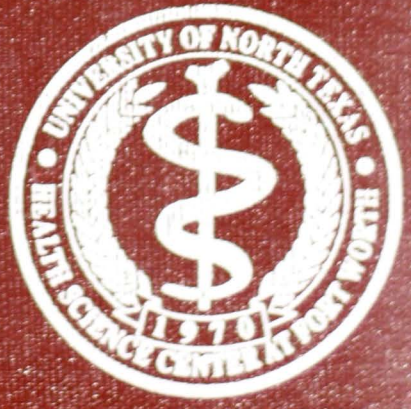
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Arterial baroreflex control of cardiac function is dependent upon afferent input from both the aortic arch and carotid sinus baroreceptors. Extensive research in animals has generated conflicting results as to the range of arterial pressures over which each baroreflex operates. Further, the complex integration of afferent signals within the medullary cardiovascular center, in reference to aortic and carotid baroreceptor input, has been characterized as additive, inhibitory, and facilitatory in nature. Such reports make it difficult to draw definitive conclusions about the behavior of central neural processing within the brainstem. In addition, these relationships have yet to be examined in humans. Therefore, the purpose of the investigations described herein, was to quantify the range of pressures over which the arterial, aortic, and carotid baroreflexes operate as well as to describe the interactive relationship between the aortic and carotid baroreceptors. In order to investigate these questions, we isolated the arterial, aortic, and carotid-cardiac baroreflexes in volunteer subjects generating sigmoidal stimulus-response curves for each reflex arc. Arterial and aortic baroreflex (ABR) control of heart rate (HR) was assessed by inducing graded increases and decreases in mean arterial pressure (MAP) by bolus infusion of the vasoactive agents phenylephrine (PE) and sodium nitroprusside (SN), respectively. Carotid baroreflex

(CBR) function was determined utilizing ramped five second pulses of both pressure and suction applied to the carotid sinus via a neck chamber collar, independent of drug administration. The MAP at which the threshold and saturation were elicited did not differ among the reflexes examined indicating each reflex operated over a similar range of arterial pressures. Further, the simple sum of the independently derived HR response ranges of the CBR and ABR was significantly greater than that produced when both baroreceptor populations were concomitantly stimulated (i.e. arterial baroreflex) suggesting an inhibitory interaction.

To investigate differential baroreflex control of HR in response to chronic endurance exercise training, a second investigation was designed implementing the reflex isolation techniques described previously. Stimulus-response relationships were compared between high fit (maximal oxygen uptake, $VO_{2max} > 60$ ml·kg^{-1}·min^{-1}) and average fit ($VO_{2max} < 45$ ml·kg^{-1}·min^{-1}) individuals. Interestingly, neither the range of operating pressures for each reflex nor the integrative relationship between the ABR and CBR were altered as a result of aerobic training. However, the HR response range elicited from the aortic baroreceptors as a result of hypotensive and hypertensive insult was markedly attenuated in the aerobically trained population compared to their sedentary counterparts, exclusively causing a requisite reduction in arterial baroreflex sensitivity.

EFFECTS OF ENDURANCE TRAINING ON AORTIC AND

CAROTID BAROREFLEX FUNCTION

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EFFECTS OF ENDURANCE TRAINING ON AORTIC AND CAROTID BAROREFLEX FUNCTION

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University of Texas Southwestern Medical Center at Dallas – Differential Baroreflex Control of Cardiac Function, January 1999.

Texas Chapter of the American College of Sports Medicine – Carotid Baroreflex Resetting During Static Exercise: Effect of Epidural Anesthesia, February 1999.

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LIST OF ABBREVIATIONS

ABP	arterial blood pressure
ABR	aortic baroreflex
AF	average fit
ANOVA	analysis of variance
BR	baroreflex
CBR	carotid baroreflex
CP	centering point
CSP	carotid sinus transmural pressure
CVP	central venous pressure
DBP	diastolic blood pressure
ECG	electrocardiogram
ECSP	estimated carotid sinus transmural pressure
G_{max}	maximal gain
HF	high fit
HR	heart rate
MAP	mean arterial pressure
NP	neck pressure
NS	neck suction
NTS	nucleus tractus solatarius

LIST OF ABBREVIATIONS, continued

OP	operating point
PC	personal computer
PE	phenylephrine
PP	pulse pressure
Q_c	cardiac output
SBP	systolic blood pressure
SE	standard error
SN	sodium nitroprusside
SNA	sympathetic nerve activity
SNK	Student Neuman-Keuls
SV	stroke volume
TBV	total blood volume
TPR	total peripheral resistance
VO_{2max}	maximal oxygen uptake

CHAPTER I

INTRODUCTION

The primary impetus for the investigations described in this dissertation was the lack of information in the current literature in reference to the neural processing of afferent aortic and carotid baroreceptor signals in humans. In addition, characterizations of the functional operating ranges of the arterial, aortic, and carotid-cardiac baroreflexes have been limited primarily to animal preparations with conflicting results (1, 3, 6, 18, 20). Even less has been described about these relationships in response to endurance exercise training. Carotid baroreflex responsiveness has been extensively investigated since the development of the variable neck chamber (12, 56) illuminating the basic physiological behavior of this baroreflex arc. However, due to anatomical location and, therefore, lack of accessibility, characterization of the aortic-cardiac baroreflex has been difficult in humans. Therefore, we modified a technique previously developed by Ferguson et al. (16) and Sanders and coworkers (46) which allows the selective alteration of aortic distending pressure by the use of vasoactive drugs. By implementation of this technique, we have been able to successfully produce stimulus-response curves describing the arterial, aortic, and carotid-cardiac baroreflexes. This dissertation is intended to discern the interactive relationships inherent to these baroreflex arcs, the range of arterial pressures over which these

reflexes operate, and alterations in their function that may occur in response to endurance exercise training.

REVIEW OF RELATED LITERATURE

Arterial Baroreceptor Reflex

The baroreflex control of a variety of end organ systems has been best characterized as a multi-input, multi-output, and multi-level complex (45). As a good example, the baroreflex mediated control of arterial blood pressure (ABP) has been shown to be elicited by inputs from several discrete baroreceptor populations reflexively activating multiple efferent pathways to produce appropriate alterations in heart rate (HR), stroke volume (SV), and total peripheral resistance (TPR). The arterial baroreflex, consisting of inputs from both the carotid sinus and aortic arch baroreceptors, has been reported to acutely alter both cardiac function (i.e., HR and SV) and vasomotion (i.e., TPR) in this regulatory process. As has been described previously (45), the net result of arterial baroreflex activation and deactivation is a reflex bradycardia and vasodilatory response and a reflex tachycardia and vasoconstrictor response, respectively. As a result, the integration of input from the aortic and carotid baroreflexes appropriately corrects alterations in ABP. Unfortunately, due to the complexity of the system and limitations in the techniques that can be employed, the integrative relationship between these two baroreceptor populations has yet to be elucidated in humans.

Autonomic Pathways

As described in animal preparations, the main afferent inputs to the cardiovascular control center emanating from arterial baroreceptors travel to the medulla via cranial nerves nine (glossopharyngeal nerve) and ten (vagus nerve) (5, 30). Within the medulla, the afferent nerve fibers have been reported to project first to the nucleus tractus solatarius (NTS). From the NTS, autonomic parasympathetic outflow has been shown to be mediated primarily through cardiac vagal efferents traveling first via central parasympathetic neurons in the nucleus ambiguus to post-ganglionic neurons next to or in the walls of the heart chambers (29). Sympathetic efferent signals, regulated by baroreceptor afferent information projected to the NTS and relayed first to the caudal ventral-lateral medulla and then to the rostral ventral-lateral medulla, travel via the inner medial-lateral cell column within the spinal cord. These efferent signals have been reported to travel via pre-ganglionic white ramus fibers which synapse with post-ganglionic neurons in the sympathetic ganglia (29). In humans, direct stimulation or denervation of afferent and efferent neural pathways is not possible. As a result, less invasive techniques, such as administration of receptor blocking agents, have been utilized to discern the signal transduction mechanisms and central neural pathways involved in the arterial baroreflex arc. For example, it has been reported that the bradycardia produced during arterial baroreceptor activation is primarily mediated through vagal cholinergic mechanisms due to finding phenylephrine (PE)-induced increases in ABP are not reduced by propranolol (a β-adrenergic blocking agent) but are abolished by atropine (23, 39). Although slower (7, 58, 59) and to a lesser extent, it

has been found that the sympathetic nervous system also contributes to the cardio-decelerator response by reducing its efferent outflow (43). In contrast, the mechanisms involved in the tachycardiac response to acute decreases in ABP are not as well defined. Pickering et al. (39) observed the early cardio-accelerator response to administration of amyl nitrate to be potentiated by propranolol but abolished by atropine suggesting a vagally mediated reflex response. However, others have reported that the tachycardiac response to nitroglycerin infusion was only attenuated by atropine but could be abolished by concomitant administration of atropine and a β-adrenergic blocker (44). Together, these results suggested the arterial baroreflex mediated increase in HR in response to acute alterations in ABP was elicited by both sympathetic and parasympathetic neural control (35).

Autonomic Rhythms

The presence of respiratory related oscillations in HR have been confirmed in several animal preparations. The variability is due primarily to fluctuations in vagal discharge with efferent activity being inhibited during inspiration and potentiated during expiration (4, 21). In addition, it has been elucidated that respiration similarly affects sympathetic nervous discharge frequency becoming maximal during mid-inspiration and minimal during early expiration (17). Respiratory related oscillations in vagal and sympathetic nervous system excitability have also been noted (21). This finding has resulted in the development of experimental protocols which are designed to deliver stimuli to the arterial baroreceptors during expiration, when neural

excitability is maximum, as opposed to during inspiration, when excitability is low. In humans, this phenomenon was first described by Smyth et al. (55), who reported that the reflex lengthening of the R-R interval in response to drug-induced hypertension displayed a greater slope if values obtained during the inspiratory phase of the respiratory cycle were not included in the analyses. However, application of neck suction to the carotid sinus baroreceptors has further elucidated that not only is this respiratory related fluctuation in baroreflex sensitivity continuous but it is also out of phase with the inspiratory-expiratory periods (i.e., sensitivity is reduced maximally during early inspiration and midexpiration and minimally during the early expiratory period) (13, 14).

In animal investigations, cardiac vagal efferent activity has also been associated with circulatory rhythms (i.e., the cardiac cycle) as vagal discharge has been demonstrated to begin during the falling phase of the aortic pressure pulse when cycle lengths are greater than 350 ms (31). In addition, it has been shown in dogs, with intact vagi, that application of stimuli to the carotid sinus nerve produces larger HR responses when administered in a pulsatile fashion than when delivered continuously (47). Further, pulse-synchronous discharge patterns have also been shown to be present for sympathetic neural discharge similar to the way outflow behaves during the respiratory cycle (17). Again, this finding has resulted in the development of experimental protocols which are designed to deliver stimuli to the arterial baroreceptors in a pulse-synchronous fashion.

Stimulus-Response Latency

In animals, stimulation of arterial baroreceptors has been shown to elicit vagal efferent activity in as short as 100 ms from the start of a fast-acute pressure change (25). Similarly, animal models have elucidated the latency in the inhibition of the sympathetic efferent response to be approximately 260 ms from the start of an aortic pressure pulse and 170 ms when the carotid sinus nerve is stimulated (28). In humans, the latency of the bradycardiac response to phenylephrine-induced increases in ABP averaged 475 ms from the beginning of the initial baroreceptor perturbation (40). Eckberg et al. (11) have since described a shorter latency for this response (approximately 200 ms) using a neck suction stimulus applied to the carotid sinus during the most sensitive portion of the cardiac cycle. Regardless of the discrepancies between these two human investigations, researchers have consistently reported that the arterial baroreflex can rapidly alter HR and adjust sinus node rhythm on a beat-to-beat basis (35).

Carotid Baroreceptor Reflex

Within the medial adventitia of the walls of the internal carotid arteries, at the sinus bifurcation (45), unencapsulated free nerve-endings responsive to mechanical deformation (i.e., stretch) comprise the receptors integral to the carotid baroreflex arc. Carotid baroreceptor mediated changes in HR and ABP function in concert with the aortic baroreflex to elicit the appropriate arterial baroreflex response to moment-to-moment alterations in blood pressure. For example, in response to hypertensive stimuli,

these receptors increase their firing rate altering parasympathetic and sympathetic neural outflow, to reduce HR and TPR, returning ABP to its steady-state value. In a rapid fashion, the carotid baroreflex effectively maintains blood pressure around a regulated value.

Carotid baroreceptors have been shown to be discretely sensitive to changes in pulse pressure (8, 10), whereas the aortic arch baroreceptors have not (2, 3, 20). The first example of pulsation affecting carotid baroreflex sensitivity was described by Ead et al. (10) in the cat in which pulsating and non-pulsating (i.e., constant pressure equal to the mean pulsating pressure) stimuli were delivered to isolated carotid sinuses. In response to a lack of pulsating stimuli, the ABP was elevated sharply despite an unchanging mean carotid sinus pressure. Subsequently, experiments conducted on vagotimized dogs determined that the application of physiological pulsation to the carotid sinus extends the operating range of the reflex to lower arterial pressures (i.e., point where threshold of the reflex was attained) than those obtained in a nonpulsatile system. Adhering to the findings of these studies, experiments designed to quantify the carotid baroreflex arc are most physiologically relevant when the pulsatility inherent to the system is maintained.

Aortic Baroreceptor Reflex vs. Carotid Baroreceptor Reflex

The available information in the literature describing the relationship between aortic and carotid baroreflexes in reference to their respective ranges of operation is scant, at best, and limited exclusively to animal investigations. Since the development

of the variable neck chamber (12, 56), carotid baroreflex (CBR) control of HR has been extensively examined in humans. Unfortunately, only a few attempts have been made to isolate aortic baroreceptor function in humans (16, 34, 46, 48, 49) and none have described the range of arterial pressures over which the aortic baroreflex (ABR) operates. In addition, in the animal investigations that have attempted to quantify this relationship, several different end organ systems have been examined leading to variable conclusions about each baroreceptor population. One of the first investigations expressly designed to examine this relationship was conducted using an isolated carotid sinus and aortic arch preparation in dogs in which both baroreceptor populations were stimulated with nonpulsatile pressures in order to quantify the reflexive control of vasomotion (1). Entire baroreflex stimulus-response curves were developed from this study for the percent systemic arterial pressure change in relation to the percent change in aortic arch pressure. Such analyses revealed that the carotid baroreceptor reflex resembled the ABR but differed in that i) the threshold of the ABR was greater and ii) the saturation of the ABR was higher. Subsequently, Hainsworth et al. (18) and Donald and Edis (9) described a similar relationship in dogs perfused with a constant flow-pump when the baroreflex control of hindlimb resistance was examined. Pelletier et al. (38), examining canine receptor nerve activity, have also reported the arterial pressures at which the thresholds of the CBR and ABR are attained are distinctly different. In contrast, electroneurographic studies in a variety of species (i.e., rat, cat, and rabbit) preparations described the operating ranges of the CBR and ABR to be quite similar (6, 20). Further, investigations utilizing the canine model, in which pulsatile stimuli were

delivered to the aortic arch and carotid sinuses, have reported similar results as those obtained in the electroneurographic studies.

Interactive Relationships

Even less is known about the integration of afferent CBR and ABR inputs within the medullary cardiovascular center in humans. Again, all information pertaining to the interactive relationship between the two baroreceptor populations has primarily been obtained in animal models. Classically, the approach most often used to quantify the integrative function of the ABR and CBR in the control of cardiovascular variables has been to stimulate one baroreceptor population while minimizing changes in the activity of other inputs within the baroreflex arc (19). Analyses conducted after implementation of this type of experimental paradigm can elicit one of three distinct integrative relationships (29, 45). For example, if the central nervous system receives information from aortic (Input A) and carotid (Input B) baroreceptors and the two inputs are completely independent, then the net effector response will be the simple sum of each input (i.e., Input A + Input B = Output C). If, however, there is an interaction at one or more of the integrative sites within the central nervous system then the reflexive response is best described in nonlinear terms. In other words, if Input A + Input B > Output C then an inhibitory interaction exists between the two inputs. If, on the other hand, Input A + Input B < Output C then a facilitatory interaction best describes the relationship. By definition, interaction means nonlinear interdependence between two inputs in eliciting an output (45). It should be noted, that in order to draw

physiologically accurate and relevant conclusions from this type of analysis, full sigmoidal baroreflex function curves must be developed for each baroreflex examined (29).

The interrelationship between carotid and aortic baroreceptor inputs in mediating the arterial baroreflex control of a wide array of end organ systems has been extensively examined using animal preparations. During combined and separated increases in carotid sinus and aortic arch pressure in the canine, the reflex control of total systemic resistance has been characterized as mildly inhibitory in nature (3). Similar findings have been reported for the sinoaortic inhibition of renal nerve discharge (36). In contrast, experimental paradigms that examined the control of perfusion pressure in the dog hindlimb have suggested that the relationship between ABR and CBR input was linear and best described by simple linear summation (9). However, studies conducted comparing the fall in arterial pressure elicited by separate and combined electrical stimulation of the aortic and carotid sinus nerves in canine models (26) reported a 70% larger reduction in pressure when the inputs were stimulated concomitantly compared to the sum of the individual responses (i.e., facilitatory interaction). Given the discrepancies in findings reported in the current literature, it is difficult to draw any strong conclusion as to the nature of the integrative relationship between the ABR and CBR in animals, let alone in humans.

In humans, Mancia and coworkers (34) have reported, as have others (16, 48, 49), that the aortic baroreflex predominates over the CBR in the arterial baroreflex control of HR in response to acute alterations in ABP induced by vasoactive drug

administration. Similar findings have been reported, utilizing comparable techniques, in the arterial baroreflex control of sympathetic nerve activity (46). Unfortunately, these studies have not attempted to fully characterize the reflex stimulus-response curves describing the ABR, CBR, and arterial baroreflex and provide little insight into the integrative relationship between the reflexes.

Interaction Between the Arterial and Cardiopulmonary Baroreceptors

The use of lower body negative pressure up to –20 torr has been shown to selectively unload the cardiopulmonary baroreceptors, decreasing central blood volume and cardiac filling pressure (22). This conclusion was predicated on the finding that reflex increases in forearm vascular resistance were elicited without concomitant alterations in either ABP or HR. Use of this testing paradigm has demonstrated that the gain of the carotid baroreflex can be significantly augmented when the cardiopulmonary baroreceptors are unloaded (37). Complementing these reports, Shi et al. (51) have indicated that increases in central venous pressure (CVP), taken as an index of cardiopulmonary baroreceptor loading, can significantly reduce carotid-cardiac baroreflex sensitivity. Therefore, any assessment of arterial baroreflex function in humans must take into account the inducible modification of the reflex response by loading or unloading of the cardiopulmonary baroreceptors.

Training Induced Alterations in Arterial Baroreflex Function in Humans

Longitudinally and cross-sectionally designed investigations have documented that resting HR was significantly reduced by chronic aerobic training (15, 27, 42) whereas total blood volume (TBV) was increased (48, 57). However, resting mean arterial pressure (MAP) was shown to be unaffected by endurance training (48, 49). The increased TBV and decreased HR have been reported to mediate elevations in cardiac preload, filling time, and stroke volume (32, 33). CVP, being linearly related to TBV, has also been demonstrated to be augmented (49). Further, several investigators have reported that exercise training induces cardiac eccentric hypertrophy (24) and increases in both ventricular (33) and vascular compliance (50). The ramifications of such hemodynamic and structural changes induced by exercise training are, in part, alterations in baroreflex mediated circulatory control. In addition, it has been hypothesized that the development of an "autonomic imbalance" between resting sympathetic and parasympathetic influence may depress baroreflex control of cardiac function and vasomotion due to increased vagal efferent activity (53, 54). As a consequence, the incidence of syncope and the development of orthostatic intolerance in high fit individuals has been reported to be higher than in the sedentary population (42).

In humans, the use of lower-body negative pressure (42, 52) and steady-state infusion of sodium nitroprusside (49), to induce hypotension, demonstrated the arterial baroreflex cardio-accelerator response to be diminished in aerobically trained individuals. A similar attenuation in baroreflex sensitivity was described for the

bradycardiac response to phenylephrine infusion (48, 52). Subsequently, the diminution in arterial baroreflex responsiveness was attributed to a decrease in aortic baroreceptor sensitivity (48, 49) complementing the finding that the carotid-cardiac baroreflex was not altered by endurance exercise training (60). Again, the limitation inherent within studies examining the aortic baroreflex was their inability to fully characterize the reflex stimulus-response curve of the ABR. As a result, definitive information regarding alterations in operating point (i.e., resting MAP) position on the reflex curve, reflex mediated response range, and shape and position of stimulus-response relationship, which could result from diminished aortic baroreceptor sensitivity, could not be discerned. In addition, these studies provided little insight as to the interactive relationship between ABR and CBR function in high fit and average fit individuals.

SPECIFIC AIMS

Given the limitations and lack of information regarding aortic and carotid baroreflex interactions in humans as described in the review of related literature, two primary objectives were developed for this dissertation. These are i) to elicit discrete reflex changes in HR from the arterial, aortic, and carotid baroreceptors from which individual baroreflex stimulus-response curves can be characterized in order to reasonably describe the range of arterial pressure over which each baroreflex operates and to discern the interrelationship existing between the aortic and carotid baroreflexes; and ii) to develop baroreflex stimulus-response curves for each baroreceptor reflex in both aerobically fit and sedentary populations from which alterations in operating point

position, reflex response range, and integrative relationships can be determined. Specifically, we propose that the aortic and carotid baroreflexes exhibit an inhibitory interaction and functionally operate over similar ranges of arterial pressures. Further, we do not expect these relationships to be altered by exercise training. In addition, we postulate that the diminution in aortic baroreflex sensitivity, previously described, results in an effective reduction in the response range inducible by acute changes in arterial blood pressure and, as such, produces a vertical downward shift within the stimulus response curve describing this function. In order to investigate these proposals the following specific aims were submitted:

I. To test the hypothesis that baroreflex responsiveness to acute alterations in arterial blood pressure elicits similar pressure operating ranges for the arterial, aortic, and carotid baroreflexes and that neural processing of afferent information emanating from aortic and carotid baroreceptors is inhibitory in nature.

II. To test the hypothesis that the reduction in aortic baroreflex sensitivity in high fit individuals produces a reduced response range for the reflex functionally shifting the baroreflex stimulus-response curve vertically downward and that neural processing of afferent information from aortic and carotid baroreceptors is not altered by endurance exercise training.

EXPERIMENTAL DESIGN

Two individual experiments were designed to investigate specific aims I and II. These experiments are discussed in detail in the following chapters, however a brief description of the rationale and experimental design for each follow:

Baroreflex Responsiveness. In order to quantify the stimulus-response curves for the arterial, aortic, and carotid baroreflexes we implemented procedures to selectively perturb each reflex. By inducing ramped increases in arterial blood pressure utilizing the vasoactive agents phenylephrine and sodium nitroprusside, we intended to alter MAP by ±10, ±15, and ±20 mmHg assuming this to be a sufficiently large enough range to predict reflex threshold and saturation pressures. It was assumed during this phase of testing that the aortic arch and carotid sinus baroreceptors would be stimulated similarly as the subjects were in a supine position. This protocol was then repeated with counteracting neck pressure and neck suction applied to the carotid sinus via a malleable lead neck collar. It was assumed during execution of this testing paradigm, that the aortic baroreceptors would be functionally isolated by negating the drug-induced changes in pressure at the carotid sinus with the neck pressure manipulations. In order to functionally isolate the carotid baroreflex, we then applied neck pressure and suction, in short five second pulses to the carotid sinus, independent of drug infusion. Pressures and suctions were carefully chosen in order to simulate the changes in arterial blood pressure produced during vasoactive drug administration at the carotid sinus. We anticipated that by examining the same range of pressures over which each baroreceptor was stimulated we could accurately predict the arterial pressure range over which each

baroreflex operated. Furthermore, by comparing the HR response ranges elicited by each isolated reflex we concluded that the interactive relationships between the aortic and carotid-cardiac baroreflexes could be characterized. In order to confirm that we had not inadvertently forced the stimulus-response curves developed over a particular range of arterial pressures, we additionally assessed carotid baroreflex responsiveness using a rapid neck pressure/neck suction protocol which supplies stimuli to the carotid sinus over a wider range of pressures than those that could be safely induced by drug infusion. We reasoned that if the range of pressures over which the CBR operated were not significantly different between the two perturbations utilized, then we had accurately characterized the pressures at which threshold and saturation had been obtained on the respective stimulus-response curves.

Comparison of Baroreflex Function in Average Fit and High Fit Individuals. The same techniques employed in the first investigation were utilized in this experiment. As such, the rationale for completing this project was to discern fitness related differences in baroreflex function and interactive relationships. We anticipated that the baroreflex stimulus-response curves describing arterial and aortic baroreflex function would be shifted vertically downward without a significant relocation of the operating point on the curve. Further, we did not foresee any changes in the neural processing of afferent information projected from the aortic and carotid baroreceptors as there was little evidence in the literature to support such a contention.

METHODS

Although the methodology for each investigation is described within the following chapters, it is appropriate to discuss here special considerations taken under advisement in choosing the techniques and methods of analyses utilized in our experimentation. To begin, we chose to plot the absolute values recorded for MAP and HR rather than changes in these variables from baseline. By incorporating this method into our analyses, we were able to preserve information on the vertical and horizontal positioning of each stimulus-response curve developed. This allowed for a careful and physiologically significant assessment of the changes in HR elicited by acute alterations in blood pressure. Upon review of the current literature, it became apparent that it was more accurate to fit each logistic function curve to data from individual subjects and then determine the mean ± SE of the individually fitted curve parameters, rather than fitting the function to group mean HR and MAP responses as our subject population was not large enough to account for errors that can arise using the latter technique (45). Several methodological concerns were recognized and obviated in order to accurately assess carotid baroreflex function using both the five second pulse stimuli and the rapid neck pressure/neck suction protocol. These concerns have been expertly reviewed by Raven et al. (41) and include i) the effect of respiratory related oscillations on vagal efferent sensitivity, ii) counteraction of the neck pressure/neck suction stimuli by extracarotid baroreceptors, and iii) the use of R-R interval as a means of interpretation of the reflex response, which can produce a bias due to the nonlinear mathematical relationship between R-R interval and HR. In order to eliminate these concerns, each

pressure stimulus and/or stimulus train was delivered during a breath-hold at end-expiration. The stimuli were brief (< 5 seconds) and HR was used to characterize the stimulus response curves.

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CHAPTER II

COMPARISON OF AORTIC AND CAROTID BAROREFLEX CONTROL OF HEART RATE DURING ACUTE CHANGES IN BLOOD PRESSURE IN MAN

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ABSTRACT

To determine the individual contributions of the aortic arch and carotid sinus baroreceptors to arterial baroreflex control of cardiac function, we measured heart rate (HR) responses elicited by acute changes in mean arterial pressure (MAP) and carotid sinus pressure (CSP) in healthy men (N=7) and women (N=4). The arterial-cardiac baroreflex was quantified using ramped increases and decreases in MAP induced by bolus injection of phenylephrine (PE) and sodium nitroprusside (SN), respectively. To assess aortic-cardiac responses, neck pressure (NP) and neck suction (NS) were applied during PE and SN administration, respectively, to counter the alterations in transmural CSP, functionally isolating the aortic baroreceptors. Graded levels of NP and NS pulses, of 5 sec in duration, were delivered to the carotid sinus using a customized neck collar device to assess the carotid-cardiac baroreflex, independent of drug infusion. The response range of each reflex was determined from the logistic function of HR responses to changes in MAP or estimated CSP as were the arterial pressures at which threshold and saturation of the reflexes were attained. The response range of the aortic-cardiac reflex (36.3 ± 3.6 beats·min^{-1}) was significantly greater than the carotid-cardiac reflex (15.1 ± 1.2 beats·min^{-1}, $P<0.05$). In addition, the arterial-cardiac reflex response range (42.0 ± 3.6 beats·min^{-1}) was significantly less than the algebraic sum of the aortic and carotid baroreflexes (51.4 ± 4.1 beats·min^{-1}, $P<0.05$). The MAP (or estimated CSP) at which the threshold and saturation were elicited did not differ among the reflexes examined ($P>0.05$). These data suggest that the aortic baroreflex control of HR predominates over the carotid baroreflex and, together, exhibit an inhibitory

interaction when compared to the global arterial HR response. Further, we conclude that each of the reflexes operate over the same range of arterial pressures.

KEY WORDS:

Threshold, Saturation, Gain, Inhibitory Interaction, Additive Summation

INTRODUCTION

Arterial baroreflex regulation of heart rate (HR) is dependent on the integration of neural afferent information emanating from baroreceptors located in the carotid sinus and aortic arch. Carotid baroreflex (CBR) control of cardiac function has been expertly quantified in humans since the development of the variable neck chamber (12, 36). However, with a few eloquently designed exceptions, investigation of HR reflex regulation by the aortic baroreceptors has been limited primarily to animal preparations. Ferguson et al. (14) have described a method for isolating the aortic baroreflex (ABR), in humans, independent from carotid baroreceptor input. Utilizing this technique, these investigators reported, as have others (24, 32, 33), that the aortic baroreceptors predominate over carotid baroreceptors in the reflex control of HR in humans. Unfortunately, these studies have been unable to fully characterize the reflex stimulus-response curve of the aortic baroreflex which, presumably, is sigmoidal in nature as are the arterial and carotid-cardiac baroreflexes. As such, the operating range of this reflex as well as the threshold and saturation points have yet to be elucidated. In addition, information on the interactive relationship between the carotid and aortic baroreflex in eliciting the global arterial HR response is circumspect, at best, and limited to animal investigations.

By applying stepwise variations in pressure to the isolated aortic arch in anesthetized open-chested dogs, Allison, Sagawa, and Kumada (1) reported the threshold and saturation levels of the ABR control of HR to be significantly higher than that of the CBR. Subsequently, these findings were reproduced by Hainsworth et al.

(16) in a comparable preparation in which the aortic arch was vascularly isolated and perfused with nonpulsatile pressures. In contrast, Angell-James and Daly (3) found the operating range and gain of the aortic and carotid baroreflexes to be quite similar in the control of systemic arterial perfusion when the receptors were activated by pulsatile pressure. These findings were supported by aortic nerve electroneurographic studies in a variety of animal models including the rat, cat, and rabbit (5, 18). The interactive relationship between the CBR and ABR appears to be even more complex as a wide variety of animal preparations have described conflicting results. It has been reported that the sum of separate stimulation of the ABR and CBR controlling systemic resistance in dogs was greater than the combined stimulation of these reflexes (3). Such a finding indicates an inhibitory interaction may exist between these two baroreceptor populations, at least in the control of vascular resistance. In contrast, others contend the relationship is simply additive (8). Refuting these findings, Kendrick and coworkers (20) have reported a facilitatory interaction for the control of HR in the dog. In agreement, in an investigation utilizing cold blockade of the vagus and carotid sinus denervation during 10% hemorrhage in the dog, a pronounced facilitatory interaction between the ABR and CBR control of posthemorrhagic hypotension has been observed (17). The discrepancies in the findings reported in these studies (3, 8, 17, 20) are most likely due to differences in the species studied, the techniques employed and the end organ system examined. In many respects, these investigations have provided only moderate insight about the functional characteristics and interactive relationship of the ABR and CBR in humans.

In order to resolve these discrepancies in humans, we have recently modified the techniques originally described by Ferguson et al. (14) and Sanders and coworkers (30) for stimulating the carotid and aortic baroreceptors concomitantly, as well as the ABR alone, by utilizing graded bolus injections of hypertensive and hypotensive vasoactive agents. In addition, we have implemented strategies to perturb the carotid sinus baroreceptors independently of the extracarotid baroreceptors utilizing the rapid neck pressure/neck suction technique described by Sprenkle et al. (36) as well as a modification of this technique using brief five second stimuli (28). Our purpose was to elicit discrete reflex changes in HR from the arterial, aortic, and carotid baroreceptors from which individual baroreflex stimulus-response curves could be characterized. We hypothesized that the threshold and saturation of the CBR would occur at lower arterial pressures than the ABR. We further hypothesized, that, in humans, the integration of afferent information from the ABR and CBR for the control of HR would exhibit a facilitatory interaction.

METHODS

Subjects. Seven men and four women were recruited from local universities and the general Dallas/Fort Worth area for voluntary participation in the study. The group mean (±SE) age, height, weight, and maximal oxygen uptake (VO_{2max}), were 25.3 ± 1.0 yr, 173.5 ± 3.0 cm, 73.3 ± 4.1 kg, and 46.2 ± 2.5 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively. Subjects were advised of testing protocols and the potential risks of participation. All provided written consent approved by the University of North Texas Health Science

Center Institutional Review Board for the use of Human Subjects. After the completion of a medical history questionnaire, resting electrocardiogram (ECG), and blood pressure screening, subjects were administered a graded exercise test to volitional fatigue for determination of electrocardiographic abnormalities and VO_{2max} . All subjects were normotensive nonsmokers, were not taking medication, and were asymptomatic for cardiovascular and respiratory disease. The actual experimental protocol was scheduled on a separate day from the exercise test, and the subjects were requested to abstain from caffeinated beverages, strenuous physical activity, and alcohol at least 24 h before testing. Each subject was familiarized with the equipment and procedures and was allowed to become comfortable with the experimental protocols before the actual data collection began.

Experimental Protocols

Exercise testing. The VO_{2max} for each subject was assessed from a graded treadmill exercise test. During each minute of testing, the treadmill speed was increased by 0.15 miles/h and the grade was elevated 1.5% until a plateau of oxygen uptake was observed or the subject reached his limit of tolerance and requested testing to be terminated. Breath-by-breath oxygen uptake was measured via mass spectrometer (Perkin-Elmer MGA-1100A, Pomona, CA) analog signals digitally converted by a personal computer (Gateway 2000, N. Sioux City, SD) for on-line data acquisition and analysis using customized software.

Measurements. All testing was performed with each subject in a supine position. The subjects were instrumented with standard ECG electrodes for beat-to-beat

measurement of HR. The ECG signal was output to a pressure monitor (Hewlett-Packard 78342A, Andover, MA) interfaced with the personal computer (PC). In nine of the subjects tested, arterial blood pressure (ABP) was measured directly from a radial artery using a 1.25"-long, 20 gauge Teflon catheter. A topical anesthetic cream was applied to the surface of the skin in the area to be instrumented and Lidocaine (1%) was injected subcutaneously before catheterization to minimize discomfort. Systolic (SBP), diastolic (DBP), mean (MAP) and pulse (PP) pressures were transduced using a sterile disposable pressure transducer (Cobe, Lakewood, CO) and the aforementioned pressure system, monitored in real-time and recorded by the PC. Before obtaining blood pressure measurements, the transducer was zeroed to the mid-axillary line of the subject. The catheter was kept patent by a continuous drip (2ml/h) of heparinized saline (2 U/ml). In two subjects, ABP was measured using a finger photoplethysmographic method (Finapres, Ohmeda), placing the recording finger cuff at the level of the heart. Using a standard arm arterial cuff, DBP was obtained by auscultation and matched to the DBP reading from the recording device. Previous data from our laboratory (32) indicated that directly measured ABP was highly correlated with the well-controlled indirect method afforded by the Finapres over a wide range of pressures. In eight subjects, central venous pressure (CVP) was measured by a sterile disposable pressure transducer (Cobe, Lakewood, CO) interfaced with the Hewlett-Packard monitoring system via a double-lumen catheter (Cook Critical Care, Bloomington, IN). The central catheter was placed in the median antecubital vein of the right arm and advanced to the superior vena cava at the level between the 3rd and 4th intercostal space. Placement of the line was

confirmed by fluoroscopic observation (BV22, Philips, Eindhoven, the Netherlands). The reference point was zeroed at the subject's midaxillary line. Patency was maintained by a continuous drip of heparinized saline (2 U/ml).

Arterial and aortic baroreceptor responsiveness. After instrumentation, the subjects rested quietly for approximately 1h before testing began. The arterial and aortic baroreflex control of HR was assessed using a modification of the technique originally described by Ferguson et al. (14) and Sanders and coworkers (30) and since used by others (7, 32, 33, 35). This procedure enables the selective alteration of aortic distending pressure using the vasoactive agents phenylephrine (PE) and sodium nitroprusside (SN) infusion in combination with sustained neck pressure (NP) and neck suction (NS), respectively. Utilizing placement of a peripheral catheter in an antecubital vein of the arm opposite to that used for estimating CVP, we administered three doses of PE (PE1 = 0.59 ± 0.06 $\mu g \cdot kg^{-1}$; PE2 = 1.18 ± 0.13 $\mu g \cdot kg^{-1}$; and PE3 = 1.91 ± 0.18 $\mu g \cdot kg^{-1}$) and SN (SN1 = 0.77 ± 0.08 $\mu g \cdot kg^{-1}$; SN2 = 1.39 ± 0.15 $\mu g \cdot kg^{-1}$; and SN3 = 2.00 ± 0.22 $\mu g \cdot kg^{-1}$) in order to acutely alter ABP with the goal of increasing and decreasing MAP by 10,15, and 20 mmHg. The drug was introduced to the circulation via bolus injection and each dose was administered in duplicate. Before each injection, one minute of baseline data of HR, ABP, and CVP was obtained and averaged over that time period. Subsequently, the drug was rapidly injected and the catheter flushed with 5 ml of heparinized saline. Data was then analyzed by taking 10 beats evenly distributed around the peak and nadir of the MAP response to PE and SN, respectively. Five minutes elapsed between the time of the greatest change in pressure and the succeeding

baseline data collection after it was evident that all cardiovascular variables had returned to basal levels. We assumed, during this phase of testing, that the high pressure side of the circulation, including both the aortic and carotid baroreceptors , was stimulated by the acute change in ABP and would accurately characterize the arterial baroreflex control of HR. Immediately following, the protocol was repeated with sustained NP and NS applied to the anterior two-thirds of the neck through a malleable lead collar (12) to counteract the PE and SN-induced changes in carotid sinus transmural pressure. The amount of NP and NS utilized were derived using the neck pressure/suction transmission characteristics described by Ludbrook et al. (22) which assumes 86% and 64% transmission of NP and NS, respectively. The negating stimuli were delivered to the carotid sinus close to the peak and nadir of the pressure change (the delay being estimated from the initial drug administration). Again, data were analyzed over a 10-beat period bilaterally distributed around the largest change in MAP. The levels of NP and NS applied during this phase of experimentation corresponded to the following: PE1 = 12.7 ± 1.1 torr; PE2 = 16.5 ± 1.3 torr; PE3 = 23.1 ± 1.3 torr; SN1 = -15.5 ± 1.0 torr; SN2 = -23.8 ± 2.5 torr; and SN3 = -29.9 ± 1.9 torr. We assumed implementation of this procedure would successfully negate drug-induced alterations in mean pressure at the carotid sinus and therefore functionally isolate the aortic baroreflex. This assumption does not take into account increases and decreases in afterload which could activate or deactivate ventricular mechanoreceptors (35) in response to the vasoactive drug administration. However, as the stimulus presented was the same in both phases of the experiment, the repeated-measures design

controls for this unaccounted effect. Data collected from execution of these procedures allowed the calculation of closed-loop stimulus-response curves for arterial and aortic baroreflex control of HR.

Carotid baroreceptor responsiveness. The carotid-cardiac response was assessed using two distinct techniques independent of drug infusion. First, we attempted to simulate the changes in ABP elicited during vasoactive drug infusion by applying three absolute levels of NS (to mimic alterations elicited during PE1, PE2, and PE3) and NP (to simulate changes produced during SN1, SN2, and SN3) to the carotid sinus through the lead neck collar. The amount of pressure or suction applied was corrected for reported neck transmission characteristics (22) and corresponded to the following levels: PE1, -17.1 ± 1.9 torr; PE2, -22.3 ± 2.3 torr; PE3, -31.8 ± 2.3 torr; SN1, 12.2 ± 0.8 torr; SN2, 19.0 ± 2.0 torr; and SN3, 24.4 ± 1.6 torr. We have described in detail our approach for completing the open-loop stimulus-response curve using this technique previously (28). This technique employs the delivery of each stimulus for a five second period during a 10 to 15 second breath hold at end expiration to minimize the effects of respiratory related oscillations in HR and counteraction by the aortic baroreceptors. Three to four perturbations were performed at each of the six pressure levels, and the peak HR response (consistently observed during the five second period of NP/NS) to each stimuli was averaged to provide a mean response for each subject. Beat-to-beat responses of HR and the generated level of neck collar pressure were measured throughout the breath hold period and recorded on-line. The peak HR responses were then paired with the estimated changes in carotid sinus transmural

pressure [(ECSP) = MAP - neck chamber pressure (0.86 (NP) or 0.64(NS))] to "build" a complete baroreflex curve. By calculation of ECSP in this manner, the actual change in pressure at the carotid sinus could be estimated and, therefore, were comparable to changes in MAP elicited during arterial and aortic baroreceptor manipulations. In order to validate the aforementioned technique and to ensure that we were not forcing the stimulus-response curves developed over a particular operating range of pressures, we used a second technique to assess CBR control of HR utilizing a rapid neck pressure/neck suction protocol (36). Previously, we have described in detail our approach for completing the CBR curve implementing this technique (27). Briefly, after a normal expiration and end expiratory breath hold, 12 consecutive pulses (range: 40 to –80 torr), each lasting 500 ms, were delivered to the neck via the flexible neck collar precisely 50 ms after the R wave of the cardiac cycle. Previously, this combination of timing and duration have elicited maximum CBR-HR responses (9, 10). Between each pulse in the stimulus train, the neck chamber was vented to atmospheric pressure to minimize carotid baroreceptor resetting (25). Three to six trains of NP/NS were executed for each subject with a minimum of 90 sec between successive trials. Heart rate responses from at least three trains were paired with the calculated changes in ECSP, as aforementioned, to derive three "pulsed train" stimulus-response curves per subject. The parameters of each curve were averaged to provide a mean response for each subject. The implementation of these two techniques allowed complete evaluation of CBR mediated changes in HR, making it possible to construct a family of stimulus-

response curves that were strictly comparable to those developed for the arterial and aortic baroreflexes.

Data analyses. Arterial, aortic, "built" carotid, and "pulsed train" carotid baroreflex stimulus-response curves were individually fit for each subject to a four-parameter logistic function described by Kent et al. (21) using the following equation:

$$HR = A_1 (1 + e^{[A_2(MAP \text{ or } ECSP - A_3)]})^{-1} + A_4$$

where A_1 is the HR response range (maximum to minimum), A_2 is the gain coefficient (i.e., slope), A_3 is the MAP or ECSP required to elicit equal pressor or depressor responses (i.e., centering point), and A_4 is the minimum HR response. Data were fit to this model by a nonlinear least-squares regression (utilizing a Marquardt-Levenberg algorithm), which minimizes the sum-of-squares error term to predict a curve of "best fit" to each set of raw data. The gain of the arterial, aortic, and carotid-cardiac reflexes was determined from the first derivative of the logistic function, whereas the maximal gain (G_{max}) was calculated as the gain value located at parameter A_3. Values for threshold (i.e., where no further increases in HR were elicited by reduction in baroreceptor pressure) and saturation (i.e., where no further decreases in HR were elicited by increase in baroreceptor pressure) were calculated as the maximum and minimum second derivatives, respectively, of the logistic function for the sigmoid curve. These parameters were averaged and presented as group means.

Statistical analyses. Comparison of cardiovascular variables (HR, SBP, DBP, MAP, PP, CVP, and ECSP) for each of the four techniques employed were made utilizing a repeated measures two-way analysis of variance (ANOVA) with a Student

Neuman-Keuls (SNK) test employed *post hoc* when main effects (i.e., baroreflex tested and drug trial) were significant. Comparison of stimulus-response parameters (G_{max}, threshold, saturation, response range, slope, centering point, and minimum HR response) for each of the four baroreflexes studied were made by executing a repeated measures one-way ANOVA with a SNK test utilized *post hoc* when main effects (i.e., baroreflex tested) were significant. The alpha level was set at $P < 0.05$. Results are presented as means (± SE). Analyses were conducted using SigmaStat for Windows (Jandel Scientific Software, SPSS Inc., Chicago, IL).

RESULTS

Cardiovascular responses. Alterations in ABP variables and CVP in response to vasoactive drug infusion produced during arterial and aortic baroreflex manipulations are presented in Table 1. Changes in pressure are not presented for either CBR maneuvers as blood pressure was not vasoactively clamped during these protocols and, therefore, is not strictly comparable to the changes produced during arterial baroreflex and ABR testing. The baseline values for all variables were not significantly different between the two groups. MAP was significantly increased and decreased from baseline at all levels of PE and SN bolus injection, respectively, in both groups. During arterial baroreflex testing, the change in mean pressure appeared to be induced primarily by alterations in DBP. Diastolic blood pressure was significantly different from baseline at all levels of drug infusion, whereas, SBP was significantly diminished only during SN3 and SN2 trials and significantly elevated only in the PE3 trial. In ABR testing, DBP and

SBP (except during SN1) were significantly different from baseline at all levels of drug administration contributing to the observed MAP response. The MAP response to trial SN3, PE2, and PE3 were significantly different from those obtained during arterial baroreflex perturbation during ABR testing as was the DBP during SN3 and the SBP during PE3. Although modest increases and decreases in PP and CVP occurred with the injection of PE and SN, respectively, these variables were not significantly affected by the perturbations presented nor were they different between arterial baroreceptor and aortic baroreceptor manipulations.

Interventions during arterial and aortic baroreflex testing induced significant changes in HR from baseline values during all trials of drug administration (Table 2). Similarly, the application of neck pressure or suction simulating changes in ABP at the carotid sinus during CBR testing produced significant alterations in HR from baseline with two exceptions: the HR response to SN1 and PE1. In addition, the HR responses obtained during "built" CBR perturbation and "pulsed train" CBR manipulation were not different and, therefore, the former is only presented for comparison in Table 2. During CBR testing, the changes in HR were significantly less during trials simulating SN1, SN2, and SN3 from either of the responses observed during arterial or aortic baroreflex manipulation. Further, during trials simulating the increases in pressure produced by PE1, PE2, and PE3, the HR response mediated by the CBR was significantly less than that obtained during arterial baroreflex testing.

Manipulation of carotid sinus pressure. The effects of drug administration and application of neck pressure or suction on ECSP are presented in Table 3. During

manipulation of the arterial baroreflex, the mean changes in carotid sinus pressure were assumed to be the same as those developed throughout the systemic circulation as subjects were placed in the supine position. As a result, the changes in ECSP reproduce the alterations in MAP (Table 1) induced by vasoactive drug administration. During ABR testing, changes in ABP induced by drug administration were counteracted by application of neck pressure or suction where appropriate. As a point of technique, the amount of pressure or suction applied was corrected (22) and subtracted from the MAP produced systemically by the vasoactive drug administered during any trial. As a result, ECSP was not significantly different from baseline except during the SN3 trial where pressure dropped 6.4 mmHg at the carotid sinus. Further, the ECSP produced during ABR perturbation was significantly different from that obtained during arterial and carotid baroreflex testing at all levels of experimental trial with the exception of baseline. Estimated carotid sinus pressure was significantly increased and decreased from baseline at all levels of NS and NP, respectively, during "built" CBR perturbation independent of drug administration. No significant differences in ECSP existed at any experimental level tested between arterial and carotid baroreflex manipulation.

Assessment of baroreflex control of HR. The HR responses (Figure 1A) and gain (Figure 1B) elicited by the two techniques employed to perturb the carotid baroreceptors (i.e. "built" vs. "pulsed train") in this investigation are presented for one representative subject. Upon visual inspection, the HR curves appeared to be similar, and there were no significant differences in the group calculated values for threshold, saturation, slope, centering point, minimum HR response (Table 4), response range, and

G_{max}, despite the larger range of pressure stimulation utilized in the "pulsed train" protocol. As such, "built" CBR curves were used to characterize CBR function in comparison to responses elicited from the arterial and aortic baroreflexes.

Beat-to-beat changes in HR (Figure 2A) and gains (Figure 2B) of the arterial, aortic, and carotid-cardiac reflexes, as determined from logistic modeling, are presented. Upon close inspection, the reflex curves appeared to be markedly different. Interestingly, the threshold, saturation, slope, and centering point between the three baroreflexes were not significantly altered (Table 4) although the average threshold of the ABR was 8.4 mmHg less than the average threshold of the CBR. Likewise, baseline cardiovascular variables were unchanged across all conditions. However, the minimum HR response of the ABR was significantly higher than that attained during manipulation of the arterial baroreflex while the minimum HR response of the CBR was significantly greater than both the arterial baroreflex and ABR (Table 4). Maximal gains for the ABR, CBR, simple summation of the ABR and CBR, and arterial baroreflex are presented in Figure 3. As expected, the calculated G_{max} of the arterial baroreflex (-2.00 ± 0.44 beats·min^{-1}·mmHg^{-1}) was significantly greater than either the ABR (-1.17 ± 0.12 beats·min^{-1}·mmHg^{-1}) or CBR (-0.65 ± 0.11 beats·min^{-1}·mmHg^{-1}) with no significant difference existing between the latter two. However, the summed response of the ABR and CBR (-1.82 ± 0.21 beats·min^{-1}·mmHg^{-1}) was not different from that of the arterial baroreflex. Similarly, the HR response range of the ABR (36.3 ± 3.6 beats·min^{-1}) was significantly less than that of the arterial baroreflex (42.0± 3.6 beats·min^{-1}). In addition, the CBR (15.1± 1.2 beats·min^{-1}) was significantly reduced

from both of these reflexes (Figure 4). In contrast to the G_{max} relationship, the summed response of the ABR and CBR response range (51.4± 4.1 beats·min^{-1}) was significantly greater when compared to the arterial baroreflex.

DISCUSSION

The two major findings elucidated from this investigation were i) the existence of an inhibitory interaction between the carotid and aortic baroreflex control of HR when comparing recorded response ranges, and ii) the absence of significant differences among the arterial pressures at which threshold and saturation occurred when comparing the arterial, aortic, and carotid-cardiac baroreflexes in humans. Both of these findings were contrary to our original hypotheses. In addition, the response range of the ABR was significantly greater than that elicited by CBR perturbation complementing previously reported findings that the extracarotid baroreflexes (presumably the ABR) play a more important role than the CBR in the control of HR in humans (14, 24, 32, 33). The finding that an inhibitory interaction existed between the ABR and CBR suggests that neural occlusion of afferent information occurs during signal processing, and points to a certain redundancy inherent within the system. This finding was not surprising, as similar processing characteristics have been described for the regulation of many end-organ systems. For example, our laboratory previously reported the simple sum of the R-R interval responses to left and right carotid sinus stimulation were greater than the bilateral response, again suggesting an inhibitory interaction between the individual reflexes (39).

Surprisingly, analysis of the baroreflex stimulus-response curves constructed for each baroreceptor population tested in this investigation suggested that the arterial, aortic and carotid baroreflexes operated over similar ranges of arterial pressures in controlling the appropriate HR response to acute alterations in pressure. In contrast, animal studies presenting nonpulsatile pressure changes to the aortic and carotid baroreflexes have reported the threshold and saturation pressures to be consistently elevated for the ABR regulation of HR when compared to the CBR (1, 16). The discrepancy between our findings and those reported in dog models was likely due to species differences as well as the techniques employed. More importantly, the use of nonpulsatile pressure to perturb the various baroreceptors may provide the best explanation for the differences observed. For example, using a canine model, Angell-James and Daly (3) have shown that the application of pulsatile stimuli to the carotid sinus markedly increased the pressure at which the threshold of the reflex occurred. In contrast, aortic baroreceptors appear to be insensitive to pulsation (2). In our subjects, the pharmacological and mechanical means utilized to alter arterial pressure would not have prevented the pulsation of the systemic circulation from occurring and most likely contributed to the finding that the operating ranges between the two reflexes were similar. However, in this investigation we were limited in our ability to alter systemic pressure over a large range (i.e., only ±20 mmHg) due to the pronounced tachycardia and bradycardia produced by pharmacological intervention in several subjects. As a consequence, it was plausible that we forced the threshold and saturation of the arterial, aortic, and carotid-cardiac reflexes to occur over a reduced range of arterial pressures.

To address this concern, we additionally stimulated the carotid sinus baroreceptors over a greater range of pressures (Figure 1) using a modification of the rapid neck pressure/neck suction technique (36). The analyses determined that the threshold, saturation, maximal gain, response range, slope, centering point, and minimum HR response elicited from this maneuver were not different from those obtained utilizing brief five second stimuli over the range of pressures produced by pharmacological intervention (i.e., "built" curves). Therefore, we conclude, with relative certainty, that the threshold and saturation pressures described in this study accurately reflect the operating ranges of the arterial, aortic, and carotid-cardiac baroreflexes.

Analysis of the maximal gains of the ABR and CBR suggested that linear summation existed between the reflexes as the simple sum of the gains was not different than the global arterial baroreflex G_{max}. This is in contrast to the conclusions presented in reference to the response ranges for the ABR and CBR which clearly exhibited an inhibitory interaction (or occlusive summation). To discern whether a summative relationship is either linear or nonlinear, stimulus-response curves should be developed for the separate effects of two inputs (i.e., ABR and CBR control of HR) for comparison with the combined effect of inputs (i.e., arterial baroreflex control of HR) (29). Vertical and parallel shifts in the curves will be produced if the relationship is linear. However, if the shifts are horizontally oriented or there is a change in the shape of the curve then the relationship should only be described in nonlinear terms (29). Visual inspection of the stimulus-response curves for the arterial, aortic, and carotid-cardiac reflexes clearly displayed a nonlinear relationship (Figure 2). This was not

surprising as most baroreceptor reflexes behave in a nonlinear manner (29). The calculation of gain used in this study incorrectly assumed a linear relationship in its analysis and therefore may not have accurately reflected the actual behavior of the physiological processes investigated. Although the calculation for the response range for each reflex was also predicated on the assumption of linearity, the results of this prediction complemented the actual raw data collected in which response ranges of 37.5, 30.5, and 13.4 beats·min^{-1} were measured for the arterial, aortic, and carotid baroreflexes , respectively (Table 2). As absolute changes in HR in response to hyper- or hypotensive stimuli are more physiologically relevant than gains predicted by mathematical calculations, we contend that the response range relationship between these reflexes more accurately describes their interrelationship.

In this study, we attempted to functionally isolate the aortic baroreflex regulation of HR from the carotid baroreflex during pharmacologically induced alterations in arterial pressure. This required negating the changes in pressure at the carotid sinus by the application of neck pressure or suction where appropriate. It was important, therefore, to quantify the effectiveness of this technique by calculating the estimated changes in carotid sinus pressure during the aortic isolation maneuver. If the technique was successful, we reasoned that the estimated CSP should not be significantly altered from baseline values. Close examination of Table 3 reveals that we were successful in meeting this goal, albeit less so during administration of hypotensive vasoactive agents. However, we cannot discount the contribution of the CBR, to some extent, to the measured ABR response as we were unable to completely negate the

changes in pressure at the carotid sinus. This may have resulted in an overestimation of the HR response elicited by the ABR. We contend, however, that overestimations were minimal and would not have significantly affected the response ranges reported. To further support this contention, we cannot be sure that the greater increases (PE2 and PE3) and decreases (SN3) in MAP (Table 1) that developed during the aortic isolation procedure from those during the stimulation of the arterial baroreflex were not simply due to the attenuation of the HR response elicited when the CBR was negated. Physiologically, acute changes in pressure are corrected, in part, by appropriate alterations in HR that could not be fully expressed when the CBR was removed from the arterial response. As a result, this could account for the greater increases and decreases in MAP developed during the aortic isolation maneuver. Therefore, the amount of pressure or suction applied to the carotid sinus may have been completely sufficient to counteract the changes in pressure induced by PE and SN infusions.

Although cardiopulmonary baroreceptors do not directly participate in the regulation of HR in humans (19), it is known that stimulating these receptors increases afferent vagal activity to the nucleus tractus solitarius (4) which interacts with arterial baroreceptor afferent signals within the cardiovascular center of the medulla (23, 26). The net result of this interaction is an alteration in efferent neural information. In the present investigation, we did not attempt to control changes in central blood volume which can activate cardiopulmonary baroreceptors. However, using central venous pressure as an indicator of central blood volume, we found no significant alterations in this variable during administration of vasoactive agents. We did obtain modest

increases (maximum of 1.4 mmHg) and decreases (maximum -1.6 mmHg) in CVP from baseline values during arterial baroreflex and ABR testing. It has been demonstrated that unloading of cardiopulmonary baroreceptors in man (quantified as a decrease in CVP) resulted in an increased maximal gain of the carotid-cardiac baroreflex (27). A similar interaction between the aortic and cardiopulmonary baroreceptors has been reported in rabbits (4). Conversely, Shi et al. (34) have indicated that increases in CVP can diminish carotid-cardiac baroreflex sensitivity significantly. We cannot fully discount the participation of the cardiopulmonary baroreflex in the responses elicited during arterial and aortic baroreceptor testing. However, alterations in CVP comparable to those measured in this study have been shown to produce insignificant alterations in ABR and CBR function (27, 34). Therefore, we contend that any alterations in cardiopulmonary activation or deactivation induced in the present investigation would have minimal effects on the responses recorded.

As mentioned previously, it appears the aortic baroreflex is insensitive to pulsation (2, 3, 18). However, in addition to changes in arterial blood pressure and CVP, carotid baroreflex responses are influenced by changes in pulse pressure (7). In the present study, pulse pressure was moderately increased (maximum 6.4 mmHg) and decreased (maximum –3.6 mmHg) during injection of PE and SN, respectively. Further, changes in pulse pressure were similar between arterial and aortic baroreceptor testing. As a result, it was improbable that alterations in pulse pressure contributed significantly to the differences in the reflex response ranges and gains described for the arterial and aortic-cardiac baroreflexes. In support of this conclusion, larger increases

and decreases in pulse pressure than were elicited in the present study have been shown to induce little change in HR (31) and blood pressure (40) in anesthetized dogs.

In modifying the techniques of baroreceptor stimulation utilized in our investigation, we attempted to minimize confounding factors that could negatively influence the results obtained. For example, the HR response to baroreceptor stimulation is known to be dependent on the baseline HR, and the relationships to the cardiac and respiratory cycles (11, 13). To ensure that the changes in HR were due to changes in MAP and estimated CSP, baseline variables incorporating these factors were kept constant during all testing. To eliminate respiratory related variations in HR during maneuvers involving vasoactive drug administration, a ten beat average for the HR response elicited by the perturbation was calculated. Carotid baroreceptor stimulation techniques, likewise, controlled for respiratory induced oscillations in HR by being executed during a breath hold (after normal expiration) when blood pressure and HR were unchanged for a minimum three beat period. Further, short five second pulses and rapid pulsatile stimuli were applied to the carotid sinus during the execution of this technique to minimize baroreceptor "resetting" and counteraction by extracarotid baroreceptors. Similarly, during aortic isolation procedures, the counteracting pulse was delivered as close to the peak or nadir of the pressure response as possible to minimize the length of the stimulus, again to prevent baroreceptor resetting. During execution of this protocol, counteraction of the response elicited (or more correctly negated) at the carotid sinus was not a concern as arterial pressure was pharmacologically clamped at the aortic arch. As in all cases in which neck pressure or

suction are used to perturb the carotid baroreflexes, the accuracy of the technique depends critically on how completely the stimulus is transmitted to the carotid artery. In humans, Ludbrook et al. (22) have reported 86% and 64% transmission to the perivascular tissue of external NP and NS, respectively. We used these characteristics in choosing the amount of stimulus to be delivered and in the analysis for estimating carotid sinus pressure for techniques utilizing this maneuver.

Several potential limitations in the design and interpretation of this study are recognized. To begin, the use of bolus injections of vasoactive agents may have produced an overestimation of the gains and response ranges of the arterial and aortic-cardiac baroreflexes as has been previously reported during phenylephrine injection (37). In addition, it is possible that the use of PE and SN might sensitize the aortic and carotid baroreceptors, again eliciting an overestimation in the gains and response ranges of the baroreflexes tested in this manner. This, however, is of minimal concern as previous studies using similar concentrations and amounts of PE have reported little changes in the HR response to the pharmacological perturbation (14). Further, the interventions utilized primarily elicit HR changes via alterations in parasympathetic activation or deactivation as reflex cardiac sympathetic responses tend to be slower (6, 38). However, as the perturbation in ABP is prolonged (>30s), as is the case with vasoactive drug administration, the sympathetic nervous system plays a more active role in mediating the reflex response (38). This could confound our interpretation of the results obtained for arterial and aortic baroreflex perturbation in comparison to the more vagally mediated responses elicited during carotid baroreflex stimulation alone.

However, as this study was designed to determine differentiated baroreflex control of HR, the relative contributions of the parasympathetic and sympathetic nervous systems are better left to be discerned by studies designed expressly to measure their activity. Finally, as all studies were performed in the supine position, caution should be exercised in extrapolating the data reported to humans in the erect position. Compared to the supine position, pulse pressure has been demonstrated to be lower at the carotid sinus in the upright posture (15), a situation that does not present at the aortic arch where shifts in hydrostatic pressure are relatively small because of its closer location to the hydrostatic indifference point.

In summary, the present investigation supports the contention that aortic and carotid-cardiac reflexes exhibit an inhibitory interaction (i.e., the arterial baroreflex response is significantly less than the algebraic sum of the response of the ABR and CBR). In addition, the threshold and saturation of the stimulus-response curves of the aortic and carotid-cardiac baroreflexes occur at similar pressures, indicating that the aortic and carotid baroreceptors operate over the same arterial pressure range. Further these data are consistent with previous reports (14, 24, 32, 33) that the aortic baroreflex predominates over the carotid baroreflex in eliciting the global arterial baroreflex regulation of HR in response to changes in arterial pressure. It should be noted, however, that our subjects were only tested in the supine position. The interactive relationship may be altered in the upright position due to changes in pulse pressure at the carotid sinus or by alterations in central blood volume activating cardiopulmonary baroreceptors. Therefore, our results are representative of healthy normotensive young

adults with normal resting HRs in the supine position. The evaluation of aortic and carotid-cardiac responses in persons with cardiovascular disease, clinical pathologies, or between groups with differing levels of aerobic fitness, may result in a different set of conclusions.

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TABLE 1. Pressure responses during experiment

Arterial Baroreflex					
Trial	**SBP (mmHg)**	**DBP (mmHg)**	**MAP (mmHg)**	**PP (mmHg)**	**CVP** (mmHg)**
SN3	111.1±2.4*	49.4±2.5*	68.2±2.4*	61.7±1.8	5.0±0.9
SN2	115.3±2.7*	52.7±3.3*	72.0±3.0*	62.6±2.2	5.6±0.9
SN1	122.0±4.1	58.9±3.2*	77.2±2.7*	63.1±2.1	5.9±0.8
Baseline$_1$	130.2±3.5	67.4±2.5	88.1±2.7	62.8±1.6	6.4±0.9
PE1	141.0±3.9	75.0±2.5*	97.8±2.7*	65.7±1.8	7.2±1.1
PE2	143.8±3.9	77.3±2.3*	99.9±2.8*	67.0±2.4	7.7±1.1
PE3	150.9±3.3*	81.8±3.0*	106.4±2.7*	69.2±2.5	7.8±1.3
Aortic Baroreflex					
SN3	105.6±2.7*	43.2±2.2*†	63.5±2.1*†	61.2±3.2	5.5±1.0
SN2	113.1±4.1*	49.2±2.8*	69.2±2.8*	64.0±3.3	5.2±1.2
SN1	120.7±3.5	54.6±1.6*	75.9±2.3*	65.2±3.1	6.0±1.1
Baseline$_2$	132.1±3.6	67.3±1.5	89.1±2.0	64.8±3.4	6.8±1.3
PE1	147.4±2.9*	77.2±1.9*	101.5±2.0*	70.2±3.1	7.8±1.3
PE2	150.9±2.8*	80.8±2.6*	105.1±2.3*†	70.1±3.0	7.7±1.4
PE3	156.0±2.6*†	85.8±2.5*	111.0±2.2*†	70.2±3.1	8.2±1.5

Values are means ± SE. SN, sodium nitroprusside bolus infusion; PE, phenylephrine bolus infusion; Values 1-3 for SN and PE trials indicate increasing levels of drug administration; SBP, DBP, MAP, PP, and CVP, systolic blood, diastolic blood, mean arterial, pulse, and central venous pressures, respectively; Baseline$_1$ and Baseline$_2$ indicate basal values for the arterial and aortic baroreflexes, respectively. *Significantly different from baseline; †Significantly different from arterial baroreflex; ** Indicates N=8. For all other variables N=11. Group differences significant at $P<0.05$.

TABLE 2. Heart rate responses during experiment

Heart Rate (beats·min^{-1})							
Reflex	**SN3**	**SN2**	**SN1**	**Baseline**	**PE1**	**PE2**	**PE3**
Arterial BR	82.1 ±4.5*	77.6 ±4.6*	73.7 ±4.1*	59.5 ±3.5	47.9 ±2.6*	46.7 ±2.7*	44.6 ±2.5*
Aortic BR††	78.1 ±3.3*	76.7 ±4.2*	70.5 ±4.0*	59.8 ±3.3	50.1 ±2.5*	48.1 ±2.5*	47.6 ±2.8*
Carotid BR**	65.8 ±2.8*†§	65.7 ±2.8*†§	62.9 ±2.8†§	59.9 ±2.9	54.4 ±2.7†	52.4 ±2.6*†	52.6 ±2.5*†

Values are means ± SE. BR, baroreflex; SN, sodium nitroprusside bolus infusion; PE, phenylephrine bolus infusion; Values 1-3 for SN and PE trials indicate increasing levels of drug administration. †† SN and PE bolus infusion combined with neck suction and neck pressure, respectively. ** SN and PE were not administered during carotid baroreflex isolation procedures. However, neck pressure and suction were utilized to simulate the changes in pressure produced during evaluation of arterial and aortic baroreflex function. *Significantly different from baseline; †Significantly different from arterial baroreflex; §Significantly different from aortic baroreflex. Group differences significant at $P<0.05$.

TABLE 3. Estimated Carotid Sinus Pressure during experiment

Estimated Carotid Sinus Pressure (mmHg)							
Reflex	**SN3**	**SN2**	**SN1**	**Baseline**	**PE1**	**PE2**	**PE3**
Arterial BR	68.2 ±2.4*	72.0 ±3.0*	77.2 ±2.7*	88.1 ±2.7	97.8 ±2.7*	99.9 ±2.8*	106.4 ±2.7*
Aortic BR††	82.7 ±2.3*‡	84.5 ±2.5‡	85.8 ±2.4‡	89.1 ±2.0	90.6 ±2.0‡	91.0 ±2.6‡	91.1 ±2.4‡
Carotid BR**	68.1 ±2.4*	72.3 ±2.7*	78.4 ±2.6*	89.0 ±2.6	100.0 ±2.9*	103.3 ±3.0*	109.4 ±3.1*

Values are means ± SE. BR, baroreflex; SN, sodium nitroprusside bolus infusion; PE, phenylephrine bolus infusion; Values 1-3 for SN and PE trials indicate increasing levels of drug administration. †† SN and PE bolus infusion combined with neck suction and neck pressure, respectively. ** SN and PE were not administered during carotid baroreflex isolation procedures. However, neck pressure and suction were utilized to simulate the changes in pressure produced during evaluation of arterial and aortic baroreflex function. *Significantly different from baseline; ‡Significantly different from arterial baroreflex and carotid baroreflex. Group differences significant at $P<0.05$.

TABLE 4. Baroreflex function curve parameters

Reflex	Threshold (mmHg)	Saturation (mmHg)	Slope Coefficient	Centering Pt (mmHg)	Min HR (beats·min^{-1})
Arterial BR	71.5 ±3.7	98.1 ±3.3	0.18 ±0.03	84.8 ±3.2	42.3 ±2.7
Aortic BR	66.8 ±2.7	99.1 ±2.2	0.13 ±0.01	82.9 ±2.2	46.0 ±2.7†
Built Carotid BR	75.2 ±2.1	102.0 ±2.8	0.17 ±0.02	88.6 ±2.0	51.5 ±2.5†§
Pulsed Train Carotid BR	72.4 ±4.3	101.5 ±2.8	0.18 ±0.02	87.0 ±3.1	49.4 ±2.1†

Values are means ± SE. BR, baroreflex; Pt, point; Min HR, minimum heart rate response. The carotid baroreflex was evaluated by utilizing neck pressure and suction of varying levels when a five second stimulus was applied (built carotid baroreflex) and when rapid pulsed stimuli were gated to the R-wave of the cardiac cycle (pulsed train carotid baroreflex). †Significantly different from arterial baroreflex; §Significantly different from aortic baroreflex; Group differences significant at $P<0.05$.

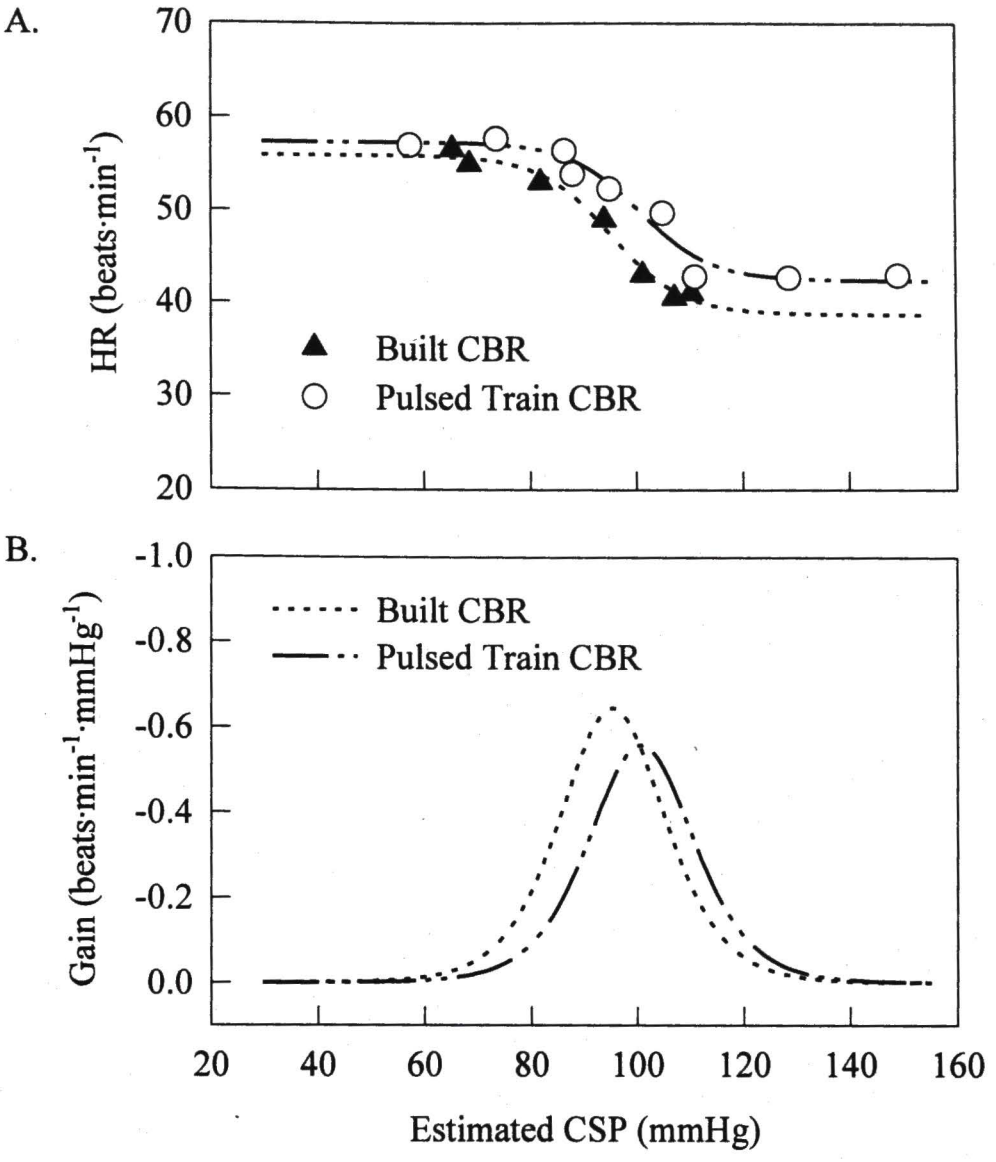

Figure 1. Panel A: Carotid baroreflex (CBR) regulation of heart rate (HR) elicited by neck pressure and suction applied as five second stimuli (Built CBR) and as pulsed train stimuli gated to the cardiac cycle R-wave (Pulsed Train CBR) in one subject. Note the larger range of stimuli applied during the "pulsed train" perturbation. Panel B: Reflex gain responses as calculated from the first derivative of the logistic function for each method of CBR analysis evaluated in the same subject. There were no significant group differences in the threshold, saturation, maximal gain, or HR response range between the two methods of CBR analysis utilized in this investigation. CBR stimulation was measured over a range of estimated changes in carotid sinus pressure (CSP) corrected for neck transmission characteristics (22).

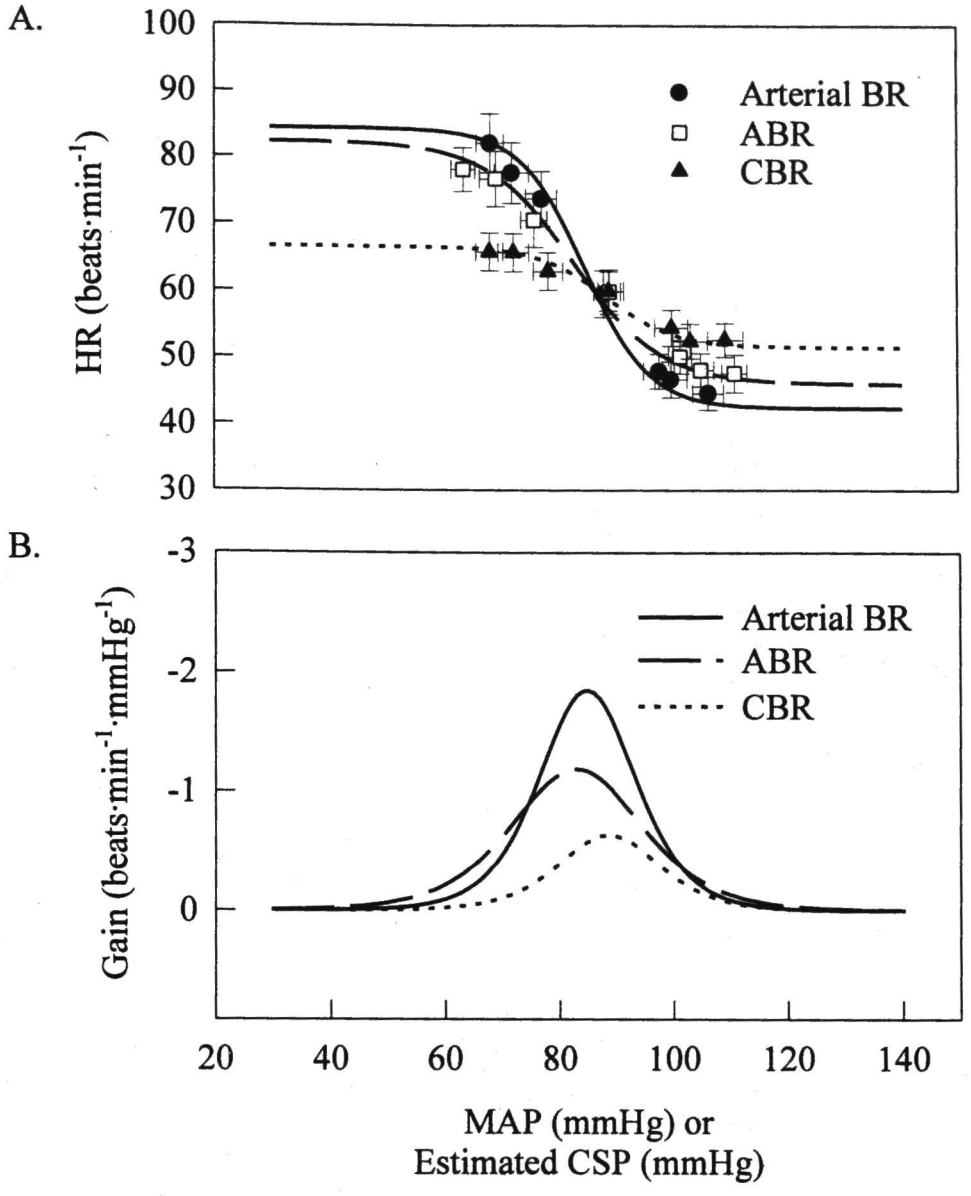

Figure 2. Panel A: Changes in heart rate (HR) elicited during arterial, aortic, and carotid baroreceptor isolation procedures. Symbols denote actual group data (means ± SE), and lines represent fitted logistic functions developed from group mean baroreflex curve parameters. Panel B: Reflex gain responses as calculated from the first derivative of the logistic function for each baroreceptor population evaluated. Note the operating ranges of the reflexes are not significantly different. Arterial baroreflex (BR) and aortic baroreflex (ABR) HR responses were measured over a range of changes in mean arterial pressure (MAP) whereas HR responses induced by neck pressure and suction during carotid baroreflex (CBR) stimulation were measured over a range of estimated changes in carotid sinus pressure (CSP) corrected for neck transmission characterstics (22).

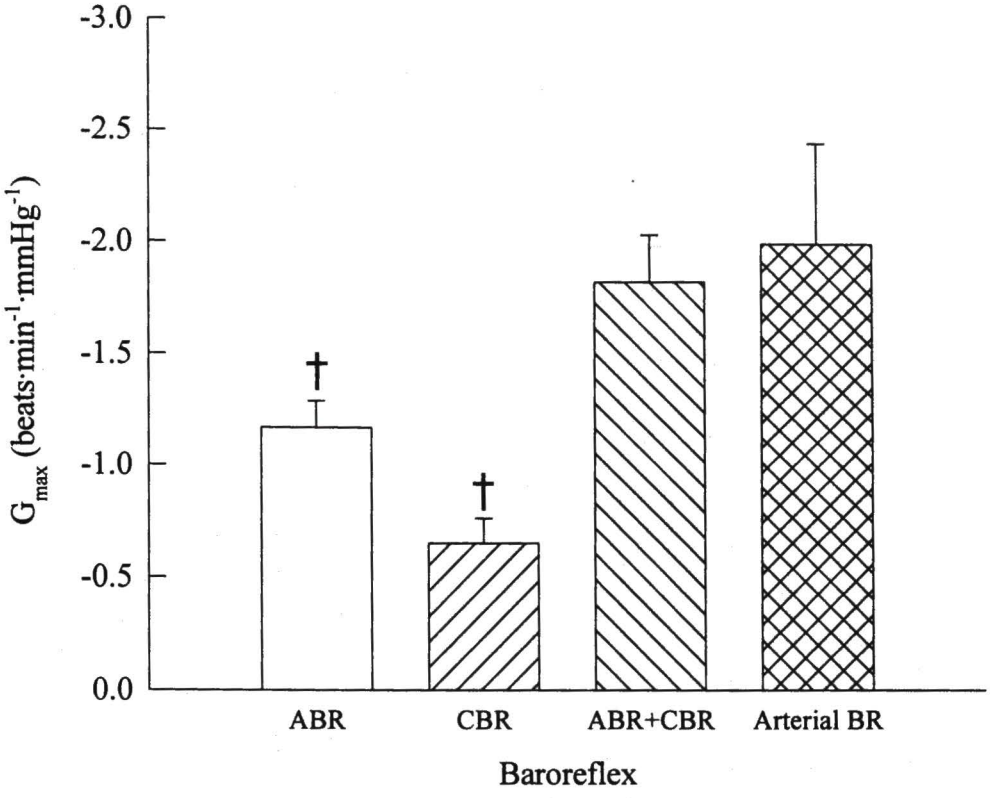

Figure 3. Maximal gain (G_{max}) responses for aortic (ABR), carotid (CBR), ABR+CBR, and arterial baroreflexes. The individual maximal gains of the ABR and CBR were significantly less than the maximal gain of the arterial baroreflex (BR). However, the simple sum of the ABR and CBR was not significantly different from the arterial baroreflex indicating additive summation. † Indicates significantly different from arterial BR ($P<0.05$).

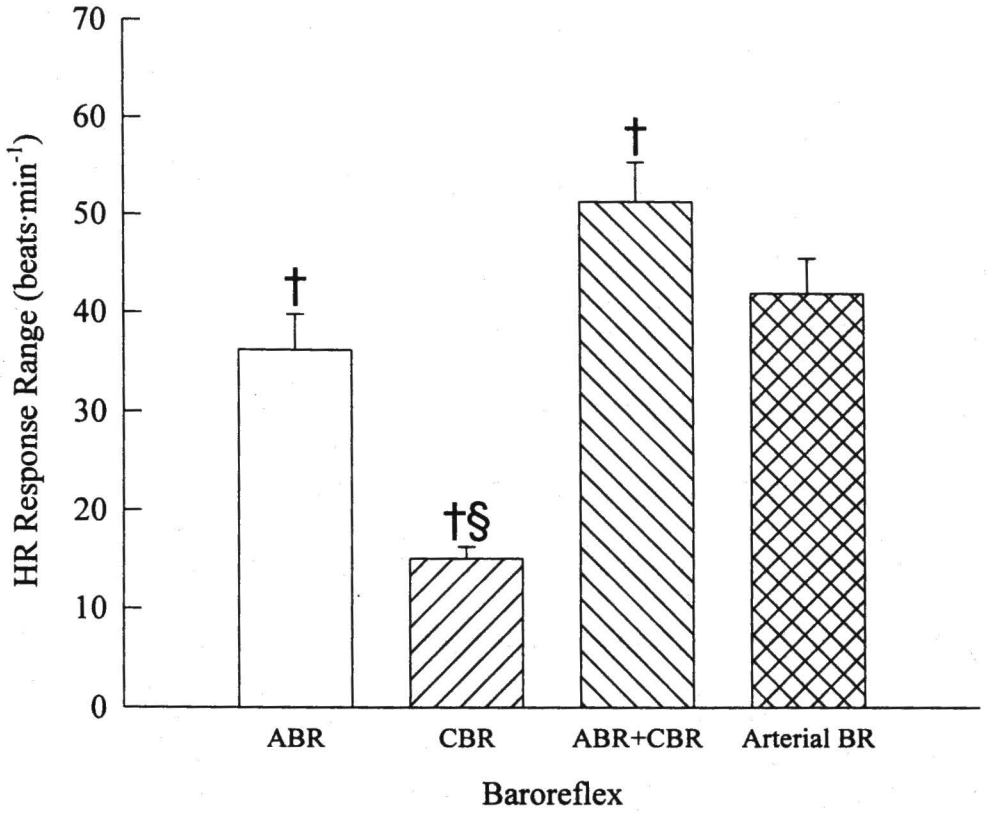

Figure 4. Heart rate (HR) response ranges for aortic (ABR), carotid (CBR), ABR+CBR, and arterial baroreflexes. The individual response ranges of the ABR and CBR were significantly less than the response range of the arterial baroreflex (BR). In addition, the response range of the CBR was significantly lower than the ABR suggesting the latter contributes more to the global arterial response. Interestingly, the simple sum of the ABR and CBR was significantly different from the arterial baroreflex indicating an inhibitory interaction. † Indicates significantly different from arterial BR. § Indicates significantly different from ABR ($P<0.05$).

PREFACE TO CHAPTER III

The results of the previous investigation suggested that afferent information transduced as a result of activation or deactivation of aortic and carotid baroreceptors was processed in an occlusive manner at the cardiovascular center within the medulla indicating redundancy within the baroreflex arc. In addition, the lack of significant differences among the arterial pressures at which threshold and saturation occurred, when comparing the arterial, aortic, and carotid-cardiac baroreflexes, supported the contention that the aortic and carotid baroreceptors operate over the same range of arterial pressures. However, the question remains as to whether these relationships are altered by endurance exercise training in humans. Arterial baroreflex control of heart rate has clearly been demonstrated to be attenuated in aerobically fit individuals compared to their untrained counterparts. In addition, several investigations have attributed this diminution in arterial baroreflex sensitivity to the development of reduced aortic baroreceptor responsiveness. Unfortunately, these studies have not attempted to fully elucidate the aortic-cardiac baroreflex stimulus-response curve. Therefore, it has yet to be discerned whether the reduction in reflex sensitivity is due to a relocation of the operating point towards the threshold or saturation of the reflex or to a reduction in the overall reflex response range. In addition, there have been no reports in the literature on the central integration of aortic and carotid afferent information in response to endurance exercise training. Therefore, the second investigation was

designed to demonstrate the effects of acute alterations in blood pressure on baroreflex heart rate control in aerobically fit and sedentary individuals.

CHAPTER III

DIFFERENTIAL BAROREFLEX CONTROL OF HEART RATE IN SEDENTARY AND AEROBICALLY FIT INDIVIDUALS

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Medicine and Science in Sports and Exercise

ABSTRACT

Purpose: We compared arterial, aortic, and carotid-cardiac baroreflex sensitivity in eight average fit (maximal oxygen uptake, VO_{2max}=42.2±1.9 ml·kg^{-1}·min^{-1}) and eight high fit (VO_{2max}=61.9±2.2 ml·kg^{-1}·min^{-1}) healthy young adults. **Methods:** Arterial and aortic (ABR) baroreflex functions were assessed utilizing hypo- and hypertensive challenges induced by graded bolus injections of sodium nitroprusside (SN) and phenylephrine (PE), respectively. Carotid baroreflex (CBR) sensitivity was determined using ramped five second pulses of both pressure and suction delivered to the carotid sinus via a neck chamber collar, independent of drug administration. A logistic function describing the HR responses to changes in mean arterial pressure (MAP) and estimated carotid sinus transmural pressure (CSP) was used to quantify the response range of each reflex. **Results:** During vasoactive drug infusion, MAP was similarly altered in average fit (AF) and high fit (HF) groups. However, the heart rate (HR) response range of the reflex was significantly attenuated ($P<0.05$) in HF (31.0±3.5 beats·min^{-1}) compared to AF individuals (45.5±4.2 beats·min^{-1}). When sustained neck suction and pressure were applied to counteract altered CSP during SN and PE administration, thereby isolating the ABR response, the response range remained diminished ($P<0.05$) in the HF population (23.6±2.9 beats·min^{-1}) compared to the AF group (40.6±4.1 beats·min^{-1}). However, during CBR perturbation the HF (14.1±1.2 beats·min^{-1}) and AF (16.3±1.4 beats·min^{-1}) response ranges were similar. In addition, the arterial baroreflex response range was significantly less than the simple sum of the CBR and ABR response ranges (HF, 37.7±3.4 beats·min^{-1} and AF, 56.8±4.4

beats·min^{-1}) in both fitness groups. **Conclusions:** These data confirm that reductions in arterial-cardiac reflex sensitivity are mediated by diminished ABR function. More importantly, these data suggest that the integrative relationship between the ABR and CBR contributing to the global arterial baroreflex control of HR is inhibitory in nature and is not altered by exercise training.

KEY WORDS:

Autonomic Control, Fitness, Baroreceptors, Gain, Inhibitory Interaction

INTRODUCTION

The cardiovascular and structural adaptations that occur in response to chronic exercise training have been well described in humans. In addition to a decreased resting heart rate (13, 20, 33), exercise training has been reported to induce hypervolemia (6), cardiac eccentric hypertrophy (18) and increases in total vascular conductance (40), ventricular compliance (24), and stroke volume (23, 24) without a concomitant alteration in resting mean arterial pressure (39). Further, several investigators have demonstrated that endurance training enhances efferent vagal activity (13, 20) while diminishing sympathetic efferent neural control at rest (13). It has been hypothesized that alterations in autonomic function depress the reflex control of cardiac performance and vasomotion by the arterial baroreflex due to enhanced parasympathetic neural influence (43). While beneficial during exercise, the physiological consequence of such alterations in tissue morphology and cardiovascular neural regulation has been suggested to be the development of intolerance to orthostatic stress (5, 16).

Several studies in humans have reported attenuated arterial baroreflex mediated tachycardia in exercise trained individuals using a wide array of hypotensive stimuli including lower-body negative pressure (33, 42, 45), upright tilt (22), and steady-state infusion of sodium nitroprusside (39). Likewise, the reflex cardio-decelerator response to hypertension induced by phenylephrine infusion has been reported to be significantly less in high fit (HF) individuals compared to their untrained counterparts (38, 42). Shi et al. (38, 39) have convincingly attributed the diminished arterial-cardiac responsiveness to a diminution in aortic baroreflex (ABR) sensitivity. Complementing

these findings, both cross-sectionally (23, 47) and longitudinally (25, 37) designed investigations have reported carotid baroreflex (CBR) control of heart rate (HR) to be unaltered when comparing HF and average fit (AF) individuals. Unfortunately, these studies have been unable to fully characterize the reflex stimulus-response curve of the ABR which, presumably, is sigmoidal in nature as are the arterial and carotid-cardiac baroreflexes. Therefore, it has yet to be elucidated if the diminished aortic-cardiac reflex responsiveness to both hypotension and hypertension results from i) a relocation of the operating point (OP) towards the threshold or saturation of the reflex thereby limiting further increases and decreases in HR, respectively; or ii) a complete reduction of the HR responding range which could indicate a vertical downward shift of the entire reflex stimulus-response curve.

The sigmoidal shape of the stimulus response curve characterizing the arterial baroreflex represents the integrated input from both the aortic and carotid baroreceptors and, as such, the global response could result from the algebraic sum of the two inputs or involve either an inhibitory or facilitatory interaction. Due to technical difficulties and required precautions, there is little information on the central integration of afferent signals from the carotid and aortic baroreceptors in humans and none in reference to the effects of exercise training. Attempts to clarify this relationship in untrained animals has produced variable results with the interrelationship being described as an inhibitory interaction (2), an additive summation (9), and a facilitatory interaction (17, 19).

The purpose of this study was, therefore, multifaceted and designed in order to i) elicit discrete reflex changes in HR from the arterial, aortic, and carotid baroreceptors

from which individual baroreflex stimulus-response curves could be characterized in both HF and AF populations; ii) quantify the position of the OP on each baroreflex curve; and iii) determine if the interactive relationship between aortic and carotid baroreceptors is altered as a result of chronic endurance exercise training indicative of a central modification to the arterial baroreflex arc.

METHODS

Subjects. Twelve men and four women were recruited for voluntary participation in the present investigation. All provided written consent approved by the University of North Texas Health Science Center Institutional Review Board for the use of Human Subjects. Subjects were administered a graded exercise test to their limit of tolerance for determination of electrocardiographic abnormalities and maximal oxygen uptake (VO_{2max}) following completion of a medical history questionnaire, resting electrocardiogram (ECG), and blood pressure screening exam. Subjects exhibiting any blood pressure or cardiovascular abnormalities were excluded from the study. Based on their exercise history and tested VO_{2max}, subjects were invited to participate in the study, informed of the testing protocols, and advised of the potential risks inherent to the procedures to be utilized. Those subjects demonstrating a $VO_{2max} > 60$ $ml \cdot kg^{-1} \cdot min^{-1}$ and having performed regular aerobic training for over one year (i.e. cyclists=3; long-distance runners=5) were considered to be high fit (HF=8), while those possessing a $VO_{2max} < 45$ $ml \cdot kg^{-1} \cdot min^{-1}$ and not performing aerobic exercise regularly were considered to be average fit (AF=8). All subjects were asymptomatic for cardiovascular

and respiratory disease, were normotensive nonsmokers, and were not currently taking medication. The actual experimental protocol was scheduled on a separate day from the exercise test. In addition, subjects were requested to abstain from caffeinated beverages, strenuous physical activity, and alcohol at least 24 h before testing. Subjects were familiarized with the equipment and procedures and were allowed to become comfortable with the experimental protocols before the actual data collection began.

Experimental Protocols

Exercise testing. Following completion of their pre-test evaluation, each subject's VO_{2max} was assessed from a graded treadmill exercise test. Both speed and grade were increased each minute, by 0.15 miles·h^{-1} and 1.5%, respectively, until a plateau of oxygen uptake was observed or the subject requested testing to be terminated. Oxygen uptake was determined using a dedicated breath-by-breath analysis system incorporating a mass spectrometer (Perkin-Elmer MGA-1100A, Pomona, CA) to determine the partial pressures of respiratory gases (O_2, CO_2, and N_2) in the inspired and expired breath volumes. The analog signals of the mass spectrometer were digitally converted by a personal computer (Gateway 2000, N. Sioux City, SD) for on-line data acquisition and analyses using customized software. Descriptive group data are presented in Table 1.

Measurements. All experimental phases were conducted with the subjects in a supine position. Cardiovascular variables were monitored beat-to-beat and recorded by a personal computer (PC) equipped with customized software. Heart rate was

monitored utilizing standard ECG electrodes. The ECG signal was output to a pressure monitor (Hewlett-Packard 78342A, Andover, MA) interfaced with the PC. In five HF and five AF subjects, central venous pressure (CVP) was monitored via a double lumen catheter (50 cm, French 5, Cook Critical Care, Bloomington, IN) placed through the median antecubital vein and advanced, under fluoroscopy (Phillips BV22, Eindhoven, Netherlands), until the tip was at the level between the 3rd and 4th rib. In thirteen of the subjects, arterial blood pressure (ABP) was measured via a Teflon intra-radial arterial catheter (1.25"-long, 20 gauge). Prior to placement of both the CVP and arterial catheters, Lidocaine (1%) was injected subcutaneously to minimize subject discomfort. In addition, both CVP and ABP were monitored using a dual set of pressure transducers (Cobe, Inc., Lakewood, CO) interfaced with the on-line pressure monitor. Both pressure transducers were calibrated before and after each experiment and the zero point was set at the subject's midaxillary line. Catheter patency was maintained by a continuous drip (2 ml/h) of heparinized saline (2 U/ml). In three subjects, ABP was measured by a finger photoplethysmographic method (Finapres, Ohmeda). Previously, this well-controlled indirect method for measurement of ABP has been highly correlated with direct recording via arterial catheters over a wide range of arterial pressures (38). The hand was aligned at the subject's midaxillary line to establish zero reference for systolic (SBP), diastolic (DBP), mean arterial (MAP), and pulse (PP) pressure measurement. In addition, DBP readings from the Finapres were referenced against brachial auscultatory DBP.

Arterial and aortic baroreceptor responsiveness. Subjects rested quietly for approximately 1h before testing began after instrumentation was complete. The arterial and aortic baroreflex control of HR was assessed using a modification of a technique described previously (14, 35) in which selective alteration of aortic distending pressure is made possible by intra-venous injection of the vasoactive agents phenylephrine (PE) and sodium nitroprusside (SN). Utilizing placement of a peripheral catheter in an antecubital vein of the arm opposite to that used for estimating CVP, we administered three doses of PE and SN in both HF and AF subjects in order to acutely alter MAP by ±10, ±15, and ±20 mmHg. The doses administered in the AF group were: PE1 = 0.63 ± 0.09 $\mu g \cdot kg^{-1}$; PE2 = 1.25± 0.18 $\mu g \cdot kg^{-1}$; PE3 = 2.06 ± 0.24 $\mu g \cdot kg^{-1}$; SN1 = 0.88 ± 0.09 $\mu g \cdot kg^{-1}$; SN2 = 1.56 ± 0.16 $\mu g \cdot kg^{-1}$; and SN3 = 2.25 ± 0.25 $\mu g \cdot kg^{-1}$. In the HF population the following doses were utilized: PE1 = 0.63 ± 0.09 $\mu g \cdot kg^{-1}$; PE2 = 1.13± 0.09 $\mu g \cdot kg^{-1}$; PE3 = 1.75 ± 0.10 $\mu g \cdot kg^{-1}$; SN1 = 0.69 ± 0.10 $\mu g \cdot kg^{-1}$; SN2 = 1.22 ± 0.16 $\mu g \cdot kg^{-1}$; and SN3 = 1.81 ± 0.23 $\mu g \cdot kg^{-1}$. The drug was introduced to the circulation via bolus injection and each dose was administered in duplicate. One minute of baseline data for HR, ABP, and CVP was obtained and averaged before each infusion. Subsequently, the drug was rapidly injected and the catheter flushed with 5 ml of heparinized saline. Data was then analyzed by taking 10 beats evenly distributed around the peak and nadir of the MAP response to PE and SN, respectively. After five minutes, collection of baseline data was again resumed. During this phase of testing, we assumed that both aortic and carotid baroreceptors were stimulated similarly and, therefore, would accurately characterize the arterial baroreflex control of HR. In order to negate

PE and SN-induced changes in carotid sinus transmural pressure, the protocol was repeated with sustained neck pressure (NP) and neck suction (NS) applied to the anterior two-thirds of the neck through a malleable lead collar (11). In this phase of testing, the amount of NP and NS utilized were derived using the neck pressure/suction transmission characteristics described by Ludbrook et al. (27) assuming 86% and 64% transmission of NP and NS, respectively. The counteracting stimuli were delivered to the carotid sinus close to the peak and nadir of the pressure change (the delay being estimated from the initial drug administration). Again, data were analyzed over a 10-beat period bilaterally distributed around the largest change in MAP. In the AF population, the levels of NP and NS (torr) applied during this phase of experimentation were: PE1 = 12.7 ± 1.5; PE2 = 16.6 ± 1.9; PE3 = 23.8 ± 1.7; SN1 = -15.6 ± 1.4; SN2 = -25.6 ± 3.2; SN3 = -30.4 ± 2.4; and for the HF group: PE1 = 12.3 ± 1.4; PE2 = 17.0 ± 2.1; PE3 = 21.0 ± 2.2; SN1 = -16.0 ± 1.1; SN2 = -20.7 ± 1.3; SN3 = -27.3 ± 1.5. We assumed use of this procedure would successfully negate drug-induced alterations in mean pressure at the carotid sinus and therefore functionally isolate the aortic baroreflex. This approach allowed us to develop stimulus-response curves for the arterial and aortic-cardiac reflexes for comparison.

Carotid baroreceptor responsiveness. We assessed the carotid baroreflex control of HR, independent of drug injection, using two distinct techniques for carotid sinus manipulation. First, we attempted to simulate the changes in ABP elicited during vasoactive drug injection by applying three absolute levels of NS (to mimic alterations elicited during PE1, PE2, and PE3) and NP (to simulate changes produced during SN1,

SN2, and SN3) through the lead neck collar. In the AF subjects, the amount of applied pressure or suction (torr), corrected for reported neck transmission characteristics (27), were: PE1, -17.1 ± 2.8; PE2, -22.7 ± 3.4; PE3, -32.5 ± 3.1; SN1, 12.6 ± 1.1; SN2, 20.6 ± 2.6; and SN3, 24.9 ± 1.7; and in HF individuals the respective levels were: PE1, -16.3 ± 2.1; PE2, -22.7 ± 2.4; PE3, -29.8 ± 3.1; SN1, 12.4 ± 1.0; SN2, 15.6 ± 1.1; and SN3, 21.8 ± 1.9. Previously, we described in detail our approach for completing open-loop stimulus-response curves using this technique (32). Briefly, each level of NP and NS was delivered to the carotid sinus for a period of five seconds during a 10 to 15 second breath hold at end expiration. This method effectively minimized the effect of respiratory related oscillations in HR and counteraction of the elicited response by the aortic baroreceptors. Three to four perturbations were performed at each of the six pressure levels. The peak HR response (consistently observed during the five second period of NP/NS) to each stimulus was averaged to provide a mean response for each subject. Beat-to-beat HR responses and the generated level of neck collar pressure were measured throughout the breath hold period and recorded on-line. The peak HR responses were then paired with the estimated changes in carotid sinus transmural pressure [(ECSP) = MAP - neck chamber pressure (0.86 (NP) or 0.64(NS))] to "build" a complete baroreflex stimulus-response curve. By performing this calculation, the actual changes in pressure at the carotid sinus could be estimated and, therefore, were comparable to the alterations in MAP elicited during arterial and aortic baroreceptor testing. To ensure that we were not forcing the stimulus-response curves developed over a particular range of pressures, we used a second

technique to assess CBR control of HR that we have described, in detail, previously (31). Following a normal expiration and breath-hold (at end-expiration), 12 consecutive pulses (range: 40 to –80 torr), each 500 ms in duration, were delivered to the carotid sinus precisely 50 ms after the R wave of the ECG to elicit maximum baroreflex responses (10). This range of pressures and suctions has been typically used to produce bilateral stimulus response curves using a ramped change in neck chamber pressures (44). Neck chamber pressure was controlled manually using variable auto-transformers that regulated voltage to vacuum motors that supplied the required pressure and suction. The neck chamber was vented to atmospheric pressure between each pulse in the stimulus train to minimize any chance of baroreceptor resetting (30). Three to six trains of NP/NS were executed for each subject with a minimum of 90 sec between successive trials. Heart rate responses from at least three trains were paired with the calculated changes in ECSP (calculated as aforementioned), to derive three "pulsed train" stimulus-response curves per subject. The parameters of each curve were averaged to provide a mean response for each subject. Using these techniques, it was possible to construct a family of stimulus-response curves for the CBR that were strictly comparable to those developed for the arterial and aortic baroreflexes.

Data analyses. Using analytical methods previously described (31, 47), data for the arterial, aortic, "built" carotid, and "pulsed train" carotid-cardiac baroreflex stimulus-response curves, using HR as the dependent variable, were fit to a four-parameter logistic function described by Kent et al. (21) using the equation:

$$HR = A_1 (1 + e^{[A_2 (MAP \text{ or } ECSP - A_3)]})^{-1} + A_4$$

where A_1 is the range of the HR response (maximum to minimum), A_2 is the gain coefficient (i.e., slope), A_3 is the MAP or ECSP required to elicit equal pressor or depressor responses (i.e., centering point, CP), and A_4 is the minimum HR response. The baroreflex stimulus response curves were developed from logistic modeling of the HR change elicited for a given change in MAP or ECSP. These curves are sigmoidal in nature and were fit to the function using a nonlinear least squares regression. The gain of the arterial, aortic, and carotid-cardiac reflexes was determined from the first derivative of the logistic function, whereas the maximal gain (G_{max}) was calculated as the gain value located at parameter A_3. Values for threshold (i.e. where no further increases in HR were elicited) and saturation (i.e. where no further decreases in HR were produced) were calculated as the maximum and minimum second derivatives, respectively, of the logistic function for the sigmoid curve. In addition, the position of the operating point (i.e. resting MAP) on each stimulus-response curve derived was quantified by subtracting parameter A_3 (i.e. centering point) from the OP. Subject parameters were averaged and presented as group means.

Statistical analyses. Statistical comparisons of descriptive variables for AF and HF groups were performed using paired t-tests. Comparison of cardiovascular variables (HR, SBP, DBP, MAP, PP, CVP, and ECSP) for each of the four techniques employed were made utilizing a repeated measures two-way analysis of variance (ANOVA) with a 4 x 7 design (baroreflex tested x drug trial). Similarly, the effects of fitness and gender were conducted for each baroreflex examined using a repeated measures two-way ANOVA with a 2 x 7 design (fitness or gender group x drug trial). Comparison of

stimulus-response curve parameters (G_{max}, threshold, saturation, response range, slope, centering point, minimum HR response and OP – CP relationships) were made by executing a repeated measures two-way ANOVA with a 2 x 4 design (fitness group x baroreflex tested). In all ANOVA analyses, a Student Neuman-Keuls (SNK) test was employed *post hoc* when main effects were significant. The alpha level was set at $P < 0.05$. Results are presented as means (± SE). Analyses were conducted using SigmaStat for Windows (Jandel Scientific Software, SPSS Inc., Chicago, IL).

RESULTS

There were no significant fitness group differences in age, height, weight, and resting MAP (Table 1). By design, the group mean VO_{2max} of the HF subjects was significantly greater than the AF subjects when normalized for body weight. The resting HR was lower in the HF than in the AF subjects, albeit not significantly. This lack of fitness group difference in resting HR was attributed to one HF subject that had an unusually elevated resting HR (66.7 beats·min^{-1}) and two AF subjects with extraordinarily low resting HRs (below 48 beats·min^{-1}). When these subjects were excluded from HR analysis, the mean resting HR was 64.9±3.5 beats·min^{-1} and 52.9±2.6 beats·min^{-1} in the AF and HF subjects, respectively, ($P<0.05$). In addition, there were no significant differences in cardiovascular variables or baroreflex parameters examined between men and women ($P>0.05$).

Cardiovascular responses

Arterial baroreflex. During bolus infusion of SN and PE to assess arterial baroreflex function, decreases and increases, respectively, in MAP were similar between the AF (maximum decrease, 64.7±1.8 mmHg and increase 104.9±3.7 mmHg) and HF (maximum decrease, 70.0±4.5 mmHg and increase, 102.7±5.5 mmHg) subjects (Figure 1). In addition, MAP was significantly decreased and increased from baseline at all levels of SN and PE bolus infusion, respectively. The observed changes in MAP were accompanied by significant alterations in DBP and SBP in both fitness groups (Figure 1). Changes in pressure are not presented for either "built" or "pulsed train" CBR maneuvers as blood pressure was not vasoactively clamped during these procedures and, therefore, is not strictly comparable to the changes produced during arterial baroreflex and ABR testing. The tachycardiac responses elicited by presentation of hypotensive challenges during arterial baroreflex testing were markedly attenuated in HF individuals compared to their sedentary counterparts for each level of SN administered (Table 2). In contrast, although the changes in HR (from baseline) were smaller in HF individuals in response to PE infusion, the absolute levels to which the HR could be lowered were similar between the AF and HF populations.

Aortic baroreflex. As the change in MAP of both groups was similar during SN and PE challenges, the amount of neck suction and neck pressure, respectively, applied during the aortic isolation procedure was comparable between AF and HF individuals. However, in both fitness groups, the MAP response was significantly greater during

bolus infusion of PE than that produced during arterial baroreflex testing (Figure 1). As a point of technique, the amount of pressure or suction applied was corrected (27) and subtracted from the MAP produced systemically, by the vasoactive drug administered during any aortic isolation trial, in order to estimate CSP. Estimations of carotid sinus pressure (ECSP), implemented to verify that we had counteracted the pressure changes induced by bolus drug infusion at the carotid sinus, demonstrated a slight underestimation of the amount of NP and NS needed to completely ameliorate CBR participation in this phase of the study. However, these underestimations were minimal as ECSP was maximally changed from baseline ECSP (i.e., resting MAP) by –6.3 mmHg and +3.1 mmHg in the AF group and –3.5 and + 1.5 mmHg in the HF group. As during arterial baroreflex testing, MAP was significantly altered from baseline at all levels of experimental trial in both fitness groups being mediated by significant alterations in SBP and DBP. Likewise, alterations in MAP induced by vasoactive drug administration were similar between AF and HF subject groups. The reflex increases in HR during SN bolus infusion (i.e., SN1, SN2, and SN3) were significantly diminished in the HF group compared to the AF group (Table 2). In addition, the changes in HR (from baseline) were smaller in HF individuals in response to PE infusion; however, the absolute HR to which it was lowered was similar between the AF and HF populations.

Carotid baroreflex. During carotid baroreceptor stimulation, the application of NS and NP simulating the increases and decreases, respectively, in MAP induced by bolus drug infusion during arterial baroreflex perturbation produced similar tachycardiac and bradycardiac responses in both fitness groups (Table 2). In addition,

the HR responses obtained during "built" CBR perturbation and "pulsed train" CBR manipulation were not different. Therefore, only the "built" CBR responses are presented for comparison in Table 2. In both fitness groups, the increases in HR in response to simulated hypotension at the carotid sinus were significantly less than those elicited during arterial baroreflex testing for all trials (i.e., pressures equivalent to SN1, SN2, and SN3). In the AF group only, CBR-HR responses to simulated hypotension were significantly smaller than those elicited during ABR testing.

Baseline central venous pressure and pulse pressure were not significantly different between fitness groups although CVP was slightly lower and PP moderately higher in HF subjects than in AF subjects (Table 3). Sodium nitroprusside and phenylephrine bolus infusion during both arterial and aortic baroreflex manipulations did not produce significant alterations in CVP or PP ($P>0.05$) in either sedentary or aerobically fit individuals (Table 3). However, CVP was moderately decreased (maximum AF, -1.5±0.5 mmHg and HF, -1.3±0.7 mmHg) and increased (maximum AF, 1.5±0.4 mmHg and HF 1.4±0.3 mmHg) during SN and PE administration, respectively. Likewise, PP was slightly diminished (maximum AF, -2.0±1.3 mmHg and HF, -6.3±1.5 mmHg) during hypotensive challenge and elevated (maximum AF, 6.8±1.8 mmHg and HF, 5.6±1.4 mmHg) during hypertensive challenge.

Baroreflex control of HR. Beat-to-beat changes in HR and gain curves developed for the arterial (Figure 2), aortic (Figure 3) and "built" carotid (Figure 4) baroreflexes, as determined from logistic modeling, are presented for both sedentary

and exercise trained individuals. Visual inspection of the arterial and aortic-cardiac stimulus response relationships clearly indicated that the curves had been altered in shape in the HF compared to the AF population. The majority of change was a result of the attenuated responsiveness to hypotensive stimuli. Further, the gain curves demonstrate a marked decrease in the gain of these reflexes in the HF group. In contrast, the CBR stimulus response and gain curves produced for AF and HF populations were similar. As there were no differences in the group calculated values for threshold, saturation, slope, centering point, minimum HR response (Table 4), response range, and G_{max} between "built" CBR curves and "pulsed train" CBR curves in either fitness group, the former was used to characterize CBR function in comparison to responses elicited from the arterial and aortic-cardiac reflexes. Interestingly, the threshold, saturation, slope, and centering point of the arterial, aortic, and carotid-cardiac curves were not significantly different ($P>0.05$) between the baroreflexes tested or between fitness groups (Table 4). It should be noted, however, that the threshold of the CBR tended to be slightly higher than the ABR (AF, 7.3 mmHg higher and HF, 12.2 mmHg higher) and, in the HF group, saturation pressures were slightly elevated for the CBR (7.4 mmHg higher) relative to those obtained in the AF group. In addition, although the reference point (i.e., resting HR) was lower in the HF stimulus response curves, the operating point pressure (i.e., pre-stimulus MAP) was positioned similarly on all curves, as mathematically indicated by the OP – CP difference (Table 4), for both HF and AF groups.

Maximal gains for the ABR, CBR, algebraic sum of the ABR and CBR, and arterial baroreflex for AF and HF groups are presented in Figure 5. The calculated gains of the arterial and aortic baroreflexes for AF individuals (-2.36±0.58 and –1.33±0.12 beats·min^{-1}·mmHg^{-1}, respectively) were significantly greater than those for the HF group (-1.24±0.23 and –0.85±0.17 beats·min^{-1}·mmHg^{-1}, respectively). In contrast, CBR G_{max} was unaltered between the two groups. As expected, in the AF group the maximal gain of the arterial baroreflex was significantly larger than either the ABR or CBR (-0.74±0.15 beats·min^{-1}·mmHg^{-1}) with no significant difference between the latter two. However, the summed response of the ABR and CBR (-2.07±0.24 beats·min^{-1}·mmHg^{-1}) was not different from that of the arterial baroreflex. This relationship was also demonstrated in the HF group although the differences in gain between the baroreflexes did not reach significance. Heart rate response ranges for the ABR, CBR, simple sum of the ABR and CBR, and arterial baroreflex for AF and HF groups are presented in Figure 6. The response range of the arterial and aortic baroreflexes for AF individuals (45.5±4.2 and 40.6±4.1 beats·min^{-1}, respectively) were significantly larger than those for the HF group (31.0±3.5 and 23.6±2.9 beats·min^{-1}, respectively). However, CBR response ranges were unaltered between the two fitness populations. Not surprisingly, in the AF group the response ranges of the arterial baroreflex and the ABR were significantly larger than the CBR (16.3±1.4 beats·min^{-1}). In addition, the summed response of the ABR and CBR (56.8±4.4 beats·min^{-1}) was significantly larger from that of the arterial baroreflex. In the HF group the response range of the arterial baroreflex was significantly greater than either the ABR or CBR (14.1±1.2 beats·min^{-1}). Further,

the algebraic sum of the ABR and CBR (37.7±3.4 beats·min^{-1}) was significantly augmented from that of the arterial baroreflex.

DISCUSSION

The major findings from this investigation were that i) the HR response ranges of the arterial and aortic baroreflexes were significantly attenuated in HF individuals compared to untrained counterparts while carotid baroreceptor sensitivity was unaltered by endurance training; ii) the operating point was positioned similarly on all baroreflex stimulus-response curves characterizing arterial, aortic, and carotid-cardiac reflexes in HF and AF groups; and iii) both groups exhibited an inhibitory interaction between ABR and CBR reflex control of HR. As a consequence of the reduced response ranges exhibited during arterial baroreflex and ABR perturbation, the stimulus response curves describing HF baroreflex sensitivity were shifted vertically downward at the end characterizing hypotensive buffering capacities, an alteration that was not manifest on the hypertensive end of the curves. However, these alterations in baroreflex function induced by exercise training had no effect on the arterial pressures over which the baroreflexes operated in HF compared to AF subjects as the threshold and saturation pressures of the three baroreceptor populations examined were not markedly different. In addition, supporting previous reports (14, 29, 38, 39), the response range of the CBR was consistently less than that of the ABR in both HF and AF populations suggesting the ABR may play a more dominant role in arterial baroreflex control of cardiac function.

As expected (13, 20, 33), the resting HR of the HF individuals was lower than the AF population without an alteration in resting MAP. It has been proposed (38, 39) that diminished baroreflex responsiveness in HF individuals may be due to relocation of the operating point pressure to a position of lower gain on the stimulus-response curves describing the arterial and aortic-cardiac reflexes. For example, if the OP was repositioned closer to the locus of the threshold (i.e., minimal arterial pressure that would elicit a maximal tachycardiac response) then the ability to increase HR, for any given response range, would be decreased (39). Likewise, shifting of the OP closer to saturation (i.e., maximal arterial pressure that would elicit a minimal bradycardiac response) would limit the ability to buffer hypertensive insults (38). To quantify shifts or repositioning of the reflex OP on the stimulus-response curves comparing AF and HF subjects, we calculated the difference between the OP (i.e. resting MAP) and a common reference point (i.e., the centering point). We reasoned that if the OP was relocated on the stimulus-response curve of any reflex tested, then the difference between the OP and CP would signify that the OP had moved closer to or away from the threshold or saturation pressure of the reflex. Analysis of this relationship determined that the distance between the OP and CP was not different among the arterial baroreflex, ABR, or CBR nor were there any alterations induced by exercise training. This finding suggests that endurance exercise trained HF subjects have an established reduction in arterial and aortic baroreflex regulation of HR that is not due to relocation of the OP point on the stimulus-response curves of the reflexes but rather to the observed attenuated response range.

The finding of an inhibitory interaction between the ABR and CBR suggested that a neural occlusion of afferent information had occurred, most likely at the processing center within the medulla (48). Since the relationship was similar in both groups, it was possible that the attenuated responsiveness of the arterial and aortic-cardiac reflexes was due to changes occurring at sites other than central neural processing centers. The described relationship was predicated on the behavior of the system in controlling the HR response range. In contrast, although the gains of the arterial and aortic baroreceptor mediated reflex responses were clearly attenuated in the HF group compared to the AF group, the simple sum of the maximal gains calculated for the ABR and CBR were not significantly different than that of the arterial baroreflex in either fitness population. This would indicate that the ABR-CBR relationship was one of additive summation rather than occlusion. However, our maximal gain calculations were based on an assumption of linearity and may not have accurately described the actual behavior of the physiological processes investigated (34). This conclusion is supported by the observation that the stimulus-response curves generated for the arterial, aortic, and carotid baroreflexes were clearly nonlinear functions. For example, assuming a linear relationship, Shi et al. (38, 39) calculated the maximal gain of the carotid-cardiac reflex by subtracting the aortic-cardiac from the total arterial-cardiac maximal gain produced during steady-state infusion of SN and PE. These analyses determined that, in a HF population, the ABR predominated over the CBR reflex control of HR in response to hypotensive insult (39) but the relationship was reversed during PE-induced hypertension (CBR=59%, ABR=41%) (38). The

discrepancy most likely results from the incorrect assumption that the reflexes are related in a linear manner and therefore can be simply added. Close examination of our HF group data found that the arterial, aortic, and carotid baroreceptor mediated HR responses to hypertensive stimuli (-10.3, -6.9, and -6.1 beats·min^{-1} from baseline, respectively) suggested that the CBR contribution was increased in HF subjects but remained less than that of the ABR. Further, when the entire baroreflex stimulus-response curve was analyzed, including responses to both hypertensive and hypotensive stimuli, the ABR clearly predominated over the CBR in determining the global arterial baroreflex response in both fitness groups. Therefore, we contend that the use of the HR response range more accurately characterizes the reflex arcs described. Further, they are more physiologically relevant as direct measurement is possible and not dependent on mathematical calculation.

Interestingly, statistical comparison of the threshold and saturation pressures determined for the arterial, aortic, and carotid-cardiac reflexes were not found to be different being unaltered between fitness groups. These findings indicate that each baroreceptor population examined in this investigation operates over a similar range of arterial pressures, a finding in direct conflict from that reported in several animal preparations (1, 15). The discrepancy between our findings and those elucidated from animal models are most likely due to species differences, techniques employed, and end-organ systems examined. For example, Allison et al. (1), using a canine model, determined the ABR operated at higher arterial pressures than the CBR utilizing an isolated carotid sinus-aortic arch preparation in which nonpulsatile stimuli were

applied. It has been shown that carotid baroreceptors are discretely sensitive to pulsation (2) and therefore may be more accurately characterized in preparations in which pulsatile stimuli are left intact such as that utilized in the current experimental design. Unfortunately, in this investigation we were hampered in our ability to alter systemic blood pressure being forced to stay within the parameters of ±20 mmHg due to exaggerated increases and decreases in HR in response to pharmacological alterations in pressure. In order to eliminate the possibility that we had forced the operating range over a particular range of pressures, we examined the CBR not only using 5 sec pulses of neck pressure and suction but also over a wider range of pressures using a modification of the rapid NP/NS technique (44). The analysis determined that the arterial pressures at which threshold and saturation were attained were not significantly different between the two techniques employed, in both fitness groups. Therefore, we concluded, with relative confidence, that the operating ranges determined from our analyses were accurate.

The current investigation did not employ the techniques and experimental design needed to definitively determine the mechanisms responsible for the diminished ABR regulation of HR in aerobically fit individuals. However, it was possible that changes at the heart may have produced the attenuated response ranges reported. Endurance exercise training has been shown to induce cardiac hypertrophy (12, 18, 26) and increased ventricular diastolic chamber compliance and distensibility (24). In addition, changes may occur in β-adrenergic and muscarinic cholinergic receptor density or sensitivity. It is plausible that downregulation of receptor density or reduced

sensitivity could mediate the diminished HR responses observed without an attenuation in efferent autonomic signals produced by aortic baroreceptor activation or deactivation. However, since the CBR was able to elicit the same changes in HR in both HF and AF individuals, it was unlikely that changes in cardiac adrenergic and/or cholinergic receptor number or transduction properties were the primary cause of the attenuated response ranges of the arterial and aortic-cardiac reflexes. This finding also deters arguments regarding signal processing in medullary nuclei. For example, it could be reasoned that changes in the central neural processing of afferent signals from the carotid and aortic baroreceptors may mediate the characteristic decrease in arterial-cardiac reflex sensitivity. However, as the relationship between ABR and CBR input remained occlusive in nature in both fitness populations and the response to CBR perturbation was unaltered, it was hard to proffer such an argument strongly.

More likely, the mechanisms contributing to the attenuated responsiveness of the ABR in the aerobically fit population were the development of an altered cardiac autonomic balance and a training-induced chronic hypervolemia (6, 7, 38, 39). The former has been shown to produce a resting sinus bradycardia mediated by reductions in sympathetic influence and elevations in parasympathetic tone (13, 20, 36, 42, 43). In this investigation, the result was a decrease in resting HR in HF individuals that most likely contributed to the downward vertical shift of the arterial and aortic baroreflex stimulus-response curves (34). A consequence of an increased central blood volume could be chronic loading of cardiopulmonary baroreceptors which have been reported to reflexively inhibit arterial baroreflex function, presumably at the medullary level (3,

4, 46). However, this mechanism is usually presented in association with increases in CVP (38, 39) in HF individuals that were not observed in the present investigation. Therefore, while this mechanism cannot be discarded as a possible means for the decrease in arterial and aortic-cardiac reflex sensitivity, it is not the best explanation for the findings reported. The combination of a slower HR, hypervolemia, and increased ventricular compliance in endurance trained individuals invariably leads to an increased stroke volume (23, 24). An increase in the volume of blood pumped out of the cardiac chamber with each beat may impose a more forceful impact on the locus of the aortic baroreceptors (38, 39) inducing either a downregulation in the number of aortic arch receptors or an adaptive response to continuous increased pulsatile stretch, or both. As a result, a diminished intensity of the afferent signal transduced to the cardiovascular medullary center may be the primary cause of reduced aortic baroreflex responsiveness in endurance trained individuals.

The physiological consequence of reduced arterial and aortic baroreflex sensitivities has been reported to be the development of orthostatic intolerance (i.e., inability to buffer decreases in blood pressure sufficiently) in aerobically fit individuals (5, 16). However, it appears the ability to buffer hypertensive insult was relatively preserved in HF individuals, an adaptive response that may be beneficial during moderate and intense exercise. For example, when we examined the absolute HR changes, from baseline, in the HF population in response to PE-induced hypertension (arterial baroreflex = -10.3 beats·min^{-1}, ABR = -6.9 beats·min^{-1}) compared to those elicited in the AF group (arterial baroreflex = -16.2 beats·min^{-1}, ABR = -14.5 beats·min^{-}

^{1}), arterial and aortic-cardiac reflexes were clearly impaired in endurance trained individuals. However, visual inspection of the stimulus-response curves described in this study revealed that the absolute level to which the arterial and aortic-cardiac reflexes reduced HR were not different between AF and HF populations. Therefore, the ability to decrease cardiac output (Q_c) in response to hypertensive challenge may not have been appreciably different between the two fitness groups. Using stroke volumes (SV) previously obtained from HF (110 ml) and AF (83 ml) individuals (24) that displayed VO_{2max} levels similar to the subjects that participated in this investigation, we calculated the expected alterations in Q_c using the observed changes in HR obtained during arterial baroreflex testing. For example, a change in HR of –16.2 beats·min^{-1} (AF) and –10.3 beats·min^{-1} (HF) would produce a change in Q_c of –1.34 l·min^{-1} and –1.13 l·min^{-1}, respectively. In contrast, performing the same calculation in response to hypotensive stimuli would produce a change in CO of +2.14 l·min^{-1} in AF individuals and only +1.64 l·min^{-1} in HF individuals, a marked difference. Interpretation of such calculations validated the conclusion that aerobic training reduced hypotensive buffering capacity while moderately preserving the ability to buffer increases in ABP. The latter conclusion was based on the possibility that increased parasympathetic influence functionally set resting HR closer to the maximum inducible bradycardiac response (43) and that SV may have been augmented due to increases in both cardiac filling time and ventricular compliance (24), in the HF population, leading to the preservation of appropriate Q_c responses. It should be noted, however, these calculations were predicated on the assumption that resistance and SV remained

unchanged in response to alterations in ABP between HF and AF populations. Recently, it has been shown that increases in ventricular compliance elicited greater changes in stroke volume in response to a given change in filling pressure in endurance trained athletes compared to their sedentary counterparts (24). Further, the regulation of vasomotion has been reported to be attenuated in HF individuals (28, 43). In any event, the orthostatic intolerance observed in endurance athletes is most likely due to a combination of diminished neural control of HR and sympathetic nerve activity (i.e., resistance) as well as alterations in cardiac structure and morphology.

Several potential limitations in the design and interpretation of this study were recognized. To begin, in this investigation we attempted to functionally isolate the aortic from the carotid baroreceptors by applying counteracting NP and NS to the carotid sinus during vasoactive drug administration. Estimations of CSP during the aortic isolation maneuver demonstrated that the technique was successful although not complete. Therefore, we cannot discount, to some extent, the contribution of the CBR to the response ranges reported for the ABR. In addition, cardiopulmonary baroreceptor loading and unloading (quantified by changes in CVP) have been shown to reflexively inhibit (41) and potentiate (31) baroreflex function, respectively. However, as the changes in CVP produced during pharmacological intervention were small and similar between both HF and AF testing this effect was minimal. Crandall et al. (8), have reported that changes in pulse pressure influence CBR responsiveness. In the present study, PP was similarly increased and decreased during infusion of PE and SN, respectively, in HF and AF individuals. As a result, it was improbable that alterations in

PP contributed significantly to the differences in the reflex response ranges and gains described for the two fitness groups. It should be noted that the techniques implemented primarily induced changes in HR via parasympathetic activation or deactivation. In contrast, control of arterial resistance in humans is mediated by the sympathetic nervous system. Therefore, care should be taken in extrapolating these data to differences in baroreflex regulation of vasomotion between aerobically fit and sedentary individuals.

In summary, the present investigation indicated that the sensitivity of the arterial baroreflex control of HR was significantly reduced in aerobically fit individuals. Further, this reduction in responsiveness was mediated exclusively by an attenuated ABR control of cardiac function. As a result of a smaller HR response range, stimulus-response curves characterizing HF arterial and aortic-cardiac reflexes were shifted vertically downward, predominately on the hypotensive end of the curve, without a concomitant relocation of the operating point. However, the integrative relationship, determined to be inhibitory in nature, between aortic and carotid baroreceptor inputs was retained in both HF and AF populations. A combination of alterations in autonomic balance (i.e., parasympathetic and sympathetic influence) and reductions in aortic baroreceptor density and/or changes in transduction characteristics are the most likely cause of the reduced ABR sensitivity. As a consequence, endurance trained individuals may be more susceptible to syncopal episodes resulting from the development of orthostatic intolerance.

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TABLE 1. Subject demographic and physiological characteristics

Subject Group	Age (yr)	Weight (kg)	Height (cm)	VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$)	HR_{rest} ($beats \cdot min^{-1}$)	MAP_{rest} (mmHg)
AF	25.1±1.4	72.6±5.5	172.5±4.1	42.2±1.9	60.5±4.4	85.7±2.4
HF	24.3±0.9	76.8±2.5	180.1±2.0	61.9±2.2‡	55.7±3.1	88.7±4.8

Values are mean ±SE. AF and HF, average fit and high fit subjects, respectively; VO_{2max}, maximal oxygen uptake; HR_{rest}, resting heart rate; MAP_{rest}, resting mean arterial pressure. ‡Significantly different from AF. Group differences significant at $P<0.05$.

TABLE 2. Heart rate responses during experiment

Heart Rate (beats·min^{-1})						
Trial	Arterial BR		ABR ††		CBR**	
	AF	HF	AF	HF	AF	HF
SN3	86.3± 5.3*	69.6± 2.4*‡	81.3± 3.6*	66.5± 2.5*‡	66.4± 3.9†§	61.8± 2.3†
SN2	81.7± 5.8*	68.2± 2.3*‡	79.9± 4.9*	66.0± 3.0*‡	66.5± 3.7†§	61.0± 2.6†
SN1	77.2± 4.8*	64.1± 3.0*‡	74.5± 4.1*	60.5± 3.1*‡	63.5± 3.8†§	59.1± 2.5†
Baseline	60.5± 4.4	54.7± 3.1	61.0± 4.0	54.6± 3.1	60.1± 3.9	56.7± 2.6
PE1	47.0± 2.9*	48.0± 3.1*	49.5± 2.8*	50.4± 2.9	53.9± 3.5*	52.0± 2.8
PE2	47.0± 3.4*	46.1± 3.3*	47.4± 3.0*	47.7± 3.1*	51.9± 3.1*	50.6± 3.0*
PE3	44.3± 3.2*	44.4± 3.2*	46.5± 3.2*	48.1± 3.4*	51.7± 3.2*	50.7± 2.9*†

Values are means ± SE. Arterial BR, ABR, and CBR are arterial, aortic, and carotid baroreflexes, respectively; AF and HF are average fit and high fit subjects, respectively. SN, sodium nitroprusside bolus injection; PE, phenylephrine bolus injection; Values 1-3 for SN and PE trials indicate increasing levels of drug administration. †† SN and PE bolus infusion combined with neck suction and neck pressure, respectively. ** SN and PE were not administered during carotid baroreflex isolation procedures. However, neck pressure and suction were utilized to simulate the changes in pressure produced during evaluation of arterial and aortic baroreflex function. *Significantly different from baseline (within fitness group); †Significantly different from arterial baroreflex (within fitness group); §Significantly different from aortic baroreflex (within fitness group). ‡Significantly different from AF. Group differences significant at $P<0.05$.

TABLE 3. Pressure responses during experiment

Trial	Pulse Pressure (mmHg)				Central Venous Pressure (mmHg)**			
	Arterial BR		ABR		Arterial BR		ABR	
	AF	HF	AF	HF	AF	HF	AF	HF
SN3	62.5± 2.3	58.7± 2.5	58.2± 3.1	62.1± 4.2	4.6± 0.5	3.3± 0.7	5.1± 0.5	4.7± 0.4
SN2	63.5± 1.3	62.6± 4.2	60.6± 2.1	63.9± 5.1	5.2± 0.7	3.9± 0.6	5.2± 0.5	5.0± 0.5
SN1	62.9± 1.0	62.0± 3.7	62.3± 1.7	62.3± 5.0	5.7± 0.6	4.5± 0.6	5.6± 0.7	5.0± 0.6
Base	60.9± 1.2	64.4± 2.7	60.2± 1.1	68.4± 4.9	6.1± 0.8	4.6± 0.5	6.5± 1.1	5.1± 0.4
PE1	62.9± 1.2	67.3± 3.4	66.1± 0.8	72.5± 5.1	6.8± 1.2	5.2± 0.4	7.1± 1.2	5.8± 0.6
PE2	64.4± 2.0	67.5± 3.5	65.9± 1.7	72.9± 5.0	7.6± 1.1	5.7± 0.3	7.5± 1.1	5.9± 0.5
PE3	65.7± 2.3	70.0± 3.3	67.0± 1.4	72.1± 5.0	7.4± 1.4	6.0± 0.4	8.0± 1.6	6.0± 0.5

Values are means ± SE. SN, sodium nitroprusside bolus injection; PE, phenylephrine bolus injection; Values 1-3 for SN and PE trials indicate increasing levels of drug administration; Base, indicates basal values for the arterial and aortic baroreflexes; Arterial BR, arterial baroreflex; ABR, aortic baroreflex; AF and HF, average fit and high fit subjects, respectively. There were no significant differences for either variable between experimental trial, reflex, or fitness level. **Indicates N=5 in both fitness groups. For pulse pressure, N=8 for both fitness groups.

TABLE 4. Baroreflex function curve parameters

Reflex		Threshold (mmHg)	Saturation (mmHg)	Slope Coefficient	CP (mmHg)	Min HR (beats·min^{-1})	OP-CP (mmHg)
Arterial BR	AF	67.9±4.4	92.4±1.6	0.20±0.03	80.2±2.7	43.0±3.6	4.3±2.2
	HF	71.3±5.0	98.3±5.7	0.16±0.02	84.8±5.2	42.3±3.1	3.7±2.2
ABR	AF	66.8±3.7	97.9±3.7	0.14±0.01	82.4±3.1	44.8±3.7	4.3±3.8
	HF	63.0±2.5	95.8±5.3	0.13±0.02	79.2±3.4	47.2±3.1	9.8±2.5
Built CBR	AF	74.1±2.6	98.8±2.8	0.18±0.03	86.5±2.3	50.7±3.2†	-0.8±2.9
	HF	75.2±4.9	106.2±4.1	0.15±0.02	90.7±4.1	48.7±3.3	-0.1±2.2
Pulsed Train CBR	AF	72.6±5.6	99.0±3.1	0.19±0.01	85.8±3.9	48.9±2.3	0.1±3.6
	HF	71.6±5.3	105.3±3.8	0.15±0.02	88.6±4.1	48.2±2.6	1.8±2.1

Values are means ± SE. Arterial BR, ABR, and CBR are arterial, aortic, and carotid baroreflexes, respectively; OP, operating point pressure (i.e. pre-stimulus mean arterial pressure); CP, centering point; Min HR, minimum heart rate response; AF and HF are average fit and high fit subjects, respectively. The carotid baroreflex was evaluated by utilizing neck pressure and suction of varying levels when a five second stimulus was applied (built CBR) and when rapid pulsed stimuli were gated to the R-wave of the cardiac cycle (pulsed train CBR). †Significantly different from arterial baroreflex (within fitness group). There were no significant differences for any of the parameters when comparing fitness groups. Group differences significant at $P<0.05$.

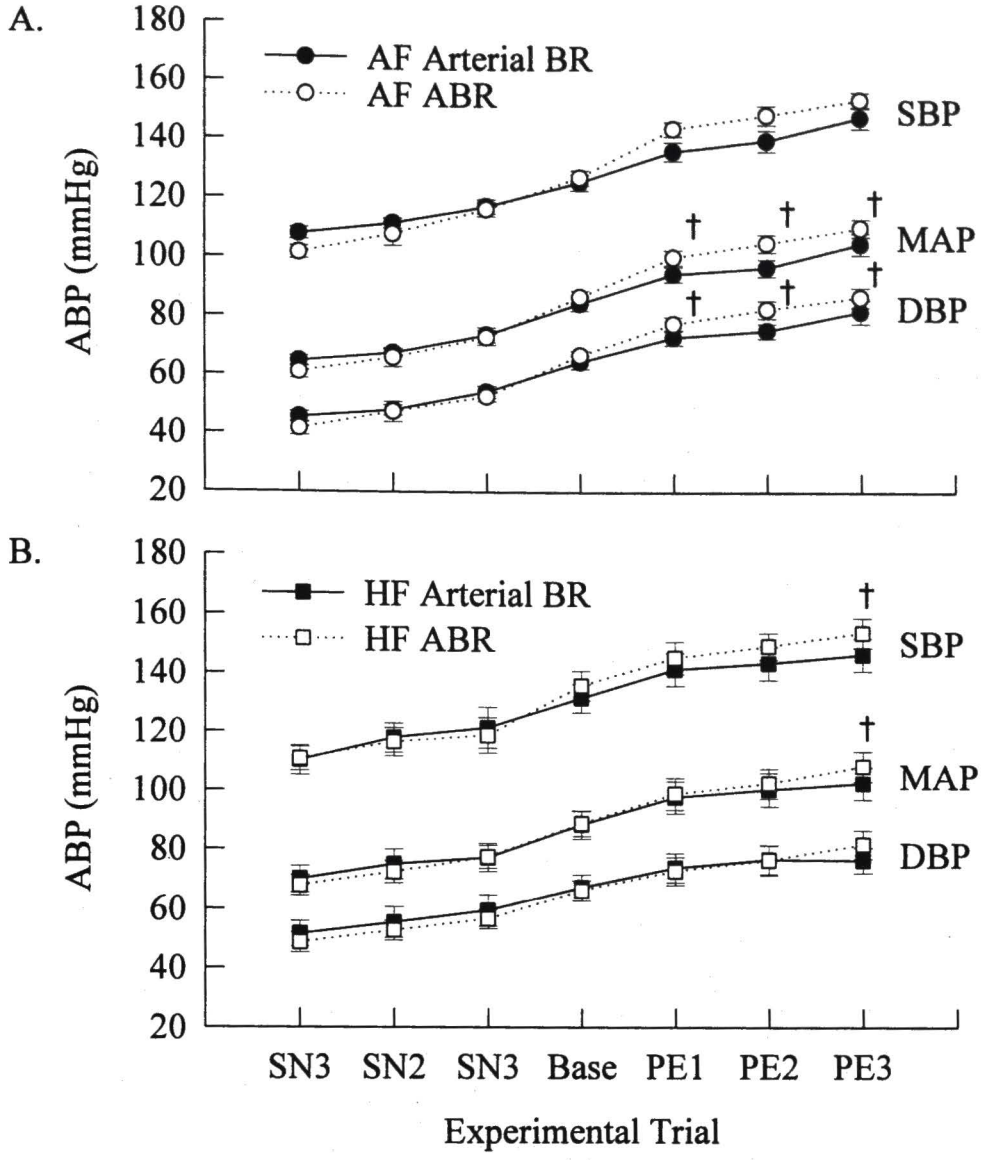

Figure 1. Panel A: Changes in arterial blood pressure (ABP) in response to phenylephrine (PE) and sodium nitroprusside (SN) bolus infusion alone (arterial baroreflex , BR) and during neck pressure and neck suction application concomitantly (aortic baroreflex , ABR). In the average fit (AF) population, diastolic (DBP) and mean arterial (MAP) pressures were significantly greater during all hypertensive challenges in ABR testing than during arterial BR testing. Panel B: In high fit (HF) individuals, systolic blood pressure (SBP) and MAP were significantly elevated during arterial BR testing compared to ABR testing only during the largest PE challenge. Sodium nitroprusside and phenylephrine administration induced significant decreases and increases, respectively, when compared to baseline values for all variables reported. No group fitness differences were observed at any level of experimental trial or during execution of specific baroreflex testing protocols. † Indicates significantly different from arterial baroreflex ($P<0.05$).

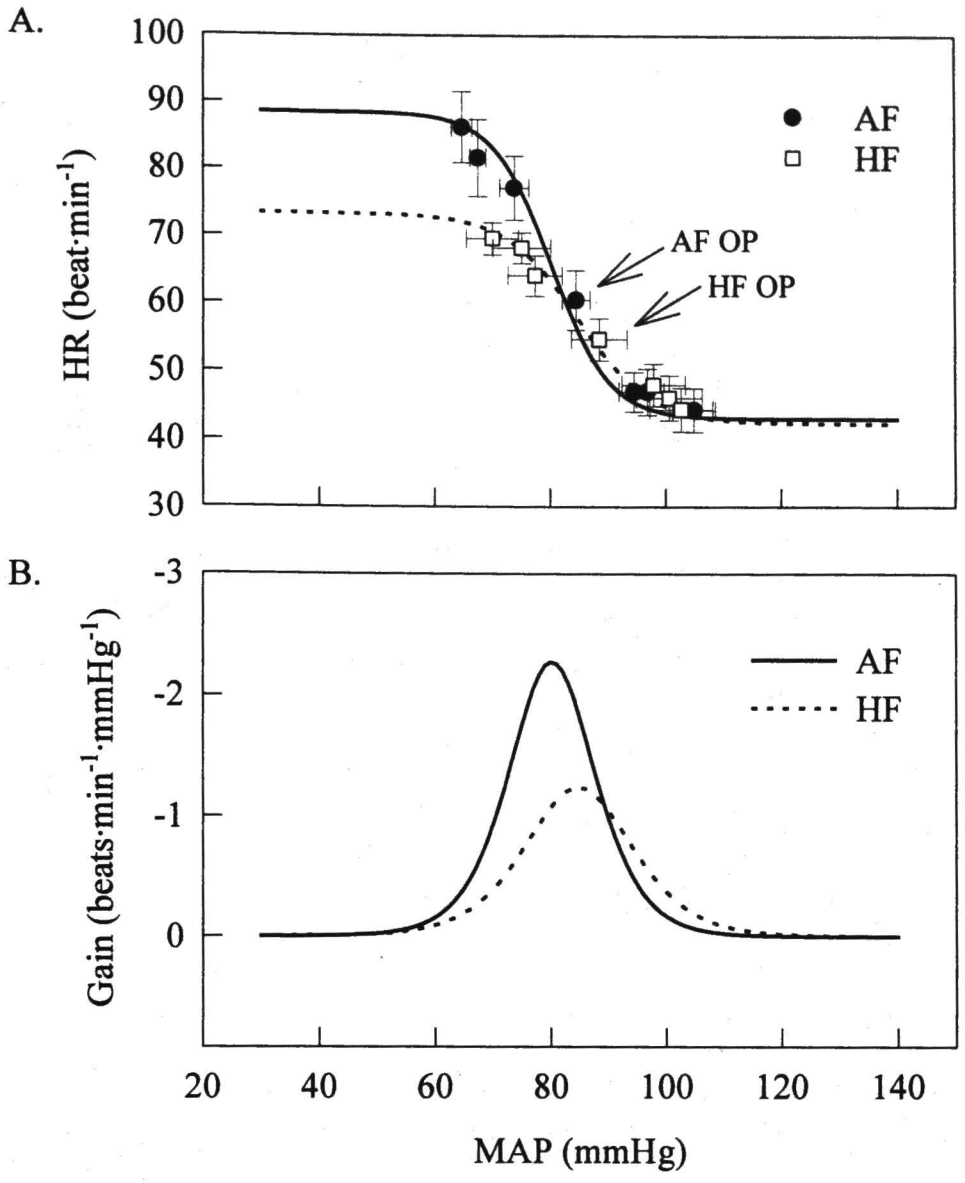

Figure 2. Panel A: Heart rate (HR) response to arterial baroreceptor perturbation in average fit (AF) and high fit (HF) populations. Symbols denote group data (means±SE) and lines exhibit fitted logistic function. Arrows indicate the position of the mean arterial pressure (MAP) operating point (OP) for each population tested. Visual inspection clearly reveals a shift downward in the baroreflex curve in response to hypotensive stimuli. Panel B: Reflex gain was calculated from the first derivative of the logistic function. Note the operating range of the reflex is similar between each fitness group. However, the peak of the gain curve is markedly attenuated in the HF population compared to AF individuals.

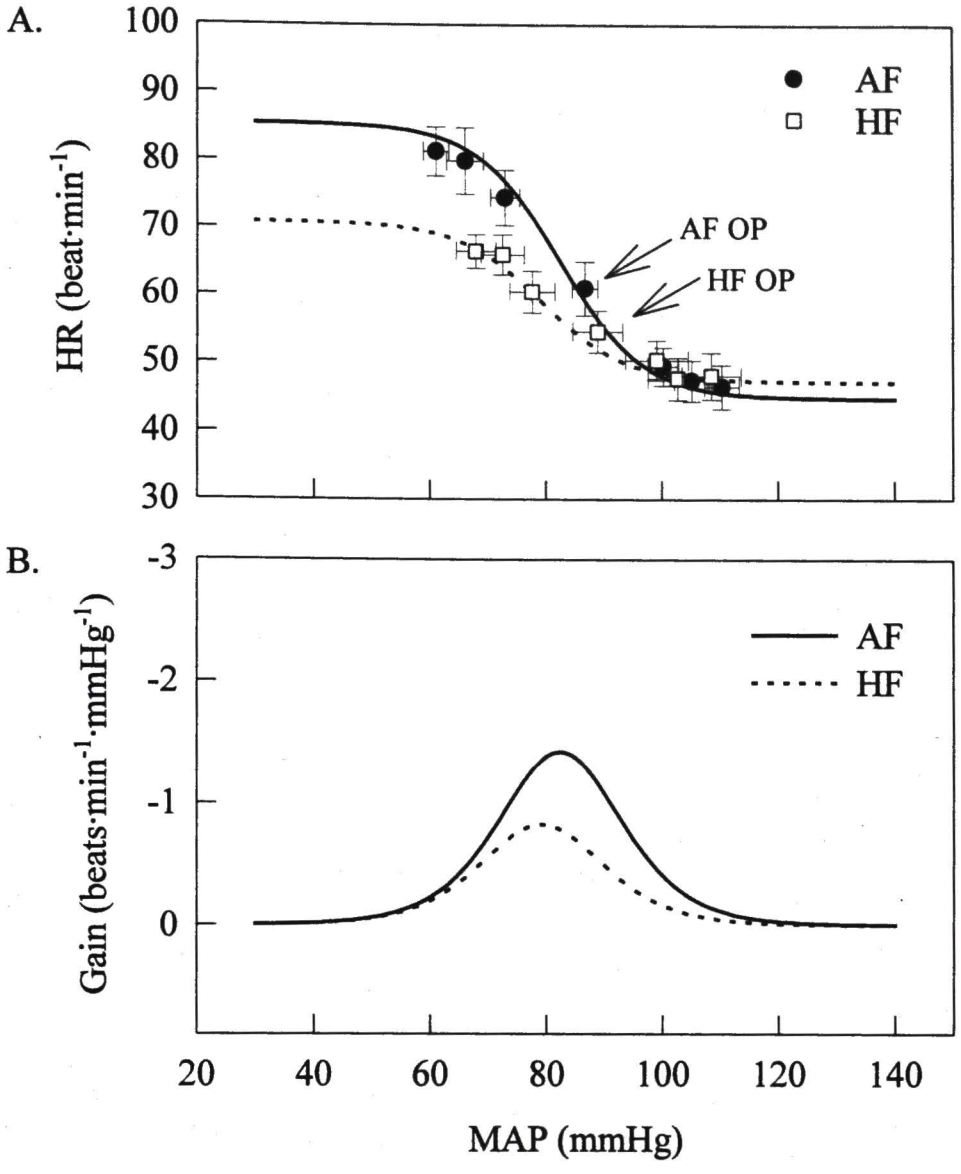

Figure 3. Panel A: Changes in heart rate (HR) elicited during aortic baroreceptor perturbation in average fit (AF) and high fit (HF) populations. Symbols denote group data (means±SE) and lines exhibit fitted logistic function. Arrows indicate the position of the mean arterial pressure (MAP) operating point (OP) for each population tested. Visual inspection clearly reveals a shift downward in the baroreflex curve in response to hypotensive stimuli. Panel B: Reflex gain was calculated from the first derivative of the logistic function . Note the operating range of the reflex is similar between each fitness group. However, the peak of the gain curve is markedly attenuated in the HF population compared to AF individuals.

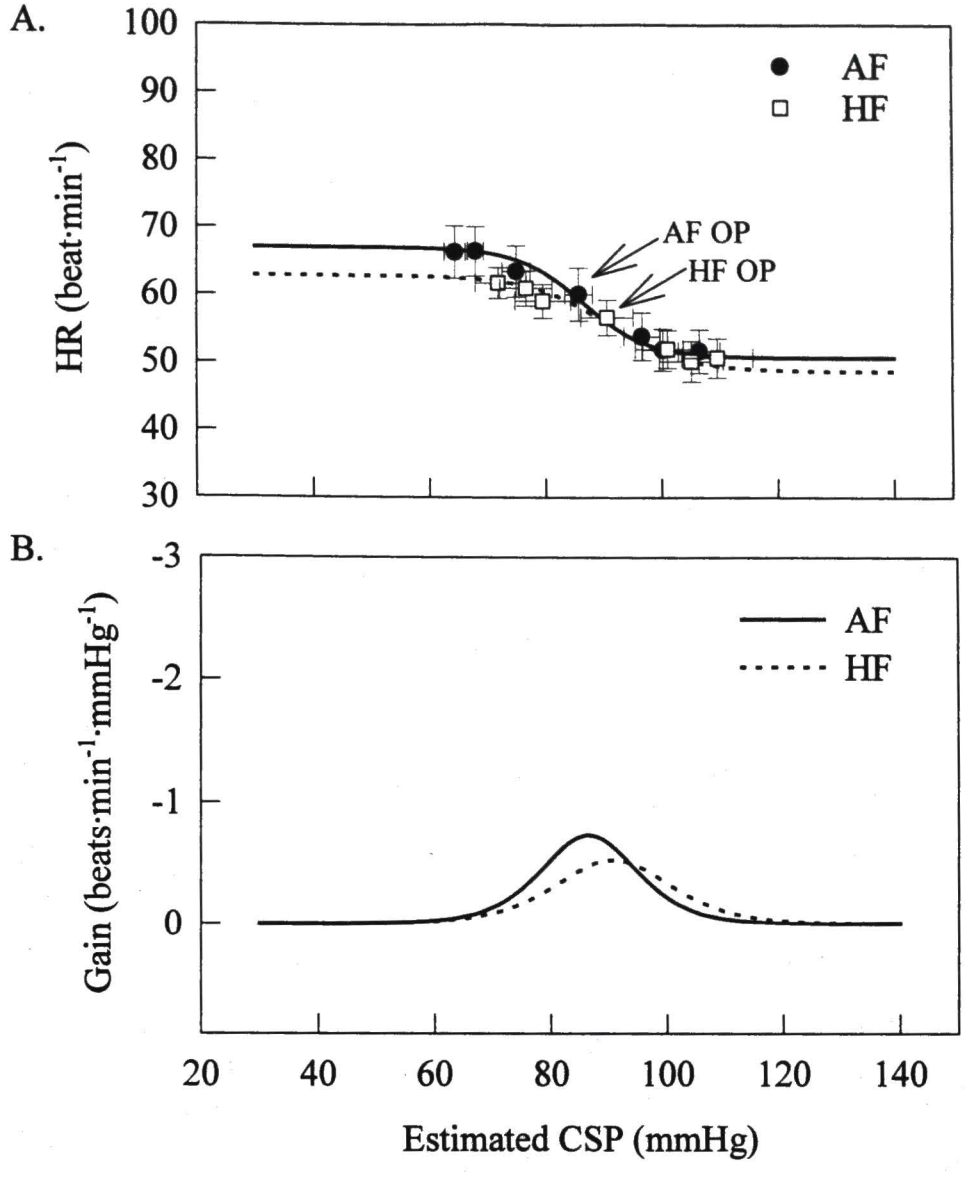

Figure 4. Panel A: Changes in heart rate (HR) elicited during carotid baroreceptor perturbation in average fit (AF) and high fit (HF) populations. Symbols denote group data (means±SE) and lines exhibit fitted logistic function. Arrows indicate the position of the mean arterial pressure (MAP) operating point (OP) for each population tested. Note the operating range as well as shape of the reflex curve is similar between each fitness group. Panel B: Reflex gain was calculated from the first derivative of the logistic function. There were no significant differences in the gain curves describing each fitness population indicating CBR function was similar between AF and HF individuals. The HR responses induced by neck pressure (NP) and suction (NS) during CBR stimulation were measured over a range of carotid sinus pressures (CSP). Estimated CSP was determined as MAP – neck chamber pressure (0.86 (NP) or 0.64 (NS)).

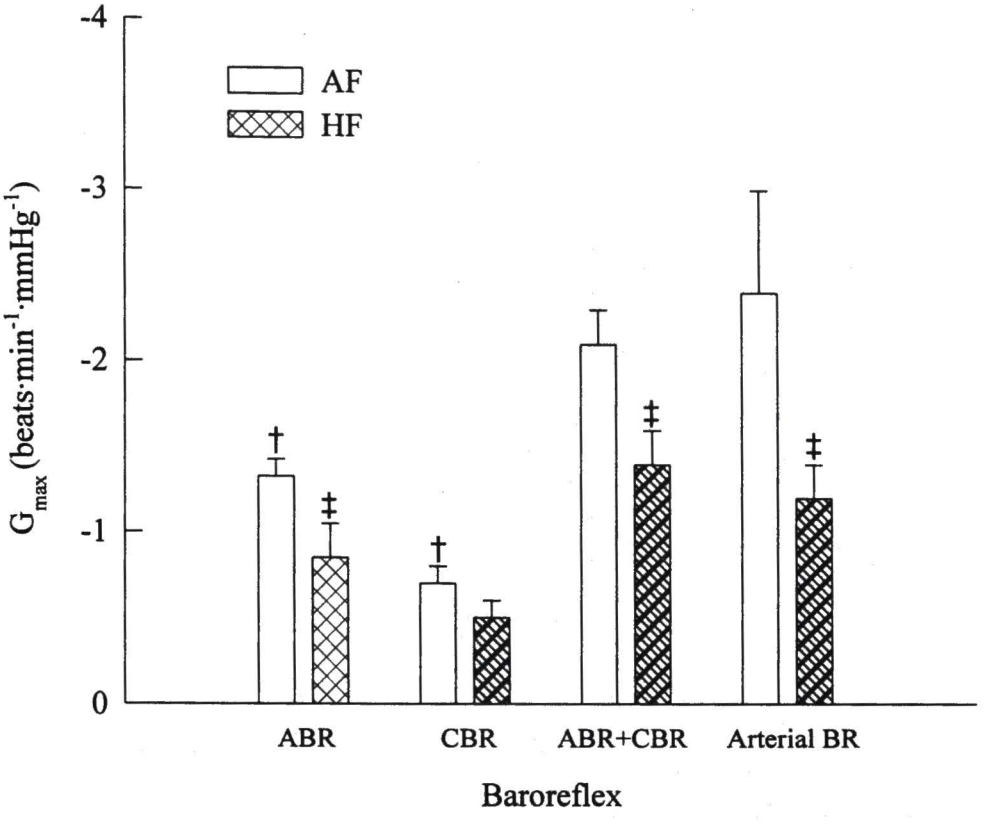

Figure 5. Maximal gain (G_{max}) responses from aortic (ABR), carotid (CBR), ABR+CBR, and arterial baroreflexes in both average fit (AF) and high fit (HF) individuals. The individual maximal gains of the arterial baroreflex (BR), ABR and ABR+CBR were significantly reduced in the aerobically fit population compared to their sedentary counterparts without a change in CBR G_{max}. However, the comparison of the simple sum of the ABR and CBR maximal gains to the G_{max} of the arterial BR, within a fitness group, demonstrated no appreciable difference indicating additive summation. This relationship was observed in both AF and HF populations. † Indicates significantly different from arterial BR; ‡ Indicates significantly different from AF population ($P<0.05$).

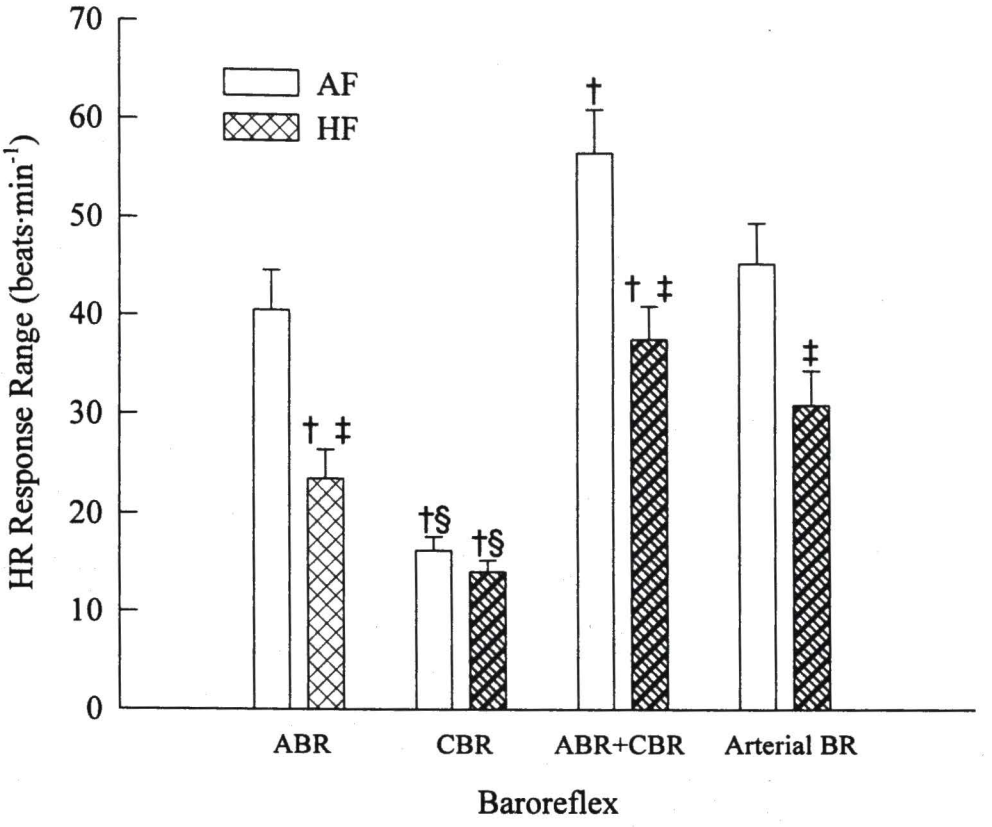

Figure 6. Heart rate (HR) response ranges for aortic (ABR), carotid (CBR), ABR+CBR, and arterial baroreflexes in both average fit (AF) and high fit (HF) individuals. The individual response ranges of the arterial baroreflex (BR), ABR and ABR+CBR were significantly reduced in the aerobically fit population compared to their sedentary counterparts without a change in CBR response range. However, the response range of the CBR was significantly lower than the ABR, regardless of level of fitness, suggesting aortic baroreceptors contribute more to the global arterial response in both AF and HF individuals. In addition, the comparison of the simple sum of the ABR and CBR response range to the response range of the arterial BR, within a fitness group, demonstrated the former to be significantly potentiated indicating an inhibitory interaction. This relationship was observed in both AF and HF populations. † Indicates significantly different from arterial BR; § Indicates significantly different from ABR; ‡ Indicates significantly different from AF population ($P<0.05$).

CHAPTER IV

CONCLUSIONS

The results of the two investigations described herein support the concept that the aortic baroreflex predominately mediates the global arterial baroreflex control of heart rate in response to acute alterations in arterial blood pressure. The primary investigation demonstrated that the aortic and carotid baroreceptors operate over similar ranges of arterial pressure. In addition, it was elucidated that the aortic and carotid-cardiac baroreflexes exhibit an inhibitory interaction in mediating the appropriate HR response ranges necessary to buffer hypotensive and hypertensive challenges. As a point of technique, it was also demonstrated that conclusions drawn from the characterization of stimulus-response curves developed for any sigmoidal relationship should acknowledge the non-linearity of the system described. Conclusions assuming linear relationships should be tempered by the recognition that their ability to accurately describe physiological systems may be limited.

The second investigation demonstrated that the sensitivity of the arterial baroreflex control of heart rate was markedly attenuated in aerobically fit individuals. Further, this reduction in baroreflex responsiveness was exclusively mediated by diminished aortic baroreflex control of cardiac function, a finding previously reported. Although the relative contribution of the carotid-cardiac baroreflex to arterial

baroreflex control of heart rate was increased in high fit individuals compared to their sedentary counterparts, the predominance of aortic baroreflex control of cardiac function was maintained in both fitness populations. The diminution of arterial and aortic baroreflex sensitivity occurred in direct relation to a decrease in the response ranges inducible by vasoactive drug administration without a concomitant relocation of the operating point. The net result of the alterations in baroreflex function was a shifting of the arterial and aortic baroreflex stimulus-response curves vertically downward. These shifts occurred primarily on the end of the curves characterizing baroreflex responsiveness to hypotensive stimuli and may, in part, explain the development of orthostatic intolerance in endurance trained athletes. In addition, the interactive relationship between aortic and carotid baroreceptor afferent information processing remained one of neural occlusion. Therefore, we contend that the alterations in baroreflex sensitivity observed in this investigation are not due to changes in central neural processing mechanisms but may be more accurately attributed to down-regulation or adaptation of aortic arch baroreceptors.

CHAPTER V

SUGGESTIONS FOR FUTURE RESEARCH

Although the research presented produced several new findings in reference to differential baroreflex function in humans, many questions have yet to be addressed. For example, we only examined baroreflex control of one end organ system, the heart. Due to technique limitations, we were unable to proffer any conclusions in respect to baroreflex regulation of vasomotion and, hence, blood pressure. Below is a list of several potential investigations designed to further support the research presented and explore new areas in which baroreflex function may be discretely different. The investigations proposed are intended: i) to examine the baroreflex control of sympathetic nerve activity in both aerobically fit and sedentary populations; ii) to describe alterations in baroreflex function that occur with aging; and iii) to determine if the interrelationship between aortic and carotid baroreflexes is altered during exercise.

I. To test the hypothesis that arterial and aortic baroreflex control of sympathetic nerve activity (SNA) is diminished in response to chronic aerobic training, an experiment could be designed with a protocol similar to that described in Chapter II and

Chapter III. Unfortunately, the primary limitation of this protocol is that arterial blood pressure changes mediated by baroreflex perturbation cannot be directly assessed due to the use of pharmacological agents. Although the sympathetic response to activation and deactivation of the baroreceptors could not be functionally realized at the level of the vascular smooth muscle, changes in SNA would still be elicited and are measurable. By using microneurography to measure muscle SNA from the peroneal nerve of the leg, it should be possible to model the respective baroreflexes in a similar manner to that utilized in the work described in this dissertation. Based on the findings reported for baroreflex control of HR, we would anticipate the arterial and aortic-vasomotor reflexes to be attenuated in aerobically fit individuals compared to their untrained counterparts. Mechanistically, such a finding would implicate that diminished control of SNA contributes to the development of orthostatic intolerance in endurance athletes.

II. Cardiovascular regulation by arterial baroreceptors has been shown to be progressively impaired with aging. In humans, this finding has been determined using vasoactive drugs, the Valsalva maneuver, tilting, and application of pressure stimuli via a neck collar chamber. However, it has yet to be determined to what extent the aortic baroreflex contributes to this diminution in function. Further, the effect of aging on neural processing of afferent information projected from aortic and carotid baroreceptor afferents have yet to be investigated. To test the hypotheses that i) aortic baroreflex control of HR is reduced with aging and ii) processing of neural afferent information is

not altered with age, an experiment could be designed utilizing the protocol described in Chapters II and III. Based on the current literature, we would expect aortic baroreflex responsiveness to be diminished in the aging population as compared to younger adults. Further, we would anticipate the interactive relationship between aortic and carotid baroreflex control to remain unchanged with aging.

III. The carotid baroreflex has been shown to be classically reset during exercise, operating at progressively higher arterial pressures as exercise intensity increases. In addition, during low-intensity exercise, the gain of the aortic-cardiac reflex has been shown to be unaltered. From these investigations, it appears that both baroreflexes are functionally operative during exercise. However, complete baroreflex stimulus-response curves have not been developed for the aortic baroreflex. As such, limited information is available on the range of arterial pressures over which the reflex operates or on its interrelationship with the carotid baroreflex in producing the appropriate arterial-cardiac reflex response to exercise. To test the hypotheses that i) the range of arterial pressures over which the arterial and carotid baroreflexes operate during exercise are not different and ii) that the integration of afferent information from the ABR and CBR for the control of HR does not change with exercise, an experiment could be designed incorporating the techniques described in this dissertation.