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Respiratory sinus arrhythmia: Autonomic origins, physiological mechanisms, and psychophysiological implications

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Abstract

Respiratory sinus arrhythmia (RSA) is being used increasingly in psychophysiological studies as an index of vagal control of the heart and may be among the most selective noninvasive indices of parasympathetic control of cardiac functions. A comprehensive understanding of RSA, however, requires an appreciation of its multiple autonomic and physiological origins. We review the physiological bases of RSA and show that RSA arises from multiple tonic and phasic processes of both central and peripheral origin. These underlying mechanisms are at least partially differentiated, have distinct dynamics and consequences, and may be differentially sensitive to behavioral and cognitive events. These multiple mechanisms are relevant for psychophysiological studies of RSA, and a thorough understanding of RSA can only be achieved through an appreciation of the dynamics of its underlying origins. There is a distinction between the psychophysiological and neurophysiological domains, and conceptual and empirical bridges between these domains are needed.

Descriptors: Respiratory sinus arrhythmia, Autonomic nervous system, Cardiac chronotropy, Heart rate

Respiratory sinus arrhythmia (RSA) is a rhythmical fluctuation in heart periods at the respiratory frequency that is characterized by a shortening and lengthening of heart periods in a phase relationship with inspiration and expiration, respectively. Although RSA was recognized by Ludwig well over a century ago (Daly, 1985), its origins were still being debated well into the present century (see Anrep, Pascual, & Rössler, 1936a). Modern perspectives on RSA were spearheaded by the work of Anrep and colleagues (Anrep et al., 1936a, 1936b), and a relatively clear picture has now emerged of the determinants and underlying mechanisms of RSA (Daly, 1985; Feldman & Ellenberger, 1988; Richter & Spyer, 1990; Spyer, 1990). Over the past decade, an increasing number of studies of RSA have appeared in the psychological, physiological, and clinical literatures. Each of these disciplines has utilized RSA as an index of vagal control of the heart, which is highly sensitive to behavioral as well as physiological variables. In recent applications, RSA measures have been employed in (a) behavioral studies of stress, attention, learning, and cognitive effort (Grossman & Svebak, 1987; Hatch, Borcherding, & Norris, 1990; Porges et al., 1981; Richards, 1988; Shin, Tapp, Reisman, & Natelson, 1989); (b) physiological studies of exercise, diurnal rhythms, and central autonomic control (Berger, Saul, & Cohen, 1989b; Billman & Dujardin, 1990; Hayano et al., 1990); and (c) clinical studies of infants at risk, attentional dysfunctions, and cardiovascular disease (Bigger et al., 1988; Fox & Porges, 1985; Malliani, Pagani, Lombardi, & Cerutti, 1991; Porges et al., 1981).

The potential utility of RSA as a noninvasive index of vagal effects on the heart assumes special importance in view of the emerging understandings of the complexities of autonomic control. Cannon (1939) and Langley (1921) viewed the two divisions of the autonomic nervous system as subject to reciprocal central control, with increases in one division associated with decreases in the other. More recently, it has become apparent that the two divisions of the autonomic nervous system may covary reciprocally, independently, or nonreciprocally (as evidenced by coactivation or coinhibition of both divisions; Berntson, Cacioppo, & Quigley, 1991). These multiple modes of autonomic control reflect differential central states and thus may offer a more refined perspective on the relationships between cognitive/behavioral variables and physiological functions. The multiple modes of autonomic control, however, pose interpretive difficulties for psychophysiological measures of target organ state because the functional state of a dually innervated organ may be ambiguous with regard to its autonomic origins. An equivalent increase in heart rate, for example, could arise from a decrease in vagal control, an increase in sympathetic outflow, or a sympathetically dominant coactivation of both autonomic divisions (Berntson et al., 1991; Quigley & Berntson, 1990). Consequently, independent measures of activity within the two autonomic divisions may be necessary to disambiguate autonomic origins. In this regard, RSA holds considerable

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promise as a noninvasive index of vagal control that is readily derivable from the ECG signal. Methodological techniques for quantifying RSA are well developed, alternative approaches have been evaluated, and caveats in quantitation have been enumerated (Grossman, van Beek, & Wientjes, 1990b; Porges, 1986; Porges & Bohrer, 1990; Shin et al., 1989).

Equally important considerations, however, arise in the interpretation of RSA data. Individual differences in RSA have been interpreted as reflecting differences in basal cardiac vagal tone, and within-subject changes in RSA amplitude have been suggested to reflect corresponding alterations in this vagal tone. This interpretation is based, in part, on the fact that changes in tonic vagal activity may yield corresponding changes in RSA amplitude. This relationship, however, permits strong inferences from RSA to vagal tone only to the extent to which cardiac vagal tone is the sole determinant of RSA. Although RSA is certainly related to dimensions of tonic vagal control, it is clear that RSA is determined by both tonic (vagal tonic: VT) and phasic (vagal phasic: VP) processes, which have different origins, dynamics, and functional consequences (Daly, 1985; Grossman et al., 1990; Grossman, Karemaker, & Wieling, 1991; Richter & Spyer, 1990).[1] Thus,

$$\text{RSA} = f(\text{VT}, \text{VP}) + \epsilon. \quad (1)$$

It is also clear that both the tonic and phasic terms in Equation 1 are themselves functional resultants of activities in multiple mechanisms. Physiological interpretations of RSA therefore require that biometric issues be addressed—the autonomic origins and mechanisms underlying RSA must be specified, and measurement conditions must be devised to differentiate or gauge the potential determinants of a specific sample of RSA. Although many of these biometric issues have been discussed (Grossman et al., 1991; Porges, 1986; Porges, McCabe, & Yongue, 1982), there is a growing need for an integrative perspective on this literature.

Questions about the psychological significance of RSA are of particular importance to psychophysiologists. Although study of the psychometric properties of RSA does not logically require an understanding of biometric issues, an understanding of the physiology and biometric properties of RSA can contribute importantly to the design, analysis, and interpretation of RSA studies. Furthermore, a greater understanding of the multiple determinants of RSA could substantially increase its potential utility and precision in the investigation of psychophysiological relationships. Our goal in the present paper is to provide an integrative review of the physiological origins and mechanisms of RSA. Information from disparate studies are organized in terms of a general model of the tonic and phasic sources of RSA. After specification of these sources and mechanisms, we consider their implications for psychophysiological studies that use RSA to index physiological or psychological states and processes.

[1] The terms tonic and phasic as used here refer to the offset and time-varying components (respectively) of a process, function, or output. In this respect, we follow the electrical model (of DC and AC components) and its quantitative implications. No instantiated physiological process (or electrical signal) is entirely tonic or phasic but can be decomposed into a potentially broad range of frequency components (including 0 frequency or DC components). Hence, the terms tonic and phasic are necessarily relative, especially when applied to autonomic control of the heart, given circadian and even ultradian rhythms in heart periods. Consequently, these terms must be operationalized relative to some temporal frame of reference, which can be either an absolute frequency (or range of frequencies) or an operational epoch. In the present paper, we use tonic to refer to the average (DC) state over the measurement window and phasic to designate the time varying (or AC) components.

Physiological Origins and Mechanisms of RSA

Respiratory sinus arrhythmia arises from a complex interaction of central and peripheral factors. Cardiorespiratory rhythm generators, tonic and phasic baroreceptor and chemoreceptor reflexes, cardiac and pulmonary stretch reflexes, and local mechanical and metabolic factors may all contribute to RSA (Daly, 1985; Davies & Neilson, 1967a, 1967b; Feldman & Ellenberger, 1988; Grossman, 1983; Richter & Spyer, 1990; Saul, Rea, Eckberg, Berger, & Cohen, 1990; Spyer, 1990). Neural mechanisms far overshadow nonneural determinants of RSA, however, because RSA can be eliminated by autonomic denervation (see Daly, 1985). Furthermore, no appreciable RSA is evident in the transplanted heart until the apparent time of autonomic reinnervation (Sands et al., 1989; Thames, Kontos, & Lower, 1969). Consequently, our consideration is limited to the autonomic control of the chronotropic state of the heart.

Autonomic Innervation of the Heart

The cardiac sinoatrial node is directly innervated by both sympathetic and vagal efferents, which exert opposing effects on the chronotropic state of the heart (Figure 1). Additionally, the sympathetic system can indirectly influence cardiac chronotropy through its preganglionic innervation of the adrenal medulla. Although adrenomedullary catecholamines can affect heart rate, the latency of the release of catecholamines and their relatively long half-life in plasma ($\approx$2 min; Hjemdahl, 1988) are sufficiently long to preclude direct manifestation in short-term rhythmical fluctuations such as RSA (although they may contribute to lower frequency heart-period rhythms). In view of these considerations, our attention is limited to the direct neural innervation of the heart.

The two autonomic divisions exert chronotropic effects through separate but interacting synaptic channels (Levy, 1984; Morgan & Neely, 1990; Salata & Zipes, 1991). Interactions among the autonomic innervations are well established and are seen at both prejunctional and postjunctional loci (Levy, 1984; Morgan & Neely, 1990; Salata & Zipes, 1991). Although both the primary synaptic actions and the interactions between the sympathetic and vagal innervations tend to be mutually antagonistic, the neurochemical mechanisms underlying these effects are not symmetrical. Consequently, notable differences emerge in the temporal dynamics, neurophysiological properties, and frequency dependencies of the autonomic innervations of the heart. These differences have substantive implications for the autonomic origins and frequency-dependent manifestations of RSA.

Central Rhythm Generators: A Source of RSA

In early work, Anrep et al. (1936a, 1936b) recognized the contribution of central rhythm generators to RSA. Through empirical studies and a review of the existing literature, these authors noted that fluctuations in heart rate persisted at the approximate respiratory frequency even in the absence of respiration or after pulmonary reflexes were eliminated by deafferentation.

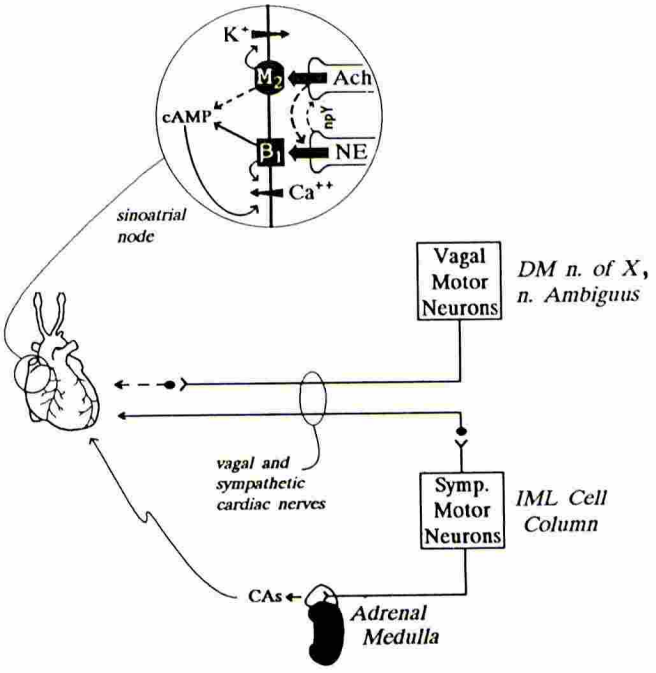

Figure 1. Schematic depiction of autonomic chronotropic control of the heart. Synaptic interactions are illustrated in the insert. Noradrenergic (beta$_1$) receptor activation leads to calcium (Ca^{++}) mobilization via the second messenger cyclic AMP (cAMP). Muscarinic (M_2) receptor action opposes this action and opens potassium (K^+) channels leading to hyperpolarization. Both innervations mutually inhibit the other via acetylcholine (Ach) released from the vagal terminals and neuropeptide Y released by the sympathetic terminals. Solid arrows depict activational effects and dashed arrows indicate inhibitory effects. DM n. of X = dorsal motor nucleus of the vagus; IML Cell Column = intermediolateral cell column; CAs = catecholamines; npY = neuropeptide Y; M_2 = postganglionic muscarinic cholinergic receptor of the parasympathetic cardiac synapses; β_1 = postganglionic adrenergic receptor of the sympathetic cardiac synapses.

These observations supported the concept of a central "respiratory generator" that could maintain respiratory heart period rhythmicity in the absence of peripheral inputs. This rhythmical fluctuation in heart rate was demonstrated to be closely related to changes in centrally driven phrenic (respiratory) nerve activity but could be dissociated from overt respiratory movements. This central rhythm generator was excited by increases in central respiratory drive induced by cerebral hypercapnia (increased CO_2 tension) and inhibited by hypocapnia (decreased CO_2 tension). The contribution of central generators to RSA has also been documented in more recent studies. Fluctuations in heart rate, baroreflex responsiveness, and autonomic outflow have been repeatedly observed in phase with phrenic nerve activity in paralyzed animals (Daly, 1985). Although the amplitude of RSA may be attenuated by apnea in human subjects, in at least some cases, characteristic heart-period rhythms (within the typical respiratory frequency band) can persist even during complete breath hold (Davies & Neilson, 1967a, Figure 2; Hirsch & Bishop, 1981; Kollai & Mizsei, 1990, Figures 1 and 2). Although these rhythms may increase in amplitude with prolonged breath hold because of "involuntary" respiratory efforts (Hirsch & Bishop, 1981), they can also be seen immediately on the suspension of breathing (Davies & Neilson, 1967a, Figure 2; Kollai & Mizsei, 1990, Figures 1 and 2).

Brain stem cardiorespiratory generators, which drive phrenic efferents and modulate central autonomic outflows, are now beginning to be understood in some detail at the neuroanatomical, neurophysiological, and functional levels (Daly, 1985; Feldman & Ellenberger, 1988; Gebber, 1990; Guyenet, 1990; Koepchen, Klussendorf, & Sommer, 1981; Richter & Spyer, 1990). The two central generators that have been most thoroughly studied are those associated with the respiratory and the cardiac rhythms. These generators, and their schematized connections, are depicted in Figure 2. The respiratory generator is related to neural networks focused in the dorsal medullary/nucleus tractus solitarius region (dorsal respiratory group) and the periambigual area of the medulla (ventral respiratory group) (Richter & Spyer, 1990). The sympathetic (cardiac rhythm) generator has foci in the medullary lateral tegmental field, ventrolateral medulla, and raphe nuclei (Gebber, 1990; Guyenet, 1990). Although normally entrained by respiration and the beat of the heart, both respiratory and cardiac rhythms can emerge from intrinsic central activities and can persist despite pulmonary and baroreceptor deafferentation (Daly, 1985; Gebber, 1990; Richter & Spyer, 1990).

The central respiratory generator modulates autonomic outflow through relatively direct central synaptic actions (see Figure 2). Vagal cardiomotor neurons are inhibited during the inspiratory phase and appear to be mildly activated during expiration (Richter & Spyer, 1990). Intracellular recordings of vagal motor neurons reveal an associated chloride-dependent inhibitory postsynaptic potential (IPSP) that occurs in phase with phrenic nerve activity and is independent of lung inflation (Gilbey, Jordan, Richter, & Spyer, 1984), indicating a relatively direct action of the central respiratory generator on vagal cardiomotor neurons. In contrast, sympathetic motor neurons are excited during inspiration and appear to be mildly inhibited during expiration (Daly, 1985; Gebber, 1990; Richter & Spyer, 1990). Thus, the central respiratory generator exerts phase-dependent excitatory and inhibitory effects on both vagal and sympathetic outflows, but with differing phase relationships among the divisions.

The central sympathetic (cardiac rhythm) generator, although normally entrained by the baroreceptor input associated with the beat of the heart, produces an intrinsic rhythm that persists despite baroreceptor deafferentation (Gebber, 1990; Guyenet, 1990). The phasic central cardiac generator, together with tonic brain stem excitatory influences (of presumptive reticular origin; Calaresu & Yardley, 1988; Richter & Spyer, 1990), provides important excitatory drive to sympathetic motor neurons in the intermediolateral cell column of the spinal cord (see Figure 2). Consequently, most sympathetic nerves have a moderate basal firing rate and an inherent cardiac rhythmicity (see sympathetic generator, Figure 2) that is not dependent on baroreceptor feedback (Gebber, 1990; Koizumi, Terui, & Kollai, 1985).

Figure 2 also depicts a central tonic drive on vagal motor neurons (central vagal drive). Although the existence of a specific neural mechanism for tonic central vagal drive is uncertain, there are a variety of central influences that enhance vagal motor activity (Daly, 1985; Richter & Spyer, 1990), including hypothalamic and amygdalar projections, which may exert direct vagoexcitatory effects or facilitate vagoexcitatory reflex substrates (e.g., Pascoe, Bradley, & Spyer, 1989; see also Berntson et al., 1991). The central vagal drive in Figure 2 is intended

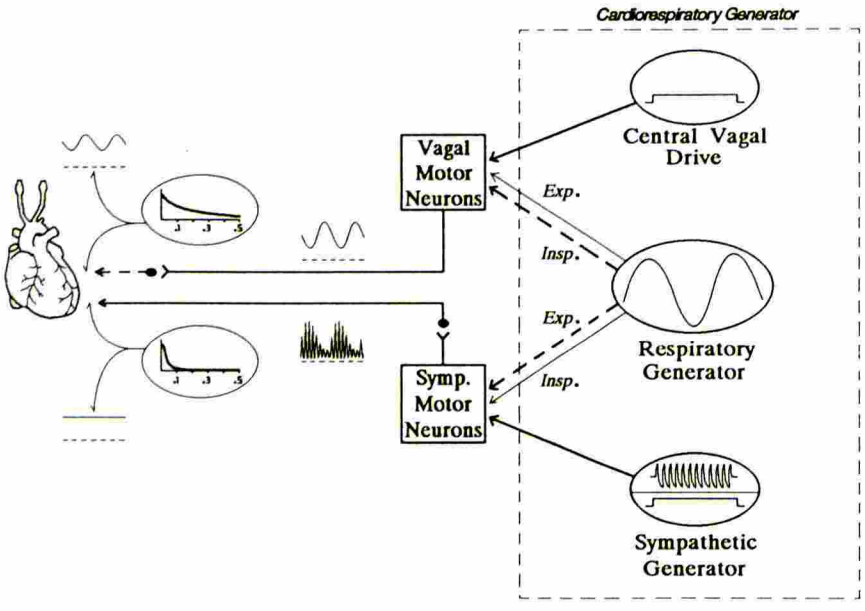

Figure 2. Components of central cardiorespiratory mechanisms. Solid lines depict excitatory effects; dashed lines represent inhibitory effects. Waveforms illustrate the time varying patterns of activity at the respective site, based on the mechanisms depicted. Graphic inserts depict the frequency-transfer functions of the cardioeffector synapses (see Figure 3), and the associated waveforms illustrate the transformations on the input functions. Tonic drive to vagal motor neurons may be due to basal influences of phasic generators rather than a functionally distinct tonic generator. Consequently, the box depicting central vagal drive is intended to represent the aggregate basal steady-state inputs to motor neurons and does not imply a specific functional entity. Exp. = expiratory phase; Insp. = inspiratory phase.

to represent the aggregate tonic components of central excitatory contributions to vagal motor outflow and is included for completeness. In some cases, these contributions may be significant, although in others they may be negligible or nonexistent (in which case, the term for this component in subsequent equations simply assumes a value of zero).

The phasic (excitatory/inhibitory) modulation of autonomic motor neurons by the respiratory generator, imposed on tonic and cardiac-frequency drives to these neurons, would contribute to respiratory-frequency modulations in both sympathetic and vagal outflows (Figure 2). Indeed, respiratory-frequency rhythms have been widely reported in vagal and sympathetic cardiac nerves (Daly, 1985; Koizumi et al., 1985; Richter & Spyer, 1990).

The Vagal Origin of RSA

In spite of the notable respiratory rhythms apparent in both sympathetic and vagal cardiac nerves, RSA has historically been considered to arise largely or exclusively from fluctuations in vagal control. Anrep et al. (1936b) reported that (a) RSA is not generally attenuated by sympathectomy, (b) sympathetic contributions are seen only under conditions of depressed vagal control, and (c) when present, sympathetic contributions are minimal. The apparent paradox between these observations and the notable respiratory rhythm in sympathetic cardiac nerves is related to the temporal dynamics and neurophysiological properties of postganglionic vagal and sympathetic effector synapses.

Filter characteristics of the autonomic divisions. The vast predominance of vagal contributions to RSA is the result, in large part, of differences in the dynamic characteristics and low-pass filter properties of the sympathetic and parasympathetic effector synapses. The latencies and time constants for sympathetic action on the heart are considerably longer than those of vagal effects. Latencies of heart rate responses to direct stimulation of vagal cardiac nerves are typically within a few hundred milliseconds, with decay constants of approximately 1 s. In contrast, latencies to stimulation of sympathetic cardiac nerves are typically 1,300–2,000 ms, with corresponding decay constants greater than 15 s (Berger et al., 1989b; Fagius, Sundlof, & Wallin, 1987; Karemaker, 1985; Salata & Zipes, 1991; Warner & Russell, 1969). Consequently, sympathetic cardioeffector synapses are less able to follow the high-frequency modulations associated with respiration (typically >0.12 Hz). Indeed, differences in the latencies and decay constants of sympathetic and vagal cardiac effectors suggest that the frequency response of the sympathetic innervation of the heart may be as much as an order of magnitude lower than that of vagal synapses. This suggestion has been directly confirmed. As schematized in Figure 3, the frequency response of the sinoatrial node of the dog to direct stimulation of sympathetic cardiac nerves declines steeply out to about 0.05 Hz, whereas the response to vagal stimulation shows a slower falloff out to about 0.5 Hz (Figure 3) (Berger et al., 1989b; Saul et al., 1990).[2]

Although vagal cardiac effectors can follow higher frequencies than can the sympathetic innervation, there is also a progressive decline in the frequency-transfer function of the vagal cardiac innervation (Figure 3). Consequently, increases in respiratory frequency, even within the typical respiratory frequency band, would be expected to lead to a progressive decline in RSA

[2] The frequency transfer functions displayed in Figure 3 were generated by imposing respiratory-frequency modulations on a given base rate of autonomic nerve stimulation. The functions displayed in this figure are smoothed and schematized depictions of those associated with intermediate base rates. A family of transfer functions emerges for each autonomic division obtained under various base rates. The general form of the individual functions within these families of curves is similar; notable deviations appear at the lowest "respiratory" frequencies (<0.1 Hz for the vagal functions and <0.02 Hz for the sympathetic functions). For both autonomic divisions, these deviations consist of an enhanced transfer of low-frequency modulations at low base rates of activity. Because the transfer functions differ primarily below typical respiratory frequencies, these differences may not seriously confound RSA measures at normal respiratory frequencies (>0.10 Hz) and typical basal levels of autonomic control. These differences could, however, complicate studies of lower frequency rhythms and/or under widely varied levels of autonomic tone because the transfer functions could differ, depending on basal levels of vagal activity.

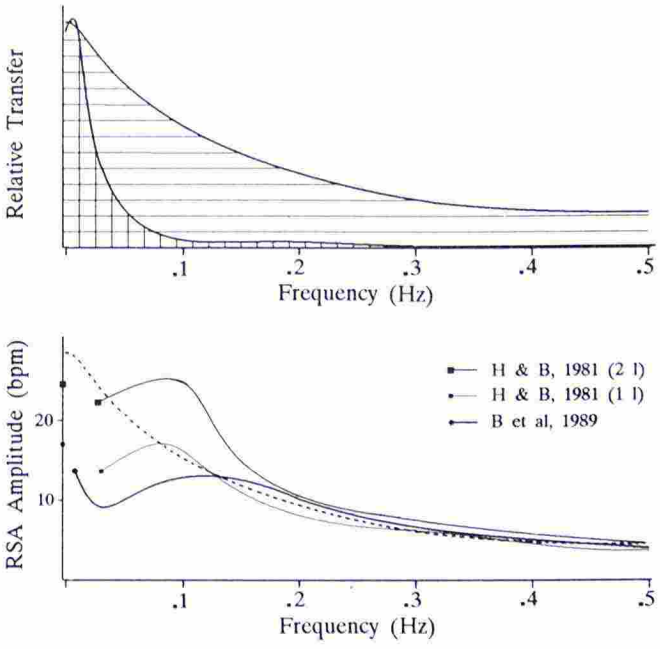

Figure 3. Top: Schematized frequency transfer functions for the cardiovagal synapses in the dog (adapted from Berger et al., 1989b). Functions were derived from direct electrical stimulation of vagal cardiac nerves in the dog. Bottom: Transfer functions for RSA as a function of respiratory frequency in human subjects (adapted from Berger et al., 1989a, and from Hirsch & Bishop, 1981, at tidal volumes of 1 and 2 L). Points on the ordinate illustrate RSA amplitudes for inspiratory breath hold in the study of Hirsch and Bishop (1981).

as vagal effectors become less able to follow the higher frequency variations. The transfer functions relating RSA amplitude to respiratory rate in humans show a frequency falloff similar to that of vagal cardiac effectors in the dog (Figure 3) (Berger, Saul, & Cohen, 1989a). This decline in RSA with increasing respiratory frequency has been widely observed (Angelone & Coulter, 1964; Eckberg, Kifle, & Roberts, 1980; Hirsch & Bishop, 1981).

Given the low-pass filter inherent in the sympathetic cardiac innervation, high-frequency sympathetic activity is not appreciably manifested in heart-period fluctuations within the typical respiratory frequency band (0.12–0.40 Hz). High-frequency sympathetic activity can still be expressed in positive cardiac chronotropy, however, because chronotropic effects continue to increase with stimulation rates up to about 20 Hz (see Salata & Zipes, 1991). At high frequencies, the sympathetic cardiac effectors behave as leaky integrators, temporally smoothing rhythmical variations. Similarly, at progressively higher respiratory frequencies, vagal effects on the heart also shift from a predominant phasic rhythm to a smoothed or integrated action on mean heart rate. Thus, both autonomic nervous system divisions exert frequency-dependent actions on the heart, but the shift from phasic driving to steady-state effects occurs at a higher frequency range for vagal synapses.

Both divisions of the autonomic nervous system may contribute to lower frequency heart-period fluctuations. For example, the Mayer wave (0.05–0.1 Hz; Penaz, 1978) appears to be a joint function of slow rhythms in both parasympathetic and sympathetic outflows (Akselrod et al., 1981, 1985; Japundzic, Grichois, Zitoun, Laude, & Elghozi, 1990; Katona & Jih, 1975; Malliani et al., 1991; Pagani et al., 1986; Pomeranz et al., 1985; Weise, Heydenreich, & Runge, 1987). Thus, the fact that sympathetic contributions to RSA are generally minimal is not a reflection of an inherent inability of sympathetic effectors to rhythmically drive the heart. Rather, it is a contingent consequence of the normal frequencies of respiration and the frequency-transfer functions of the sympathetic cardiac effectors. Sympathetic cardiac nerves can readily follow respiratory frequencies, and respiratory–sympathetic rhythms may in fact contribute to RSA at low, nontypical respiratory frequencies (<0.10 Hz).

Autonomic blockade. The low-pass filtering characteristics of the autonomic innervations of the heart are consistent with the uniform finding that RSA (at typical respiratory frequencies) is largely or completely eliminated by muscarinic receptor antagonists or vagal cooling but is generally not attenuated by beta-adrenergic blockade (Akselrod et al., 1981, 1985; Coker, Koziell, Oliver, & Smith, 1984; Grossman, Stemmler, & Meinhardt, 1990a; Japundzic et al., 1990; Katona & Jih, 1975; Kollai & Mizsei, 1990; McCabe, Yongue, Ackles, & Porges, 1985; Pagani et al., 1986; Pomeranz et al., 1985). Effects of sympathetic and parasympathetic postganglionic blockers on RSA are illustrated in Figure 4. RSA is substantially reduced after vagal blockade (by about 99%) but is not significantly altered by beta blockade. RSA is also unaffected by combined beta- and alpha-adrenergic blockade, which minimizes potential sympathetic

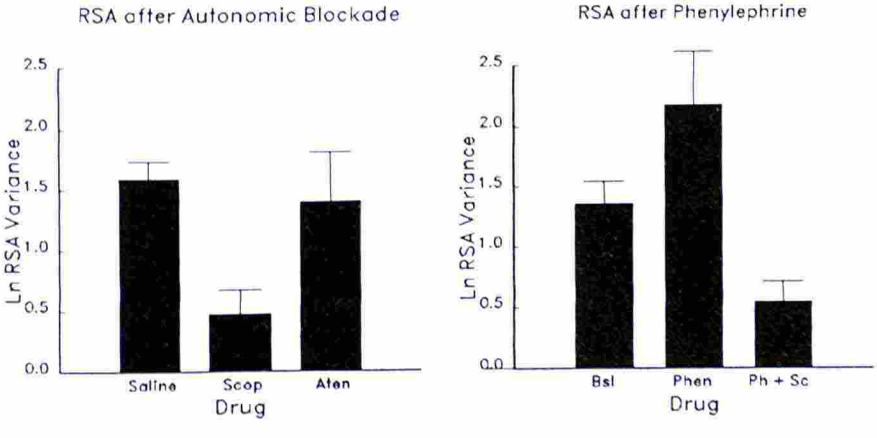

Figure 4. Effects of autonomic blockade and baroreflex drive on RSA in the rat ($n = 6$). Left: RSA after administration of saline, the parasympathetic blocker scopolamine methyl nitrate (0.1 mg/kg), or the sympathetic blocker atenolol (5 mg/kg). Right: RSA under control conditions and after administration of the vasoconstrictor agent phenylephrine alone or together with scopolamine (derived from Quigley & Berntson, 1990).

vascular actions that could yield reflex changes in vagal activity (Grossman et al., 1990a). Even thoracic sympathectomy fails to attenuate RSA amplitude within the normal respiratory frequency band (Anrep et al., 1936b). Consistent with the temporal integration imposed by the sympathetic innervation, beta-adrenergic blockade can lead to a significant decrease in mean heart rate (reflecting the loss of tonic sympathetic control), while leaving the magnitude of RSA largely unaffected (Akselrod et al., 1985; Billman & Dujardin, 1990; Kollai & Mizsei, 1990; Pagani et al., 1986).

Interactions among the autonomic divisions. Although the sympathetic cardiac effectors do not follow typical respiratory frequencies, sympathetic activity may nonetheless alter RSA through interactions with the vagal innervation of the heart. Vagal activation can inhibit sympathetic actions on the heart, not only by opposing postsynaptic processes but through a presynaptic suppression of the release of norepinephrine from sympathetic terminals (Levy, 1984). This "accentuated vagal antagonism" appears to be mediated by heteroreceptors on sympathetic nerve terminals (presumably M_3 cholinergic receptors), which permit cross-talk from nearby vagal cholinergic synapses, even in the absence of direct presynaptic synaptic contact with sympathetic terminals (Manabe et al., 1991; Salata & Zipes, 1991). Autonomic interactions in the control of the heart have been considered predominantly one way because norepinephrine and its agonists do not appreciably reduce vagal effects (Levy, 1984; Manabe et al., 1991; although see Hall & Potter, 1990). An increasing number of cotransmitters or comodulators, however, have recently been identified in sympathetic nerve terminals. The neuromodulator neuropeptide Y is colocalized with norepinephrine in sympathetic nerves and is coreleased with norepinephrine, especially at high sympathetic frequencies (Hall & Potter, 1990; Rudehill, Sollevi, Franco-Cereceda, & Lundberg, 1986).

Neuropeptide Y, released from cardiac sympathetic nerve terminals, can exert a prolonged inhibitory action on the vagal innervation of the heart (Figure 1) (Hall & Potter, 1990; Potter & McClosky, 1982; Warner & Levy, 1989). This inhibitory effect may be large (a decrease of >50% in the chronotropic effect of vagal activity) and long lasting (up to 1 hr) (Hall & Potter, 1990). The inhibition of vagal control of the heart mediated by neuropeptide Y is not eliminated by beta blockers and so is not readily assessable by standard pharmacological means (Hall & Potter, 1990). Moreover, because of its long time course, this inhibition could continue to be manifest well after neural and/or catecholaminergic measures indicate a return to low levels of sympathetic activity.

These findings raise the possibility that high levels of sympathetic activity may influence the magnitude of RSA, not through sympathetic respiratory rhythms but via the inhibition of phasic vagal driving. This possibility is consistent with the fact that RSA is eliminated by vagal blockade but is relatively unaffected by beta-adrenergic blockade, which does not affect neuropeptide Y release (Hall & Potter, 1990).

In summary, the functional predominance of vagal muscarinic over sympathetic adrenergic control of chronotropy has been historically recognized (Levy, 1984). Under conditions of high sympathetic activity and the associated neuropeptide Y inhibition of vagal effector synapses, however, RSA may offer an underestimate of respiratory-frequency modulations in central vagal outflow. Moreover, more recent studies suggest that the neuropeptide Y influence, although attenuated, may be apparent even at more modest sympathetic nerve frequencies (Warner & Levy, 1989).

Afferent Contributions: Additional Sources of RSA

In addition to central rhythm generators, Anrep et al. (1936a, 1936b) also recognized the contribution of respiratory movements to rhythmical fluctuations in heart rate. By artificially respirating at a fixed rate while ventilating with a high CO_2 concentration (to increase central respiratory drive), Anrep et al. (1936b) were able to dissociate central and respiratory rhythms. Under these conditions, the animal displayed two cardiac rhythms: one related to central generators and the other to respiratory movements. A number of peripheral afferents may contribute to variations in heart rate during the respiratory cycle, including reflexes associated with baroreceptors, chemoreceptors, and cardiac and pulmonary stretch receptors (Daly, 1985; Feldman & Ellenberger, 1988; Grossman, 1983; Spyer, 1990; Vatner & Uemura, 1991).

Among the more potent determinants of heart rate and heart rate variability are peripheral baroreceptors and chemoreceptors (see Figure 5), which exert powerful excitatory effects on vagal cardiomotor neurons via central relays in the nucleus tractus solitarius (Daly, 1985; Feldman & Ellenberger, 1988; Spyer, 1990; Vatner & Uemura, 1991). Central reflex networks that receive these baroreceptor and chemoreceptor afferent barrages are subject to phasic modulation or "gating" over the respiratory cycle (Daly, 1985; Davidson, Goldner, & McClosky, 1976; Feldman & Ellenberger, 1988; Spyer, 1990; Vatner & Uemura, 1991). Both baroreceptor and chemoreceptor reflexes (and the associated vagal excitation) are inhibited during inspiration, contributing to the increase in heart rate during this phase of respiration.

A given baroreceptor stimulus, such as neck suction in humans (Eckberg et al., 1980) or direct stimulation of the carotid sinus nerve in animals (Warzel, Eckhardt, & Hopstock, 1989), yields maximum vagal excitation during expiration; minimal effects appear during early or midinspiration (see also Daly, 1985; Richter & Spyer, 1990; Vatner & Uemura, 1991). Similarly, chemoreceptor stimuli are relatively ineffective in altering vagal control of the heart during inspiration but exert a potent vagoexcitatory effect during expiration (Daly, 1985; Vatner & Uemura, 1991). This reflex gating does not appear to be attributable to variations in the responsiveness of neurons within the nucleus tractus solitarius to afferent inputs but rather to an inhibition of subsequent links in central reflex networks (Daly, 1985; Richter & Spyer, 1990; Spyer, 1990). One source of phasic modulation of reflex responsiveness may be the postsynaptic inhibition of vagal motor neurons exerted by the central respiratory generator during the inspiratory phase (Feldman & Ellenberger, 1988; Richter & Spyer, 1990), which would reduce the sensitivity of vagal neurons to excitatory baroreceptor and chemoreceptor inputs.

The central respiratory generator, however, is not the sole source for the respiratory-coupled gating of baroreceptor and chemoreceptor reflexes, as suggested by early work of Anrep et al. (1936a) who found that lung inflation is associated with a suppression of vagal outflow that can contribute substantially to RSA. This decrease in vagal outflow reflects a suppression of vagoexcitatory baroreflexes and chemoreflexes that is mediated by slowly adapting pulmonary stretch receptors and is not dependent on central cardiorespiratory rhythms (Coleridge

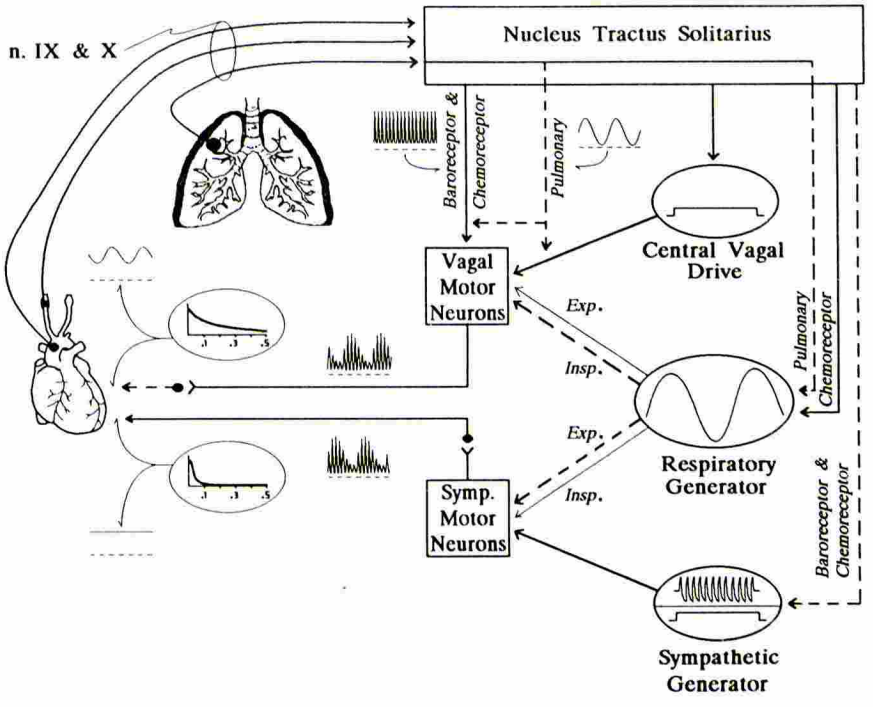

Figure 5. Schematic depiction of the interaction between central and peripheral determinants of RSA. Solid lines depict excitatory effects; dashed lines represent inhibitory effects. Waveforms illustrate the time varying patterns of activity at the respective sites. Lines from the cardiac and pulmonary depictions illustrate the trajectories of chemoreceptor and baroreceptor afferents and pulmonary stretch receptor afferents, respectively. Graphic inserts depict the frequency-transfer functions of the cardioeffector synapses (see Figure 3), and the associated waveforms illustrate the transformations on the input functions. Exp. = expiratory phase; Insp. = inspiratory phase; n. IX & X = cranial nerves IX and X.

& Coleridge, 1991; Daly, 1985; Vatner & Uemura, 1991). Consequently, increases in respiratory volume in humans yield increases in the amplitude of RSA (Grossman et al., 1990a; Hirsch & Bishop, 1981; see also Figure 5). Other classes of pulmonary receptors also exist, including J-receptors (juxtapulmonary capillary receptors), which have a high threshold and induce bradycardia. This receptor type can introduce confounding effects on heart rate with extreme pulmonary stretch but has minimal effects under normal respiratory volumes. Pulmonary stretch reflexes can also exert indirect effects on heart rate via reflexive changes in blood pressure, vascular resistance, and other aspects of hemodynamic control (Coleridge & Coleridge, 1991; Daly, 1985; Vatner & Uemura, 1991).

Pulmonary stretch receptors do not appear to exert notable direct synaptic effects on either vagal cardiomotor neurons or on nucleus tractus solitarius neurons that receive baroreceptor inputs (Gilbey et al., 1984), suggesting that stretch afferents modulate transmission through interneuronal reflex pathways to cardiomotor neurons. Thus, both the central respiratory generator and pulmonary afferents can modulate the sensitivity of brain stem networks that control vagal cardiomotor outflow. These relationships are illustrated in Figure 5, which depicts the major central and peripheral determinants of RSA.

Summary. RSA is a complex, multiply determined phenomenon, arising from a variety of interacting central and peripheral factors. Two predominant sources of the respiratory modulation of vagal outflow are (a) the phasic excitatory/inhibitory modulation of vagal motor neurons by the central respiratory generator and (b) the phasic gating of vagoexcitatory inputs by pulmonary stretch receptors. The functional interrelationships between these two basic mechanisms, during respiration, are illustrated in schematized form in Figure 6. These two mechanisms are functionally linked via the phrenic control of respiration (Daly, 1985). The central respiratory generator drives phrenic motor neurons that control inspiration, yielding lung inflation and activation of pulmonary stretch receptors. Stretch receptor afferents, in turn, gate vagoexcitatory inputs and also inhibit the inspiratory phase of the central respiratory generator (the Hering–Breuer reflex). Thus, these mechanisms mutually entrain the other and normally operate in close concert. Nevertheless, factors such as specific respiratory maneuvers, chemoreceptor actions on the respiratory generator, or psychological variables may alter the relative expression of these two mechanisms.

Relative Contributions of Central and Peripheral Mechanisms

Based on studies in dogs, in which the central and pulmonary components were independently manipulated, Anrep et al. (1936b) suggested that the respiratory generator and pulmonary stretch receptors contribute approximately equivalently to RSA. The inhibition of vagal motor neurons can yield complete or near vagal silence during the inspiratory phase, and either the central or peripheral mechanisms may be able to effect this level of inhibition. Thus, Anrep et al. (1936b) demonstrated that either the central respiratory generator or the pulmonary stretch reflex could sustain RSA of relatively typical amplitudes in the absence of the other determinant. In the intact organism, however, these two mechanisms are closely entrained and may not be readily dissociated. Nevertheless, the relative contributions of central and peripheral mechanisms may vary across behavioral conditions.

Although breath holding can largely eliminate the phasic input from pulmonary stretch receptors, respiratory-frequency fluctuations in heart period can persist in this condition (Davies & Neilson, 1967a, Figure 2; Hirsch & Bishop, 1981; Kollai & Mizsei, 1990, Figures 1 and 2). Moreover, in the anesthetized dog, these respiratory heart-period rhythms may be closely coupled with phrenic nerve activity, even in the absence of overt

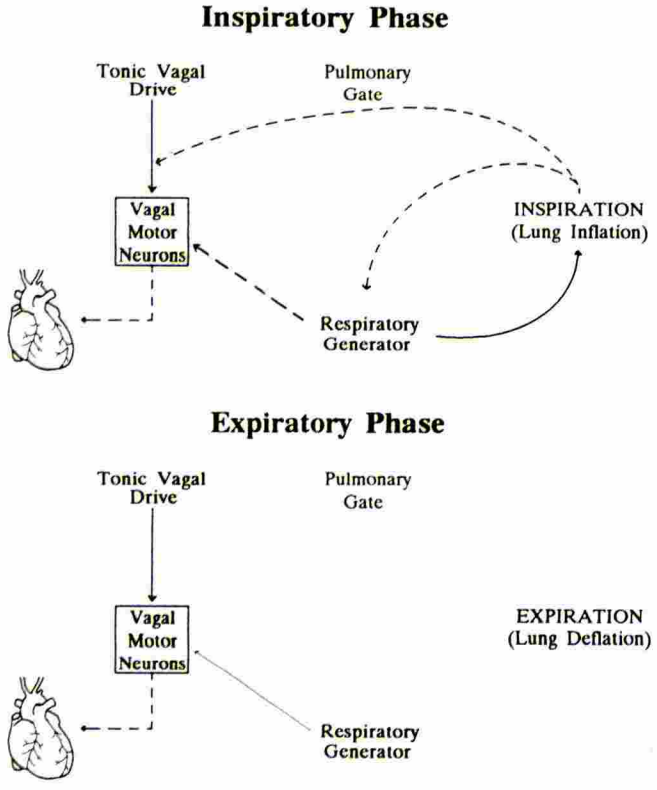

Figure 6. Schematic illustration of the primary functional interactions among central and peripheral determinants of RSA, as a function of respiratory phase. Solid lines illustrate excitatory influences; dashed lines depict inhibitory actions.

respiratory movements (Anrep et al., 1936a, 1936b; Daly, 1985). Although interpretation of the results of breath holding is confounded by the wide array of direct and indirect hemodynamic responses associated with this maneuver (Daly, 1985), these results illustrate the persistence of RSA in the absence of notable respiratory movements.

Unfortunately, when both central and peripheral mechanisms are operative in the intact organism, the relative contributions of these mechanisms to RSA are not well defined. One set of determinants appears to be respiratory parameters. With normal to low volume respiration, the lung inflation receptors are less effective in gating vagoexcitatory afferent inputs, and the central respiratory generator may be a more predominant driver of RSA (see Daly, 1985). With higher respiratory volumes, however, lung inflation receptors more effectively gate vagoexcitatory afferents and additionally exert a direct inhibition on the central respiratory generator (Daly, 1985). Under these conditions, pulmonary feedback may assume the predominant role in the generation of RSA. An additional determinant of RSA is posture. Assumption of an upright posture unloads the arterial baroreceptors and diminishes baroreflex drive on vagal motor neurons, thereby reducing the functional impact of phasic pulmonary gating. This process typically reduces RSA amplitude and may shift the relative balance toward the respiratory generator.

Nature and Locus of Behavioral Influences on RSA

Much of the current psychophysiological interest in RSA arises from its sensitivity to behavioral or cognitive states and processes (Grossman, 1983; Grossman et al., 1990a; Porges, 1986; Porges et al., 1982). Rostral brain structures exert important modulatory control over brain stem cardiorespiratory mechanisms, and many behavioral influences on RSA are likely mediated by descending projections from these higher central systems (Gonzalez-Lima, 1988; Jordan, 1990; Smith & DeVito, 1984; Spyer, 1989). Rostral (suprabulbar) systems have extensive neural links with multiple nodal points in brain stem cardiorespiratory systems, and direct anatomical projections have now been demonstrated from the amygdala, hypothalamus, and orbitofrontal cortex to the nucleus tractus solitarius, dorsal motor nucleus, nucleus ambiguus, medullary cardiorespiratory networks, and the intermediolateral cell column of the spinal cord (Danielsen, Magnuson, & Gray, 1989; Holstege, 1987; Onai, Takayama, & Miura, 1987).

In an earlier review of the literature, Bard (1960) suggested that suprabulbar systems may inhibit the baroreflex under conditions of stress, which could account for the concurrent (and baroreflex-incompatible) increases in blood pressure and heart rate during adaptive challenges. Even mild stressors, including mental arithmetic, can lead to a reduction in the sensitivity and/or gain of the baroreceptor-heart rate reflex (Conway, 1984; Nosaka, Nakase, & Murata, 1989; Stephensen, Smith, & Scher, 1981; Steptoe & Sawada, 1989). A decrease in baroreflex gain reduces the tonic baroreceptor drive on vagal motor neurons and thus diminishes the basal level of vagal activity that is subject to phasic inhibitory modulation. This process would be expected to increase heart rate and decrease the amplitude of RSA, a pattern of response commonly observed with behavioral or cognitive stressors (e.g., see Grossman et al., 1990).

A similar reduction in baroreflex gain can be induced by direct stimulation of the hypothalamus or amygdala, structures implicated in the normal response to stress (Jordan, 1990; Koizumi & Kollai, 1981; Nosaka et al., 1989; Spyer, 1989). Moreover, the hypothalamus and amygdala appear to be important nodal structures in the cardiovascular responses to behavioral manipulations. Thus, both the behavioral and cardiovascular reactions of the conditioned emotional response may be abolished or greatly diminished by lesions of the hypothalamus or amygdala in the absence of alterations in the unconditioned response (Gentile, Jarrell, Teich, McCabe, & Schneiderman, 1986; Kapp, Pascoe, & Bixler, 1984; LeDoux, Iwata, Cicchetti, & Reis, 1988; Sananes & Campbell, 1989). Rostral structures suppress the baroreflex through two mechanisms: (a) an inhibition of nucleus tractus solitarius neurons that receive baroreflex afferents and (b) an inhibition of vagal motor neurons (Nosaka et al., 1989; Spyer, 1989). Rostral areas may also override or inhibit baroreflex control indirectly via release of neuropeptides, such as thyrotropin-releasing hormone, corticotropin-releasing hormone, and the opioid peptides (Feuerstein, Siren, Vonhof, & Willette, 1991). These neuropeptides, released under conditions of stress, can alter baroreflex responses by inhibition of vagal motor neurons and/or reflex networks (Feuerstein et al., 1991).

Additional behavioral influences arising from higher systems are exerted directly on neuronal networks of the respiratory generator. In addition to modulating baroreflex gain, stressors can enhance respiratory activity (Grossman, 1983), probably through descending actions on intrinsic brain stem respiratory neurons (Spyer, 1989). Furthermore, separate subsets of brain stem respiratory neurons may be differentially active during reflexive respiration and breathing modulated through conditioning pro-

cedures (Daly, 1985; Orem, 1987). The latter appears to be mediated by descending projections from the cortex, which are able to inhibit and bypass rhythms in inspiratory neurons of the reflexive subsystem (Orem, 1987). Alternate subsets of respiratory neurons, controlled by descending cortical projections, then come to drive phrenic motor outflow. Although the above studies were completed in a minimal animal preparation, they suggest a differential cortical control of neuronal subsets within brain stem respiratory generators. Behavioral modulations of respiration also yield a clear alteration in the pulmonary afferent feedback to cardiorespiratory mechanisms. Together, the above findings suggest multiple routes by which psychological variables may alter the functional activity within brain stem cardiorespiratory networks.

Summary. Cognitive and behavioral influences on RSA are mediated in part by descending projections, or neurohumoral influences, from higher brain systems. These influences are capable of modulating RSA by actions at several nodal points in brain stem cardiorespiratory systems. These actions may include (a) direct effects on vagal motor neurons, (b) modulations of the gain of vagoexcitatory baroreceptor reflexes, (c) direct alterations in the pattern of activity of neuronal subsets of the respiratory generator, and (d) secondary changes in pulmonary reflex gating associated with respiratory variations. In view of the multiple loci through which rostral systems can affect RSA, different behavioral or cognitive manipulations may evoke somewhat differentiated patterns of influence on RSA substrates. Although this potential diversity of actions may contribute to error variance if ignored, it may also afford an important basis for a more refined differentiation of behavioral effects on RSA.

The Neurophysiological and Psychophysiological Domains

Although the psychological significance of RSA could be pursued independent of biometric issues, the material reviewed above suggests that a comprehensive understanding of RSA will require an integration of the psychophysiological and the neurophysiological levels of analysis.

The Neurophysiological Domain

Figures 5 and 6 illustrate both tonic and phasic determinants of RSA, which have a primary origin either in intrinsic central networks or in peripheral afferent inputs. These determinants can thus be characterized on two orthogonal dimensions (time course and origin) (Table 1). These dimensions may serve as a heuristic device to differentiate RSA determinants that are subject to distinct functional controls and may have differing autonomic manifestations.

Although both central and peripheral determinants ultimately converge on common vagal motor neuron pools, their antecedents, temporal dynamics, and patterns of consequence may vary. Two major sources of tonic vagal drive comprise the excitatory influences that are subject to phasic (respiratory) inhibition. The first is tonic central vagal drive, which represents the aggregate tonic central excitatory influences on vagal motor neurons. The second is afferent (or reflex) vagal drive, which arises from the vagoexcitatory actions of chemoreceptor, baroreceptor, and other afferent inputs to the nucleus tractus solitarius.[3] In addition to these tonic determinants, two major sources of phasic modulation are instrumental in the generation of RSA. The first is the central respiratory generator, which entails a phase-dependent excitatory/inhibitory modulation of vagal cardiomotor outflow. The second arises from peripheral lung inflation receptors, which impose a phasic pulmonary gate on vagoexcitatory baroreceptor and chemoreceptor reflexes. The specific physiological mechanisms listed in the cells of Table 1 are intended to be exemplary rather than exhaustive or mutually exclusive. Thus, (a) the respiratory generator may exert tonic as well as phasic influences, (b) baroreceptor afferents have phasic as well as tonic variation, and (c) the functional magnitude of central vagal drive is not clear. The categories of Table 1, however, highlight orthogonal dimensions that may serve as important organizing schema for the conceptual differentiation of RSA determinants, and the cells of this table capture the predominant features of specific neurophysiological mechanisms.

Table 1. *Neural Determinants of RSA*

	Origin	
Time course	Central	Peripheral
Phasic	respiratory generator	pulmonary gate
Tonic	central vagal drive	reflex vagal drive

The ultimate psychophysiological utility of RSA measures may be greatly enhanced if the locus of experimental actions can be defined in terms of the fundamental origins of sinus arrhythmia. Tonic or phasic vagal controls of the heart represent aggregate manifestations of interdependent tonic and phasic neurophysiological processes. Thus, both the tonic and phasic components of vagal cardiac control in the psychophysiological domain (VT and VP of Equation 1) are resultant functions of tonic and phasic neurophysiological mechanisms. These underlying mechanisms can be further parsed, with the tonic determinants (Vt) comprised of central vagal drive (Vt_c) and afferent vagal drive (Vt_a) and the phasic determinants (Vp) parsed into the respiratory generator (Vp_r) and the pulmonary gate (Vp_g). Although Equation 1 (RSA $= f[\mathrm{VT}, \mathrm{VP}] + \epsilon$) specifies functional relationships within the psychophysiological domain, these relationships can also be expressed in the neurophysiological domain:

$$\mathrm{RSA} = f(\mathrm{VT}, \mathrm{VP}) + \epsilon = f(Vt_c, Vt_a, Vp_r, Vp_g) + \epsilon. \quad (2)$$

A comprehensive explication of RSA will require specification of these relationships at both levels of analysis. The potential

[3]Although baroreceptor afferents have a phasic pulse pressure rhythm, the low-pass characteristics of the cardiac vagal effectors pass only the DC component of this rhythm. Consequently, from the standpoint of chronotropic cardiac control, both the diastolic and pulse pressure components of baroreceptor activity are reduced to tonic determinants. Other vagoexcitatory afferent inputs, including cardiac stretch receptors (e.g., Kollai, Koizumi, Yamashita, & Brooks, 1978) may also be modulated by intrathoracic pressure changes associated with respiration. Although baroreceptor and chemoreceptor inputs are considered here because of their potency and significance for RSA, other sources of relevant afferent input also exist.

advantage of the neurophysiological level is that it may afford a finer differentiation of RSA determinants, which may more closely reflect central behavioral states. Thus, questions concerning cardiac vagal tone could be cast in terms of two of its underlying determinants:

$$VT = f(Vt_c, Vt_a) + \epsilon. \quad (3)$$

Equation 3 illustrates the conceptual basis for a finer grained analysis that may permit differentiation of variations in cardiac vagal tone arising, for instance, from neurological dysfunctions, orthostatic changes, or behavioral processes. Thus, although stress reactions and orthostatic changes could yield comparable alterations in tonic vagal control of the heart, the neurophysiological origins and psychophysiological implications of these manipulations may be quite distinct. Adding phasic elements (Vp_r, Vp_g) to Equation 3 could further enhance this functional analysis by distinguishing (for example) changes in RSA attributable to respiratory manipulations.

Although the mechanisms listed in Table 1 are subject to experimental manipulation, the complex interactions among these determinants may make it impossible to completely isolate these dimensions experimentally in intact, waking subjects. A more serious limitation for psychophysiological studies is that the critical criterion indices for these mechanisms, at least at present, may entail explicit neurophysiological measures that are rarely available with human subjects.

The Psychophysiological Domain

Although the neurophysiological and psychophysiological domains are coupled via the central vagal outflow and cardiac effector synapses, measures of cardiac state are often ambiguous as to their physiological origins (Berntson et al., 1991; Stemmler, Grossman, Schmid, & Foerster, 1991). Indeed, the central/peripheral dimension, which assumes considerable significance in the neurophysiological domain, may be relatively transparent in current psychophysiological measures. These central and peripheral mechanisms, nevertheless, serve as potent determinants of the psychophysiology of RSA. Thus, although experimental manipulations of these mechanisms may yield notable changes in RSA, measures of RSA alone may not permit logical inferences as to central or peripheral origins (Cacioppo & Berntson, 1992; Cacioppo & Tassinary, 1990).

In contrast to the central/peripheral dimension, the orthogonal tonic/phasic dimension is clearly manifest in the chronotropic state of the heart, as indexed by standard autonomic measures. Even for this dimension, however, the frequency characteristics and transfer functions of ganglionic and effector synapses preclude a simple isomorphism between psychophysiological measures and underlying physiological origins. Psychophysiological measures of cardiac functional state provide a transformed index of underlying autonomic mechanisms. Refined measures and indices that would permit an ultimate convergence between the psychophysiological and neurophysiological domains are needed.

In the psychophysiological literature, the tonic component of vagal control of the heart has been defined as the average or mean level of vagal influence on cardiac chronotropy over an operationally defined epoch. The utility of this definition is strengthened by historically precedented criterion measures. Alterations in tonic vagal control of the heart have been indexed by changes in mean beta-blocked heart period, in which sympathetic actions are precluded (e.g., Grossman et al., 1991). Further, the absolute level of tonic vagal control has been estimated by the change in mean heart period after blockade of the muscarinic vagal cardioeffector synapses (Akselrod et al., 1981; Fouad, Tarazi, Ferrario, Fighaly, & Alicandri, 1984; Grossman et al., 1990; Katona & Jih, 1975; Kollai & Mizsei, 1990; Porges, 1986). Although legitimate interpretive issues arise over the use of pharmacological blockade (see Berntson et al., 1991; Stemmler et al., 1991), these measures have the advantages of (a) a conceptual rationale, (b) a historical precedence that affords a degree of consistency and comparability across the literature, and (c) potential applicability to human subjects. Although pharmacological blockade may not be feasible in all studies, these indices (when properly controlled and interpreted) offer an empirical starting point, which can be refined, supplemented, or supplanted through future developments.

In contrast to cardiac vagal tone, phasic components of cardiac control are more directly identifiable in the temporal variability of heart periods across the experimentally defined epoch. Although there are multiple sources of this variability, the frequency components of this variance can be parsed by time series analysis. Given the frequency filtering of the autonomic effector synapses, phasic variations in the respiratory frequency range are largely the product of the vagal innervation. The respiratory-frequency component of heart period variance therefore reflects the contribution of RSA to phasic vagal control of the heart. Lower frequency components of phasic heart-rate control (e.g., the Mayer wave; Penaz, 1978) can also be derived from time series approaches, although these components reflect both vagal and sympathetic contributions.

The above schema offers a descriptive basis for characterizing frequency components of vagal control of the heart within the psychophysiological domain. However, psychophysiological states and responses must be clearly distinguished from neurophysiological mechanisms and processes. The tonic and phasic aspects of vagal control of the heart are certainly related to the physiological mechanisms outlined in Table 1. At the same time, tonic vagal control of the heart cannot be equated with central and/or afferent vagal drive nor can RSA be related to a singular phasic mechanism. It is increasingly important, therefore, to seek empirical and conceptual bridges between these domains.

The Interdependence of Tonic and Phasic Components of Vagal Control

Although tonic and phasic components of vagal control are manifest in distinct frequency components of heart-rate variance, these components are not orthogonal. Given the physiological limits (i.e., the maxima and minima) of vagal control of the heart, the amplitude of phasic fluctuations are necessarily constrained as vagal outflow approaches these functional limits or boundaries. More importantly, RSA arises in part from a phasic inhibition of vagal outflow, and its magnitude is thus a partial reflection of the tonic level of vagal control, which corresponds to the fact that manipulations that are known to alter the level of excitatory drive on vagal motor neurons generally yield corresponding changes in the amplitude of RSA. Hypertension or hypoxia, which increase central vagal outflow (via baroreceptor and chemoreceptor afferents), generally lead to increases in the magnitude of RSA (Daly, 1983, 1985; Grossman, 1983). Conversely, assumption of an upright posture, which decreases tonic vagal drive, results in a diminution of RSA. This general relationship has led to the suggestion that

RSA may provide an autonomic index of tonic vagal control of the heart (Grossman, 1983; Grossman et al., 1991; McCabe et al., 1985; Porges, 1986; Yongue et al., 1982). Thus, the magnitude of RSA correlates with estimates of tonic vagal control derived from the change in heart rate after vagal blockade (Akselrod et al., 1981; Fouad et al., 1984; Katona & Jih, 1975; Kollai & Mizsei, 1990).

Variations in phasic determinants of RSA can also impact on the tonic vagal control of the heart. A close relationship exists between tidal volume and the magnitude of RSA (Grossman & Wientjes, 1986; Hirsch & Bishop, 1981; Kollai & Mizsei, 1990), which is attributable to the fact that the residual vagal control at the peak of inspiratory inhibition is a function of the degree of pulmonary stretch (Anrep et al., 1936a, 1936b; Grossman & Wientjes, 1986; Hirsch & Bishop, 1981; Kollai & Mizsei, 1990). Thus, increases in respiratory depth can lead to increasing peak vagal inhibition, with resulting increases in RSA and decreases in mean vagal control of the heart.

Variations in respiratory frequency also have established effects on RSA, which are related to the frequency-transfer function of vagal cardiac effectors (see Figure 3). Given the decline in the vagal-transfer function throughout the respiratory-frequency band, vagal rhythms would be expected to yield diminishing RSA manifestations at progressively higher respiratory frequencies. Consistent with this interpretation, Angelone and Coulter (1964) reported that RSA in humans demonstrates a frequency dependency with increasing respiratory frequencies (>0.1 Hz), yielding a progressive phase lag in RSA and a decline in RSA amplitude. More recent studies have confirmed the inverse relationship between RSA amplitude and respiratory frequency (Eckberg, 1983; Eckberg et al., 1980; Grossman et al., 1991; Hirsch & Bishop, 1981; Kollai & Mizsei, 1990; Shin et al., 1989). As illustrated in Figure 3, there may be a rather close correspondence between the function relating RSA amplitude to respiratory frequency in humans and the frequency-transfer function of vagal effectors derived from direct neural stimulation in the dog (at least within the respiratory frequency range; Berger et al., 1989a, 1989b). With variations in respiratory frequency, however, vagal activity can differentially impact on tonic and phasic components of cardiac control. At low frequencies, vagal activity can effectively translate into time-varying fluctuations in heart periods, which are characteristic of sinus arrhythmia. At progressively higher frequencies, the tonic level of vagal control may remain unaltered while rhythmical fluctuations are progressively attenuated. Moreover, the frequency-transfer functions of cardiac effectors themselves may change with variations in basal or mean levels of vagal activity (Berger et al., 1989b; see also footnote 2). Consequently, the relationship between RSA magnitude and tonic vagal control may not be constant under all conditions.

Psychophysiological indices of vagal control. Questions have arisen as to optimal psychophysiological indices and criterion measures of cardiac vagal control. In an investigation of the relations between respiratory parameters and RSA in human subjects, Grossman et al. (1991) reported that changes in respiration may influence RSA magnitude but not mean beta-blocked heart period (which would be expected to index changes in mean vagal control). Kollai and Mizsei (1990) also found only moderate within-subject correlations between RSA magnitude and beta-blocked heart period with experimentally imposed changes in respiratory parameters. RSA amplitude and beta-blocked heart period were positively correlated for some subjects and negatively correlated for others. Moreover, beta blockade itself was reported to increase RSA amplitude. Kollai and Mizsei (1990) also examined the relationship between RSA amplitude and tonic vagal control indexed by individually titrated blockade of vagal cardiac effectors with atropine. Results indicated that RSA amplitude could be best predicted in a multiple regression analysis ($r = .93$) by a combination of variables, including tonic vagal control (as indexed by vagal blockade) and respiratory parameters.

Although the findings outlined above could fuel a debate over the optimal index of tonic vagal control, a more productive effort might address the issue of how various psychophysiological measures relate to basic neurophysiological mechanisms and processes (see Equation 2). With indices derived from peripheral pharmacological blockade, it is minimally necessary to ensure that the achieved block is functionally complete and has not altered central or reflex systems that may have secondary effects on heart period. Even under optimal conditions, mean beta-blocked heart period, the change in mean heart period with vagal blockade, and RSA may differentially reflect aspects of the tonic and phasic vagal control of the heart.[4] Consequently, these indices may not represent mutually exclusive alternatives but rather can provide converging and complimentary perspectives on operations in the neurophysiological domain. A greater understanding of the underlying mechanisms of vagal control of the heart and their antecedents, dynamics, and consequents may be necessary for the ultimate illumination of the psychophysiological significance of RSA.

Summary

Respiratory sinus arrhythmia offers considerable promise as a noninvasive, selective index of vagal control of the heart. Although other noninvasive psychophysiological indices may preferentially index one autonomic division or another, none are likely to be as selective as RSA, because chronotropic, dromotropic, and inotropic functions are all controlled to various extents by both autonomic divisions. The selectivity of RSA, however, is related to differences in the frequency-transfer functions of autonomic cardiac effectors rather than to selective innervation patterns of the autonomic divisions. Respiratory sinus arrhythmia is relatively simple to derive methodologically and shows a high degree of sensitivity to psychological and behavioral variables. Equally important is the fact that the neural systems and underlying mechanisms of RSA are beginning to be understood in some detail, and the links between these mechanisms and central behavioral substrates are being enumerated. These understandings are still emerging, however, and the

[4] Differences between indices derived from beta-blocked heart period and the heart-period change after muscarinic blockade are inherent to the pattern of neurochemical control of the heart. Muscarinic blockade antagonizes the vagal innervation of the heart and also blocks the vagally mediated cholinergic inhibition of the sympathetic cardiac innervation. It does not appreciably directly alter either sympathetic neural innervation of the heart or the cardiac effects of circulating catecholamines. Beta blockers, in contrast, antagonize both the sympathetic neural innervation of the heart and the effects of circulating catecholamines. Moreover, beta blockers do not effectively antagonize sympathetic neural presynaptic inhibition of vagal cardiac innervations via neuropeptide Y (Hall & Potter, 1990). Heart-period changes under beta blockade, therefore, do not reflect the simple attenuation of sympathetic neural control.

functional models presented here represent only the broadest overview of the complex origins of RSA. Much of this information derives from minimal animal preparations, and caution must be exercised in extrapolating to behaving organisms. Clearly, the relative contributions of the multiple mechanisms of RSA must be further studied in intact, wakeful subjects and across behavioral contexts. The benefits of a multilevel analysis of RSA are not one sided, and psychophysiology is in a unique position to benefit from and contribute to our understanding of the relations between the neurophysiological and psychophysiological domains (e.g., see Somsen, Molenaar, van der Molen, & Jennings, 1991). Respiratory sinus arrhythmia constitutes an important model system for the study of psychophysiological relationships at multiple levels of analysis (behavioral, psychophysiological, neurological, and neurophysiological) and offers a striking opportunity for the broad integration of psychophysiology with other neuroscience disciplines.

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