS	F	p
A (Conditioning)	1	31016.67	14.01	.05
B (Previous restraint)	1	4389.27	1.98	
C (Current restraint)	1	5552.2	2.51	
A×B	1	3999.2	1.81	
A×C	1	3093.27	1.397	
B×C	1	22.33	.01	
A×B×C	1	272.2	.123	
Error	52	2214.205		
Within Subjects				
D (Trials)	3	401.02	1.03	
A×D	3	1021.56	2.615	
B×D	3	567.71	1.453	
C×D	3	253.98	.65	
A×B×D	3	260.98	.67	
A×C×D	3	793.2	2.03	
B×C×D	3	316.93	.811	
A×B×C×D	3	23.11	.059	
E (Measurement intervals)	3	1312.31	9.42	.01
A×E	3	1961.04	14.077	.01
B×E	3	172.73	1.24	
C×E	3	693.4	4.977	.01
A×B×E	3	305.089	2.19	
A×C×E	3	274.04	1.967	
B×C×E	3	28.756	.206	
A×B×C×E	3	39.467	.283	

Table A-21 (cont'd.).

Within Subjects (cont'd.).	DF	MS	F	p
D×E	9	80.763	1.476	
A×D×E	9	58.83	1.075	
B×D×E	9	98.948	1.808	
C×D×E	9	67.88	1.24	
A×B×D×E	9	38.99	.713	
A×C×D×E	9	123.55	2.258	.05
B×C×D×E	9	40.163	.734	
A×B×C×D×E	9	63.507	1.16	
D×Error	156	390.626		
E×Error	156	139.312		
D×E×Error	468	54.722		

Table A-22. A 2 by 2 by 2 by 4 by 4 (conditioning by previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP CRs of all groups during Reconditioning Day 1 (unweighted means).

Between Subjects	DF	MS	F	p
A (Conditioning)	1	5748.02	16.399	.01
B (Previous restraint)	1	1435.27	4.095	.05
C (Current restraint)	1	1257.86	3.589	
A×B	1	665.1	1.898	
A×C	1	1526.61	4.355	.05
B×C	1	27.53	.079	
A×B×C	1	39.67	.11	
Error	52	350.51		
Within Subjects				
D (Trials)	3	107.07	1.85	
A×D	3	76.49	1.32	
B×D	3	90.89	1.57	
C×D	3	231.28	3.99	.01
A×B×D	3	49.69	.86	
A×C×D	3	97.52	1.68	
B×C×D	3	69.85	1.205	
A×B×C×D	3	4.51	.078	
E (Measurement intervals)	3	156.697	5.59	.01
A×E	3	20.6	.73	
B×E	3	43.62	1.556	
C×E	3	18.96	.68	
A×B×E	3	34.89	1.24	
A×C×E	3	57.58	2.05	
B×C×E	3	23.76	.85	
A×B×C×E	3	5.38	.19	

Table A-22 (cont'd.).

Within Subjects (cont'd.).	DF	MS	F	p
D×E	9	6.897	.855	
A×D×E	9	7.19	.89	
B×D×E	9	7.98	.99	
C×D×E	9	13.69	1.698	
A×B×D×E	9	4.88	.61	
A×C×D×E	9	15.74	1.95	.05
B×C×D×E	9	8.48	1.05	
A×B×C×D×E	9	3.38	.42	
D×Error	156	57.963		
E×Error	156	28.042		
D×E×Error	468	8.062		

Table A-23. A 2 by 2 by 4 by 4 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR CRs of the previously restrained experimental and control groups during Reconditioning Day 2 (unweighted means).

Between Subjects	DF	MS	F	p
A (Conditioning)	1	10773.60	3.42	
B (Current restraint	1	7392.6	2.35	
A×B	1	7661.40	2.43	
Error	26	3144.18		
Within Subjects				
C (Trials)	3	960.89	3.93	.05
A×C	3	692.50	2.83	.05
B×C	3	366.69	1.50	
A×B×C	3	408.70	1.67	
D (Measurement intervals)	3	744.24	5.72	.01
A×D	3	659.05	5.06	.01
B×D	3	125.69	.96	
A×B×D	3	175.50	1.34	
C×D	9	58.81	.95	
A×C×D	9	108.88	1.93	.05
B×C×D	9	86.53	1.53	
A×B×C×D	9	33.66	.59	
C×Error	78	244.45		
D×Error	78	130.11		
C×D×Error	234	56.20		

Table A-24. A 2 by 2 by 4 by 4 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP CRs of the previously restrained experimental and control groups during Reconditioning Day 2 (unweighted means).

Between Subjects	DF	MS	F	p
A (Conditioning)	1	2672.46	9.85	.01
B (Current restraint)	1	162.36	.59	
A×B	1	974.45	3.59	
Error	26	271.28		
Within Subjects				
C (Trials)	3	63.46	1.86	
A×C	3	21.71	.63	
B×C	3	15.06	.44	
A×B×C	3	20.81	.61	
D (Measurement intervals)	3	130.28	5.49	.01
A×D	3	27.58	1.16	
B×D	3	6.29	.26	
A×B×D	3	46.63	1.96	
C×D	9	5.80	.70	
A×C×D	9	10.13	1.23	
B×C×D	9	11.11	1.35	
A×B×C×D	9	2.56	.31	
C×Error	78	34.05		
D×Error	78	23.69		
C×D×Error	234	8.19		

Table A-25. A 2 by 2 by 4 by 4 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR CRs of the previously unrestrained experimental and control groups during Reconditioning Day 2 (unweighted means).

Between Subjects	DF	MS	F	p
A (Conditioning)	1	25083.22	10.91	.01
B (Current restraint)	1	11836.12	5.15	.05
A×B	1	4965.63	2.16	
Error	26	2297.88		
Within Subjects				
C (Trials)	3	78.51	.17	
A×C	3	321.64	.69	
B×C	3	307.77	.66	
A×B×C	3	150.53	.32	
D (Measurement intervals)	3	998.46	5.77	.01
A×D	3	1830.68	10.58	.01
B×D	3	930.41	5.37	.01
A×B×D	3	235.54	1.36	
C×D	9	57.08	.88	
A×C×D	9	28.45	.44	
B×C×D	9	113.74	1.76	
A×B×C×D	9	79.42	1.22	
C×Error	78	461.29		
D×Error	78	172.95		
C×D×Error	234	64.60		

Table A-26. A 2 by 2 by 4 by 4 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP CRs of the previously unrestrained experimental and control groups during Reconditioning Day 2 (unweighted means).

Between Subjects	DF	MS	F	p
A (Conditioning)	1	5974.96	15.25	.01
B (Current restraint)	1	1019.44	2.60	
A×B	1	1512.10	3.86	
Error	26	391.63		
Within Subjects				
C (Trials)	3	92.84	3.32	.05
A×C	3	24.86	.89	
B×C	3	109.84	3.93	.05
A×B×C	3	27.93	1.00	
D (Measurement intervals)	3	80.41	2.21	
A×D	3	12.33	.33	
B×D	3	56.64	1.55	
A×B×D	3	21.69	.59	
C×D	9	11.15	1.83	
A×C×D	9	10.55	1.73	
B×C×D	9	4.47	.74	
A×B×C×D	9	3.56	.58	
C×Error	78	27.92		
D×Error	78	36.37		
C×D×Error	234	6.08		

Table A-20 (cont'd.).

Within Subjects (cont'd.).	DF	MS	F	p
D×E	12	33.167	3.01	.01
A×D×E	12	.967	.09	
B×D×E	12	10.156	.92	
C×D×E	12	10.538	.96	
A×B×D×E	12	11.146	1.01	
A×C×D×E	12	10.177	.92	
B×C×D×E	12	7.307	.66	
A×B×C×D×E	12	5.634	.51	
D×Error	208	77.553		
E×Error	156	37.49		
D×E×Error	624	11.024		

Table A-27. A 2 by 2 by 4 by 4 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR CRs of the previously restrained and previously unrestrained experimental groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	4609.07	1.25	
B (Current restraint)	1	48624.47	13.27	.01
A×B	1	64.07	.01	
Error	36	3661.74		
Within Subjects				
C (Trials)	3	1002.05	2.31	
A×C	3	852.05	1.97	
B×C	3	644.00	1.48	
A×B×C	3	275.90	.63	
D (Measurement intervals)	3	4969.66	25.31	.01
A×D	3	783.98	3.99	.01
B×D	3	1910.28	9.73	.01
A×B×D	3	197.31	1.00	
C×D	9	78.81	1.22	
A×C×D	9	61.53	.95	
B×C×D	9	124.90	1.94	
A×B×C×D	9	25.19	.39	
C×Error	108	432.27		
D×Error	108	196.31		
C×D×Error	324	64.34		

Table A-28. A 2 by 2 by 4 by 4 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP CRs of the previously restrained and previously unrestrained experimental groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	P
A (Previous restraint)	1	752.57	1.67	
B (Current restraint)	1	5191.84	11.56	.01
A×B	1	331.84	.73	
Error	36	448.97		
Within Subjects				
C (Trials)	3	142.29	4.40	.01
A×C	3	50.34	1.55	
B×C	3	56.10	1.73	
A×B×C	3	36.66	1.13	
D (Measurement intervals)	3	187.31	5.07	.01
A×D	3	26.28	.71	
B×D	3	136.17	3.69	.05
A×B×D	3	12.32	.33	
C×D	9	6.67	.90	
A×C×D	9	4.43	.60	
B×C×D	9	2.85	.38	
A×B×C×D	9	5.81	.78	
C×Error	108	32.27		
D×Error	108	36.87		
C×D×Error	324	7.37		

Table A-29. A 2 by 2 by 4 by 4 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR responses of the previously restrained and previously unrestrained control groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	43.58	.08	
B (Current restraint)	1	238.78	.48	
A×B	1	292.56	.59	
Error	16	491.55		
Within Subjects				
C (Trials)	3	525.27	3.38	.05
A×C	3	111.17	.71	
B×C	3	268.97	1.73	
A×B×C	3	205.47	1.32	
D (Measurement intervals)	3	447.59	10.49	.01
A×D	3	15.83	.37	
B×D	3	46.72	1.09	
A×B×D	3	60.00	1.40	
C×D	9	49.16	.97	
A×C×D	9	73.58	1.45	
B×C×D	9	48.67	.96	
A×B×C×D	9	110.41	2.17	.05
C×Error	48	155.09		
D×Error	48	42.64		
C×D×Error	144	50.66		

Table A-30. A 2 by 2 by 4 by 4 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP responses of the previously restrained and previously unrestrained control groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	25.69	.56	
B (Current restraint)	1	116.65	2.56	
A×B	1	28.80	.63	
Error	16	45.41		
Within Subjects				
C (Trials)	3	36.23	1.28	
A×C	3	15.72	.55	
B×C	3	73.71	2.62	
A×B×C	3	11.17	.39	
D (Measurement intervals)	3	76.67	5.80	.01
A×D	3	7.81	.59	
B×D	3	4.29	.32	
A×B×D	3	23.27	1.76	
C×D	9	8.24	1.24	
A×C×D	9	13.17	1.98	
B×C×D	9	4.54	.68	
A×B×C×D	9	7.42	1.11	
C×Error	48	28.09		
D×Error	48	13.20		
C×D×Error	144	6.63		

Table A-31. A 2 by 2 by 4 by 2 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the previously restrained experimental and control groups during Reconditioning Day 1.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	1140.83	.49	
B (Current restraint)	1	21965.06	9.58	.01
A×B	1	330.00	.14	
Error	26	2292.85		
Within Subjects				
C (Trials)	3	3920.45	9.20	.01
A×C	3	210.71	.49	
B×C	3	1936.32	4.54	.01
A×B×C	3	338.11	.79	
D (Measurement intervals)	1	13771.35	65.57	.01
A×D	1	6.07	.03	
B×D	1	33.75	.17	
A×B×D	1	.67	.00	
C×D	3	236.41	3.34	.05
A×C×D	3	38.60	.54	
B×C×D	3	41.21	.58	
A×B×C×D	3	30.80	.43	
C×Error	78	425.94		
D×Error	26	197.94		
C×D×Error	78	70.59		

Table A-32. A 2 by 2 by 4 by 2 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the previously restrained experimental and control groups during Reconditioning Day 1.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	204.41	.92	
B (Current restraint)	1	456.03	2.06	
A×B	1	7.76	.03	
Error	26	220.95		
Within Subjects				
C (Trials)	3	676.24	15.36	.01
A×C	3	17.76	.40	
B×C	3	57.54	1.30	
A×B×C	3	9.92	.22	
D (Measurement intervals)	1	1687.89	28.19	.01
A×D	1	35.91	.59	
B×D	1	626.45	10.46	.01
A×B×D	1	8.26	.13	
C×D	3	87.09	5.67	.01
A×C×D	3	15.56	1.01	
B×C×D	3	20.89	1.36	
A×B×C×D	3	15.08	.98	
C×Error	78	44.00		
D×Error	26	59.87		
C×D×Error	78	15.35		

Table A-33. A 2 by 2 by 4 by 2 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the previously restrained experimental and control groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	336.67	.17	
B (Current restraint)	1	27606.15	14.32	.01
A×B	1	67.50	.03	
Error	26	1927.20		
Within Subjects				
C (Trials)	3	280.50	.84	
A×C	3	131.47	.39	
B×C	3	548.05	1.65	
A×B×C	3	272.30	.82	
D (Measurement intervals)	1	12013.25	94.03	.00001
A×D	1	39.67	.31	
B×D	1	163.35	1.27	
A×B×D	1	81.67	.63	
C×D	3	89.75	1.14	
A×C×D	3	40.67	.51	
B×C×D	3	118.15	1.50	
A×B×C×D	3	27.87	.35	
C×Error	78	331.29		
D×Error	26	127.74		
C×D×Error	78	78.27		

Table A-34. A 2 by 2 by 4 by 2 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the previously restrained experimental and control groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	P
A (Conditioning)	1	15.30	.06	
B (Current restraint)	1	420.82	1.71	
A×B	1	85.99	.35	
Error	26	254.63		
Within Subjects				
C (Trials)	3	124.37	3.76	.01
A×C	3	53.08	1.60	
B×C	3	7.50	.22	
A×B×C	3	56.53	1.70	
D (Measurement intervals)	1	336.54	4.17	
A×D	1	13.30	.16	
B×D	1	21.60	.26	
A×B×D	1	.57	.00	
C×D	3	81.54	7.84	.01
A×C×D	3	1.21	.11	
B×C×D	3	19.36	1.86	
A×B×C×D	3	11.73	1.12	
C×Error	78	33.06		
D×Error	26	80.64		
C×D×Error	78	10.39		

Table A-35. A 2 by 2 by 4 by 2 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the previously unrestrained experimental and control groups during Reconditioning Day 1.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	4159.51	1.85	
B (Current restraint)	1	62403.72	27.88	.01
A×B	1	3167.26	1.41	
Error	26	2237.68		
Within Subjects				
C (Trials)	3	625.90	1.36	
A×C	3	588.36	1.27	
B×C	3	855.85	1.86	
A×B×C	3	1245.51	2.70	
D (Measurement intervals)	1	9677.40	68.37	.01
A×D	1	459.75	3.06	
B×D	1	1215.00	8.58	.01
A×B×D	1	780.30	5.51	.05
C×D	3	179.80	3.23	.05
A×C×D	3	174.20	3.13	.05
B×C×D	3	45.40	.81	
A×B×C×D	3	32.90	.59	
C×Error	78	459.75		
D×Error	26	141.54		
C×D×Error	78	55.60		

Table A-36. A 2 by 2 by 4 by 2 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the previously unrestrained experimental and control groups during Reconditioning Day 1.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	13.15	.03	
B (Current restraint)	1	93.32	.28	
A×B	1	820.92	2.49	
Error	26	330.08		
Within Subjects				
C (Trials)	3	684.57	11.89	.01
A×C	3	185.21	3.21	.05
B×C	3	111.46	1.93	
A×B×C	3	73.37	1.27	
D (Measurement intervals)	1	819.25	12.25	.01
A×D	1	2.56	.03	
B×D	1	378.85	5.66	.05
A×B×D	1	171.56	2.56	
C×D	3	23.55	1.91	
A×C×D	3	8.03	.65	
B×C×D	3	26.98	2.19	
A×B×C×D	3	17.22	1.39	
C×Error	78	57.55		
D×Error	26	66.83		
C×D×Error	78	78.00		

Table A-37. A 2 by 2 by 4 by 2 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the previously unrestrained experimental and control groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	35063.55	14.74	.01
B (Current restraint)	1	45581.48	19.16	.01
A×B	1	16164.60	6.79	.05
Error	26	2378.41		
Within Subjects				
C (Trials)	3	618.55	1.87	
A×C	3	471.27	1.43	
B×C	3	392.93	1.19	
A×B×C	3	79.12	.24	
D (Measurement intervals)	1	4580.63	32.04	.01
A×D	1	2.06	.01	
B×D	1	67.73	.47	
A×B×D	1	738.79	5.16	.01
C×D	3	49.73	.69	
A×C×D	3	31.76	.44	
B×C×D	3	52.23	.73	
A×B×C×D	3	77.19	1.07	
C×Error	78	329.49		
D×Error	26	142.95		
C×D×Error	78	71.54		

Table A-38. A 2 by 2 by 4 by 2 (conditioning by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the previously unrestrained experimental and control groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	542.45	.81	
B (Current restraint)	1	1154.35	1.72	
A×B	1	389.55	.58	
Error	26	667.76		
Within Subjects				
C (Trials)	3	119.21	3.03	.05
A×C	3	54.91	1.39	
B×C	3	28.67	.73	
A×B×C	3	47.85	1.21	
D (Measurement intervals)	1	.39	.00	
A×D	1	393.85	2.74	
B×D	1	.05	.00	
A×B×D	1	116.86	.81	
C×D	3	15.29	1.20	
A×C×D	3	4.40	.31	
B×C×D	3	30.68	2.42	
A×B×C×D	3	22.96	1.81	
C×Error	78	39.27		
D×Error	26	143.70		
C×D×Error	78	12.66		

Table A-39. A 2 by 2 by 4 by 2 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the previously restrained and previously unrestrained experimental groups during Reconditioning Day 1.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	4343.87	1.73	
B (Current restraint)	1	60197.87	24.05	.01
A×B	1	7930.15	3.16	
Error	36	2502.35		
Within Subjects				
C (Trials)	3	2841.47	6.14	.01
A×C	3	1011.47	2.18	
B×C	3	3330.77	7.20	.01
A×B×C	3	41.80	.09	
D (Measurement intervals)	1	13235.51	65.91	.01
A×D	1	340.31	1.69	
B×D	1	137.81	.68	
A×B×D	1	32.51	.16	
C×D	3	180.41	2.91	.05
A×C×D	3	82.01	1.32	
B×C×D	3	75.71		
A×B×C×D	3	11.21	.18	
C×Error	108	462.42		
D×Error	36	200.78		
C×D×Error	108	61.92		

Table A-40. A 2 by 2 by 4 by 2 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the previously restrained and previously unrestrained experimental groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	11430.17	4.91	.05
B (Current restraint)	1	75322.46	32.39	.01
A×B	1	5758.76	2.47	
Error	36	2324.92		
Within Subjects				
C (Trials)	3	379.15	.94	
A×C	3	809.01	2.01	
B×C	3	428.03	1.06	
A×B×C	3	688.28	1.71	
D (Measurement intervals)	1	9840.15	78.37	.01
A×D	1	493.76	3.93	
B×D	1	147.83	1.17	
A×B×D	1	381.71	3.04	
C×D	3	64.95	.92	
A×C×D	3	34.76	.49	
B×C×D	3	9.38	.13	
A×B×C×D	3	132.86	1.88	
C×Error	108	400.87		
D×Error	36	125.55		
C×D×Error	108	70.51		

Table A-41. A 2 by 2 by 4 by 2 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the previously restrained and previously unrestrained experimental groups during Reconditioning Day 1.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	399.68	1.20	
B (Current restraint)	1	25.72	.07	
A×B	1	299.67	.90	
Error	36	332.05		
Within Subjects				
C (Trials)	3	1173.84	25.11	.01
A×C	3	8.89	.19	
B×C	3	50.73	1.08	
A×B×C	3	58.52	1.25	
D (Measurement intervals)	1	1878.84	26.50	.01
A×D	1	80.77	1.13	
B×D	1	462.89	6.53	.05
A×B×D	1	94.75	1.33	
C×D	3	61.40	3.91	.05
A×C×D	3	39.47	2.51	
B×C×D	3	33.96	2.16	
A×B×C×D	3	9.47	.60	
C×Error	108	46.75		
D×Error	36	70.87		
C×D×Error	108	15.67		

Table A-42. A 2 by 2 by 4 by 2 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the previously restrained and previously unrestrained experimental groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	79.65	.17	
B (Current restraint)	1	739.17	1.62	
A×B	1	16.57	.03	
Error	36	455.54		
Within Subjects				
C (Trials)	3	91.72	2.40	
A×C	3	26.36	.69	
B×C	3	18.21	.47	
A×B×C	3	12.22	.32	
D (Measurement intervals)	1	.40	.00	
A×D	1	308.68	2.16	
B×D	1	56.84	.39	
A×B×D	1	2.41	.01	
C×D	3	45.94	4.09	.05
A×C×D	3	9.09	.81	
B×C×D	3	8.11	.72	
A×B×C×D	3	31.07	2.76	
C×Error	108	38.05		
D×Error	36	142.67		
C×D×Error	108	11.22		

Table A-43. A 2 by 2 by 4 by 2 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the previously restrained and previously unrestrained control groups during Reconditioning Day 1.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	400.05	.23	
B (Current restraint)	1	19735.80	11.41	.01
A×B	1	2.25	.00	
Error	16	1729.31		
Within Subjects				
C (Trials)	3	1170.43	2.93	.05
A×C	3	322.03	.80	
B×C	3	521.18	1.30	
A×B×C	3	482.03	1.20	
D (Measurement intervals)	1	10304.10	103.14	.01
A×D	1	8.10	.08	
B×D	1	1102.50	11.03	.01
A×B×D	1	756.90	7.57	.05
C×D	3	283.90	4.31	.01
A×C×D	3	82.70	1.25	
B×C×D	3	14.30	.21	
A×B×C×D	3	49.10		
C×Error	48	398.80		
D×Error	16	99.90		
C×D×Error	48	65.75		

Table A-44. A 2 by 2 by 4 by 2 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the HR URs of the previously restrained and previously unrestrained control groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	4995.83	2.82	
B (Current restraint)	1	5904.90	3.34	
A×B	1	2433.60	1.37	
Error	16	1765.54		
Within Subjects				
C (Trials)	3	91.57	.53	
A×C	3	222.07	1.29	
B×C	3	76.05	.44	
A×B×C	3	100.05	.58	
D (Measurement intervals)	1	5904.90	37.51	.01
A×D	1	396.90	2.52	
B×D	1	518.40	3.29	
A×B×D	1	3.60	.02	
C×D	3	101.70	1.19	
A×C×D	3	10.50	.12	
B×C×D	3	68.40	.80	
A×B×C×D	3	64.80	.76	
C×Error	48	171.79		
D×Error	16	157.38		
C×D×Error	48	84.78		

Table A-45. A 2 by 2 by 4 by 2 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the previously restrained and previously unrestrained control groups during Reconditioning Day 1.

Between Subjects	DF	MS	F	P
A (Previous restraint)	1	1.92	.01	
B (Current restraint)	1	949.45	6.46	.05
A×B	1	103.2	.7	
Error	16	146.77		
Within Subjects				
C (Trials)	3	292.03	4.87	.05
A×C	3	89.03	1.48	
B×C	3	115.85	1.93	
A×B×C	3	27.18	.45	
D (Measurement intervals)	1	579.50	12.48	.01
A×D	1	6.51	.14	
B×D	1	579.19	12.47	.01
A×B×D	1	48.31	1.04	
C×D	3	28.94	2.99	.01
A×C×D	3	4.42	.45	
B×C×D	3	35.16	3.63	.01
A×B×C×D	3	1.57	.16	
C×Error	48	59.87		
D×Error	16	46.42		
C×D×Error	48	9.67		

Table A-46. A 2 by 2 by 4 by 2 (previous restraint by current restraint by trials by measurement intervals) analysis of variance summary table comparing the BP URs of the previously restrained and previously unrestrained control groups during Reconditioning Day 2.

Between Subjects	DF	MS	F	p
A (Previous restraint)	1	533.11	1.16	
B (Current restraint)	1	800.13	1.74	
A×B	1	494.84	1.07	
Error	16	459.29		
Within Subjects				
C (Trials)	3	230.74	7.22	.01
A×C	3	2.76	.08	
B×C	3	56.25	1.76	
A×B×C	3	53.86	1.68	
D (Measurement intervals)	1	432.43	9.92	.01
A×D	1	2.57	.05	
B×D	1	21.96	.50	
A×B×D	1	57.86	1.32	
C×D	3	38.74	3.17	.05
A×C×D	3	8.30	.67	
B×C×D	3	44.08	3.60	.05
A×B×C×D	3	1.47	.12	
C×Error	48	31.91		
D×Error	16	43.55		
C×D×Error	48	12.21		

Table A-47. A 2 by 2 by 6 (restraint by conditioning by trials) analysis of variance summary table comparing the baselevel HR of the restrained and unrestrained experimental and control groups during the Conditioning Phase.

Between Subjects	DF	MS	F	p
A (Restraint)	1	241491.60	32.44	.01
B (Conditioning)	1	73568.45	9.88	.01
A×B	1	8757.11	1.17	
Error	56	7442.74		
Within Subjects				
C (Trials)	5	4147.40	7.80	.01
A×C	5	4813.00	9.06	.01
B×C	5	551.68	1.03	
A×B×C	5	3226.20	6.07	.01
C×Error	280	531.21		

Table A-48. A 2 by 2 by 6 (restraint by conditioning by trials) analysis of variance summary table comparing the baselevel BP of the restrained and unrestrained experimental and control groups during the Conditioning Phase.

Between Subjects	DF	MS	F	p
A (Restraint)	1	2439.84	2.74	
B (Conditioning)	1	845.43	.94	
A×B	1	366.36	.41	
Error	56	890.17		
Within Subjects				
C (Trials)	5	829.89	16.57	.01
A×C	5	85.08	1.69	
B×C	5	12.01	.23	
A×B×C	5	6.64	.13	
C×Error	280	50.06		

Table A-49. A 2 by 2 by 4 (conditioning by current restraint by trials) analysis of variance summary table comparing baselevel HR of the previously restrained experimental and control groups during reconditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	34222.51	3.71	
B (Current restraint)	1	16533.60	1.79	
A×B	1	155.26	.01	
Error	26	9201.11		
Within Subjects				
C (Trials)	7	2362.58	2.86	
A×C	7	605.26	.73	
B×C	7	1526.55	1.84	
A×B×C	7	1495.75	1.81	
C×Error	182	825.83		

Table A-50. A 2 by 2 by 4 (conditioning by current restraint by trials) analysis of variance table comparing baselevel HR of the previously unrestrained experimental and control groups during reconditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	35201.46	4.64	.05
B (Current restraint)	1	33219.47	4.37	.05
A×B	1	2005.54	.26	
Error	26	7585.42		
Within Subjects				
C (Trials)	7	1863.53	2.13	
A×C	7	3869.93	4.43	.01*
B×C	7	4464.42	5.11	.01
A×B×C	7	966.45	1.10	
C×Error	182	873.09		

Table A-51. A 2 by 2 by 4 (conditioning by current restraint by trials) analysis of variance summary table comparing baselevel BP of the previously restrained experimental and control groups during reconditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	28595.34	11.65	.01
B (Current restraint)	1	4253.86	1.73	
A×B	1	8374.30	3.51	
Error	26	2453.16		
Within Subjects				
C (Trials)	7	255.23	1.13	
A×C	7	32.95	.14	
B×C	7	144.50	.64	
A×B×C	7	62.54	.27	
C×Error	182	225.62		

Table A-52. A 2 by 2 by 4 (conditioning by current restraint by trials) analysis of variance summary table comparing baselevel BP of the previously unrestrained experimental and control groups during reconditioning.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	12615.12	6.42	.05
B (Current restraint)	1	104.22	.05	
A×B	1	347.86	.17	
Error	26	1964.92		
Within Subjects				
C (Trials)	7	162.41	.65	
A×C	7	768.79	3.09	.01
B×C	7	4412.30	1.66	
A×B×C	7	249.15	1.00	
C×Error	182	248.17		

Table A-53. A 2 by 2 by 2 by 4 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the HR CRs of the restrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	465.15	1.06	
B (Previous restraint)	1	393.90	.90	
A×B	1	42.26	.09	
Error	26	434.84		
Within Subjects				
C (Drug administration)	1	3097.66	16.95	.01
A×C	1	1243.04	6.80	.05
B×C	1	196.94	1.07	
A×B×C	1	143.35	.78	
D (Measurement intervals)	3	42.06	1.09	
A×D	3	40.94	1.07	
B×D	3	26.44	.69	
A×B×D	3	41.77	1.09	
C×D	3	39.88	.91	
A×C×D	3	74.71	1.70	
B×C×D	3	60.20	1.37	
A×B×C×D	3	17.20	.39	
C×Error	26	182.72		
D×Error	78	38.26		
C×D×Error	78	43.81		

Table A-54. A 2 by 2 by 2 by 4 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the BP CRs of the restrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	709.99	16.37	.01
B (Previous restraint)	1	164.01	3.78	
A×B	1	52.29	1.20	
Error	26	43.35		
Within Subjects				
C (Drug administration)	1	.01	.00	
A×C	1	5.37	.31	
B×C	1	9.11	.53	
A×B×C	1	10.37	.61	
D (Measurement intervals)	3	93.32	14.85	.01
A×D	3	18.96	3.01	.05
B×D	3	11.90	1.89	
A×B×D	3	1.81	.28	
C×D	3	22.15	6.15	.01
A×C×D	3	10.89	3.02	.05
B×C×D	3	7.76	2.15	
A×B×C×D	3	5.75	1.59	
C×Error	26	16.97		
D×Error	78	6.28		
C×D×Error	78	3.59		

Table A-55. A 2 by 2 by 2 by 4 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the HR CRs of the unrestrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	8296.37	7.16	.05
B (Previous restraint)	1	72.44	.06	
A×B	1	94.48	.08	
Error	26	1157.72		
Within Subjects				
C (Drug administration)	1	9506.96	18.81	.01
A×C	1	3244.28	6.42	.05
B×C	1	869.74	1.72	
A×B×C	1	990.09	1.95	
D (Measurement intervals)	3	1176.29	14.08	.01
A×D	3	597.34	7.15	.01
B×D	3	22.73	.27	
A×B×D	3	70.96	.84	
C×D	3	153.92	2.47	
A×C×D	3	165.02	2.65	
B×C×D	3	224.15	3.61	.05
A×B×C×D	3	180.04	2.90	.05
C×Error	26	505.30		
D×Error	78	83.48		
C×D×Error	78	62.06		

Table A-56. A 2 by 2 by 2 by 4 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the BP CRs of the unrestrained experimental and control groups during the sympahtetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	5056.81	30.08	.01
B (Previous restraint)	1	621.00	3.69	
A×B	1	132.79	.78	
Error	26	168.11		
Within Subjects				
C (Drug administration)	1	490.83	5.45	.05
A×C	1	45.23	.50	
B×C	1	80.92	.89	
A×B×C	1	1.07	.01	
D (Measurement intervals)	3	60.74	3.93	
A×D	3	97.08	6.28	.01
B×D	3	5.02	.32	
A×B×D	3	3.63	.23	
C×D	3	8.44	1.16	
A×C×D	3	.51	.07	
B×C×D	3	6.34	.87	
A×B×C×D	3	3.50	.48	
C×Error	26	90.05		
D×Error	78	15.44		
C×D×Error	78	7.26		

Table A-57. A 2 by 2 by 2 by 2 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the HR URs of the restrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	243.49	.35	
B (Previous restraint)	1	4.20	.00	
A×B	1	143.59	.20	
Error	26	694.98		
Within Subjects				
C (Drug administration)	1	4141.28	12.06	.01
A×C	1	41.20	.12	
B×C	1	22.94	.06	
A×B×C	1	100.93	.29	
D (Measurement intervals)	1	2850.90	36.02	.01
A×D	1	63.70	.80	
B×D	1	29.99	.37	
A×B×D	1	31.00	.39	
C×D	1	16.85	.28	
A×C×D	1	4.77	.08	
B×C×D	1	119.94	2.05	
A×B×C×D	1	2.87	.04	
C×Error	26	343.21		
D×Error	26	79.12		
C×D×Error	26	58.24		

Table A-58. A 2 by 2 by 2 by 2 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the BP URs of the restrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	383.77	4.56	
B (Previous restraint)	1	191.31	2.27	
A×B	1	28.93	.34	
Error	26	84.07		
Within Subjects				
C (Drug administration)	1	563.24	14.70	.01
A×C	1	78.55	2.05	
B×C	1	1.94	.05	
A×B×C	1	222.54	5.80	.05
D (Measurement intervals)	1	11.12	1.37	
A×D	1	.86	.00	
B×D	1	11.97	1.47	
A×B×D	1	.00	.00	
C×D	1	4.31	.70	
A×C×D	1	.00	.00	
B×C×D	1	9.29	1.51	
A×B×C×D	1	.00	.00	
C×Error	26	38.30		
D×Error	26	8.11		
C×D×Error	26	6.11		

Table A-59. A 2 by 2 by 2 by 2 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the HR URs of the unrestrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	802.05	.67	
B (Previous restraint)	1	109.06	.09	
A×B	1	270.89	.22	
Error	26	1180.43		
Within Subjects				
C (Drug administration)	1	27395.03	46.01	.01
A×C	1	709.12	1.19	
B×C	1	4032.16	6.77	.05
A×B×C	1	312.22	.52	
D (Measurement intervals)	1	4409.98	79.62	.01
A×D	1	28.38	.51	
B×D	1	79.21	1.43	
A×B×D	1	123.98	2.23	
C×D	1	16.86	.30	
A×C×D	1	33.76	.61	
B×C×D	1	16.86	.30	
A×B×C×D	1	8.44	.15	
C×Error	26	595.36		
D×Error	26	55.38		
C×D×Error	26	54.67		

Table A-60. A 2 by 2 by 2 by 2 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the BP URs of the unrestrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	6.68	.03	
B (Previous restraint)	1	1.52	.00	
A×B	1	1.33	.00	
Error	26	200.26		
Within Subjects				
C (Drug administration)	1	217.27	2.41	
A×C	1	.00	.00	
B×C	1	314.70	3.49	
A×B×C	1	37.93	.42	
D (Measurement intervals)	1	32.33	.50	
A×D	1	10.87	.17	
B×D	1	40.03	.63	
A×B×D	1	30.65	.48	
C×D	1	151.53	7.66	.05
A×C×D	1	3.79	.19	
B×C×D	1	34.74	1.75	
A×B×C×D	1	7.16	.36	
C×Error	26	89.92		
D×Error	26	63.52		
C×D×Error	26	19.78		

Table A-61. A 2 by 2 by 2 by 8 (conditioning by previous restraint by drug by trials) analysis of variance summary table comparing base-level HR of the restrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	36660.99	2.79	
B (Previous restraint)	1	18843.86	1.43	
A×B	1	3517.08	.26	
Error	26	13126.32		
Within Subjects				
C (Drug administration)	1	245956.05	28.98	.01
A×C	1	14589.90	1.65	
B×C	1	3037.61	.34	
A×B×C	1	3517.08	.39	
D (Trials)	7	561.81	1.59	
A×D	7	236.71	.67	
B×D	7	216.54	.61	
A×B×D	7	233.42	.66	
C×D	7	604.80	1.76	
A×C×D	7	235.70	.68	
B×C×D	7	304.40	.89	
A×B×C×D	7	143.16	.41	
C×Error	26	8796.32		
D×Error	182	352.97		
C×D×Error	182	341.79		

Table A-62. A 2 by 2 by 2 by 8 (conditioning by previous restraint by drug by trials) analysis of variance summary table comparing base-level HR of the unrestrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	108215.68	4.75	.05
B (Previous restraint	1	69570.73	3.05	
A×B	1	63741.75	2.80	
Error	26	22758.39		
Within Subjects				
C (Drug administration)	1	64954.71	8.13	.01
A×C	1	9421.93	1.18	
B×C	1	16611.69	2.08	
A×B×C	1	3991.46	.50	
D (Trials)	7	1423.12	3.10	.05
A×D	7	334.47	.72	
B×D	7	1336.80	2.91	
A×B×D	7	736.19	1.60	
C×D	7	1802.84	3.42	.05
A×C×D	7	836.97	1.58	
B×C×D	7	879.00	1.66	
A×B×C×D	7	455.61	.86	
C×Error	26	7980.89		
D×Error	182	458.70		
C×D×Error	182	526.65		

Table A-63. A 2 by 2 by 2 by 8 (conditioning by previous restraint by drug by trials) analysis of variance summary table comparing base-level BP of the restrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	1551.57	.27	
B (Previous restraint)	1	4747.12	.83	
A×B	1	5469.85	.95	
Error	26	5717.18		
Within Subjects				
C (Drug administration)	1	16162.16	21.76	.01
A×C	1	329.87	.44	
B×C	1	20.77	.02	
A×B×C	1	496.57	.66	
D (Trials)	7	32.60	.72	
A×D	7	41.89	.92	
B×D	7	43.81	.96	
A×B×D	7	36.17	.79	
C×D	7	91.45	2.10	
A×C×D	7	97.98	2.25	
B×C×D	7	50.94	1.17	
A×B×C×D	7	45.53	1.04	
C×Error	26	742.68		
D×Error	182	45.27		
C×D×Error	182	43.36		

Table A-64. A 2 by 2 by 2 by 8 (conditioning by previous restraint by drug by trials) analysis of variance summary table comparing base-level BP of the unrestrained experimental and control groups during the sympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	94224.09	12.67	.01
B (Previous restraint)	1	259.74	.03	
A×B	1	18461.99	2.48	
Error	26	7434.91		
Within Subjects				
C (Drug administration)	1	9093.59	10.45	.01
A×C	1	214.90	.24	
B×C	1	1003.75	1.15	
A×B×C	1	6.83	.00	
D (Trials)	7	85.11	.44	
A×D	7	134.12	.70	
B×D	7	175.90	.92	
A×B×D	7	107.01	.56	
C×D	7	518.95	3.71	.05
A×C×D	7	211.83	1.51	
B×C×D	7	359.42	2.57	
A×B×C×D	7	246.17	1.76	
C×Error	26	859.74		
D×Error	182	190.08		
C×D×Error	182	139.80		

Table A-65. A 2 by 2 by 2 by 4 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the HR CRs of the restrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	768.46	1.55	
B (Previous restraint)	1	627.26	1.26	
A×B	1	26.32	.05	
Error	26	494.26		
Within Subjects				
C (Drug administration)	1	342.67	1.87	
A×C	1	26.34	.14	
B×C	1	236.05	1.29	
A×B×C	1	143.35	.78	
D (Measurement intervals)	3	286.15	3.96	.05
A×D	3	335.57	4.65	.05
B×D	3	6.57	.09	
A×B×D	3	52.72	.73	
C×D	3	134.98	4.12	.05
A×C×D	3	33.17	1.01	
B×C×D	3	21.45	.65	
A×B×C×D	3	50.83		
C×Error	26	182.59		
D×Error	78	72.10		
C×D×Error	78	32.73		

Table A-66. A 2 by 2 by 2 by 4 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the BP CRs of the restrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	241.30	6.40	.05
B (Previous restraint)	1	11.28	.29	
A×B	1	.62	.01	
Error	26	37.74		
Within Subjects				
C (Drug administration)	1	7.90	.46	
A×C	1	.58	.03	
B×C	1	13.48	.78	
A×B×C	1	10.60	.62	
D (Measurement intervals)	3	111.67	10.07	.01
A×D	3	55.28	4.98	.01
B×D	3	.61	.05	
A×B×D	3	5.42	.48	
C×D	3	2.76	.73	
A×C×D	3	1.75	.46	
B×C×D	3	1.96	.52	
A×B×C×D	3	2.23	.59	
C×Error	26	17.07		
D×Error	78	11.08		
C×D×Error	78	3.75		

Table A-67. A 2 by 2 by 2 by 4 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the HR CRs of the unrestrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	13586.10	8.11	.01
B (Previous restraint)	1	80.35	.04	
A×B	1	242.43	.14	
Error	26	1674.52		
Within Subjects				
C (Drug administration)	1	1794.43	3.89	
A×C	1	959.45	2.13	
B×C	1	36.66	.08	
A×B×C	1	373.77	.83	
D (Measurement intervals)	3	2589.29	20.50	.01
A×D	3	1365.64	10.81	.01
B×D	3	57.64	.45	
A×B×D	3	42.64	.33	
C×D	3	10.46	.27	
A×C×D	3	20.91	.54	
B×C×D	3	6.64	.17	
A×B×C×D	3	23.23	.60	
C×Error	26	450.24		
D×Error	78	126.25		
C×D×Error	78	38.47		

Table A-68. A 2 by 2 by 2 by 4 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the BP CRs of the unrestrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	3469.77	10.89	.01
B (Previous restraint)	1	49.26	.15	
A×B	1	5.09	.01	
Error	26	318.55		
Within Subjects				
C (Drug administration)	1	66.33	1.46	
A×C	1	1.17	.02	
B×C	1	54.41	1.20	
A×B×C	1	19.28	.42	
D (Measurement intervals)	3	41.70	2.65	
A×D	3	29.06	1.85	
B×D	3	14.59	.93	
A×B×D	3	4.61	.29	
C×D	3	1.73	.29	
A×C×D	3	32.72	5.56	.01
B×C×D	3	.60	.10	
A×B×C×D	3	8.04	1.36	
C×Error	26	45.21		
D×Error	78	15.68		
C×D×Error	78	5.87		

Table A-69. A 2 by 2 by 2 by 2 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the HR URs of the restrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	472.61	.94	
B (Previous restraint)	1	1374.85	2.73	
A×B	1	452.12	.90	
Error	26	501.81		
Within Subjects				
C (Drug administration)	1	956.31	3.65	
A×C	1	157.41	.60	
B×C	1	455.28	1.74	
A×B×C	1	102.58	.39	
D (Measurement intervals)	1	4185.46	98.64	.01
A×D	1	103.37	2.43	
B×D	1	73.25	1.72	
A×B×D	1	.93	.02	
C×D	1	33.85	.79	
A×C×D	1	123.99	2.90	
B×C×D	1	19.78	.46	
A×B×C×D	1	3.74	.08	
C×Error	26	261.45		
D×Error	26	42.43		
C×D×Error	26	42.64		

Table A-70. A 2 by 2 by 2 by 2 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the BP URs of the restrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	85.28	.49	
B (Previous restraint)	1	22.95	.13	
A×B	1	307.83	1.77	
Error	26	173.87		
Within Subjects				
C (Drug administration)	1	251.89	3.84	
A×C	1	21.77	.33	
B×C	1	8.14	.12	
A×B×C	1	1.62	.02	
D (Measurement intervals)	1	1.71	.09	
A×D	1	61.70	3.48	
B×D	1	40.64	2.29	
A×B×D	1	.94	.05	
C×D	1	12.07	1.84	
A×C×D	1	.08	.01	
B×C×D	1	2.24	.34	
A×B×C×D	1	1.13	.17	
C×Error	26	65.55		
D×Error	26	17.68		
C×D×Error	26	6.54		

Table A-71. A 2 by 2 by 2 by 2 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the HR URs of the unrestrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	4944.60	3.40	
B (Previous restraint)	1	304.83	.21	
A×B	1	4224.36	2.91	
Error	26	1450.87		
Within Subjects				
C (Drug administration)	1	1860.15	3.03	
A×C	1	3085.96	5.03	.05
B×C	1	659.03	1.07	
A×B×C	1	2926.99	4.77	.05
D (Measurement intervals)	1	6091.87	116.65	.01
A×D	1	75.93	1.45	
B×D	1	46.87	.89	
A×B×D	1	.23	.00	
C×D	1	151.87	3.17	
A×C×D	1	210.93	4.40	
B×C×D	1	30.00	.62	
A×B×C×D	1	225.23	4.70	.05
C×Error	26	613.00		
D×Error	26	52.22		
C×D×Error	26	47.89		

Table A-72. A 2 by 2 by 2 by 2 (conditioning by previous restraint by drug by measurement intervals) analysis of variance summary table comparing the BP URs of the unrestrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	249.90	1.31	
B (Previous restraint)	1	36.27	.19	
A×B	1	9.85	.05	
Error	26	190.69		
Within Subjects				
C (Drug administration)	1	444.05	9.51	.01
A×C	1	.62	.01	
B×C	1	156.04	3.34	
A×B×C	1	3.40	.07	
D (Measurement intervals)	1	233.57	3.41	
A×D	1	74.63	1.09	
B×D	1	148.51	2.17	
A×B×D	1	.27	.00	
C×D	1	93.70	14.55	.01
A×C×D	1	36.98	5.74	.05
B×C×D	1	.48	.07	
A×B×C×D	1	5.63	.87	
C×Error	26	46.65		
D×Error	26	63.38		
C×D×Error	26	6.43		

Table A-73. A 2 by 2 by 2 by 8 (conditioning by previous restraint by drug by trials) analysis of variance summary table comparing base-level HR of the restrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	P
A (Conditioning)	1	574.27	.06	
B (Previous restraint)	1	2743.24	.29	
A×B	1	10783.65	1.14	
Error	26	9450.22		
Within Subjects				
C (Drug administration)	1	361763.55	78.37	.01
A×C	1	1556.77	.33	
B×C	1	8606.36	1.86	
A×B×C	1	203.96	.04	
D (Trials)	7	344.84	1.05	
A×D	7	308.42	.94	
B×D	7	413.42	1.26	
A×B×D	7	370.83	1.13	
C×D	7	318.19	.68	
A×C×D	7	554.05	1.19	
B×C×D	7	550.29	1.18	
A×B×C×D	7	162.84	.35	
C×Error	26	4615.54		
D×Error	182	326.07		
C×D×Error	182	182.00		

Table A-74. A 2 by 2 by 2 by 8 (conditioning by previous restraint by drug by trials) analysis of variance summary table comparing base-level HR of the unrestrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	69743.02	2.52	
B (Previous restraint)	1	13948.24	.50	
A×B	1	975.05	.03	
Error	26	27615.84		
Within Subjects				
C (Drug administration)	1	124565.74	10.50	.01
A×C	1	7806.15	.65	
B×C	1	2072.92	.17	
A×B×C	1	15904.75	1.34	
D (Trials)	7	519.76	.93	
A×D	7	687.17	1.23	
B×D	7	184.40	.33	
A×B×D	7	1097.87	1.97	
C×D	7	1863.86	3.30	.01
A×C×D	7	685.03	1.21	
B×C×D	7	1514.98	2.68	.05
A×B×C×D	7	1351.93	2.39	
C×Error	26	11855.35		
D×Error	182	555.63		
C×D×Error	182	563.37		

Table A-75. A 2 by 2 by 2 by 8 (conditioning by previous restraint by drug by trials) analysis of variance summary table comparing base-level BP of the restrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	P
A (conditioning)	1	32775.13	5.32	.05
B (Previous restraint)	1	196.50	.03	
A×B	1	5477.92	.89	
Error	26	6154.17		
Within Subjects				
C (Drug administration)	1	436.32	.43	
A×C	1	112.15	.11	
B×C	1	544.64	.54	
A×B×C	1	6.30		
D (Trials)	7	33.36	.77	
A×D	7	30.17	.70	
B×D	7	81.07	1.89	
A×B×D	7	14.25	.33	
C×D	7	74.04	1.80	
A×C×D	7	32.63	.79	
B×C×D	7	16.71	.40	
A×B×C×D	7	28.16	.68	
C×Error	26	1003.88		
D×Error	182	42.81		
C×D×Error	182	41.09		

Table A-76. A 2 by 2 by 2 by 8 (conditioning by previous restraint by drug by trials) analysis of variance summary table comparing base-level BP of the unrestrained experimental and control groups during the parasympathetic drug test.

Between Subjects	DF	MS	F	p
A (Conditioning)	1	66518.58	13.63	.01
B (Previous restraint)	1	18799.53	3.85	
A×B	1	8528.93	1.74	
Error	26	4877.23		
Within Subjects				
C (Drug administration)	1	.03	.00	
A×C	1	76.59	.12	
B×C	1	812.70	1.35	
A×B×C	1	224.99	.37	
D (Trials)	7	70.67	1.28	
A×D	7	16.87	.30	
B×D	7	48.68	.88	
A×B×D	7	22.69	.41	
C×D	7	235.88	5.31	.01
A×C×D	7	21.69	.48	
B×C×D	7	35.66	.80	
A×B×C×D	7	90.89	2.04	
C×Error	26	600.04		
D×Error	182	54.98		
C×D×Error	182	44.35		