Point: Counterpoint: Respiratory sinus arrhythmia is due to a central mechanism vs. respiratory sinus arrhythmia is due to the baroreflex mechanism

**Point: Respiratory Sinus Arrhythmia Is Due to a Central Mechanism**

Blood pressure and heart periods fluctuate at respiratory frequencies in healthy humans. Some researchers (8, 23) explain this as a cause-and-effect relation: blood pressure changes trigger baroreflex-mediated R-R interval changes. Here I make the case that respiratory sinus arrhythmia is a central phenomenon that is independent of blood pressure changes. I base this argument on several well-documented physiological facts.

Vagal-cardiac motoneuron membrane potentials fluctuate at respiratory frequencies (16), modulate responsiveness of vagal motoneurons to arterial baroreceptor inputs (12, 13), and impose a respiratory rhythm on vagal-cardiac nerve traffic and heart periods (18). Central respiratory gating of vagal motoneuron responsiveness (11) is sufficient to explain respiratory sinus arrhythmia.

The cascade of events comprising a vagal baroreflex response does not play out instantaneously; each step in the sequence takes time. Therefore, a critical question is, how much time is required between the beginning of the cascade sequence, a change of arterial pressure, and the end of the sequence, a change of heart period?

Latencies of individual components of vagal baroreflex responses have been measured directly in animals and include transduction of baroreceptive artery stretch into baroreceptor firing, 18 ms (19); polysynaptic central transactions, 26 ms (21); transmission of vagus nerve traffic from the brain stem to the sinoatrial node, 2 ms (6); and sinoatrial node responses, 120 ms (6). Simple addition of these latencies (14) yields a vagal baroreflex arc latency of 166 ms; the great majority of this latency, 72%, reflects the kinetics of sinoatrial node responses to released acetylcholine.

These animal data comport well with results obtained with electrical carotid sinus nerve stimulation and abrupt intense neck suction in humans. Minimal human vagal baroreflex latency is remarkably short—less than 0.5 s (5, 25), and possibly as short as 0.24 s (9). However, the operative word in the preceding sentence is “minimal”; data derived from highly unphysiological experimental interventions do not necessarily answer the question, what is vagal-cardiac baroreflex latency in the arterial pressure, heart period transactions that occur in everyday life? The short answer to this question is this: vagal baroreflex responses do not occur instantaneously—they take time. The question then becomes, how much time?

In one of the earliest quantitative studies of human vagal baroreflexes, Smyth, Sleigh, and Pickering (27) gave intravenous bolus injections of angiotensin, and plotted heart period responses as functions of preceding arterial pressure increases. They reported that the best linear fits were obtained when each systolic pressure during the pressure rise was correlated with the R-R interval of the heart beat that followed the pressure pulse. In 1986 (15), we confirmed this observation and showed that most spontaneously occurring baroreflex sequences (3) yield the highest correlation coefficients when each arterial pulse is related to the following R-R interval.

When baroreceptors are stimulated with abrupt intense neck suction, the time from the onset of the stimulus until the maximum P-P interval prolongation averages 1.5 s (2). (In a subject with a P-R interval of 0.15 s, the stimulus to R wave latency becomes 1.65 s.) Wallin and Nerhed (29) signal averaged arterial pressures and R-R intervals on the peaks of muscle sympathetic bursts and reported that diastolic pressure rises after sympathetic bursts and R-R intervals peak between 1.8 and 4.8 s (average, 2.9) later.

The next question is, what is the latency between respiratory frequency arterial pressure and R-R interval changes? We performed cross-spectral analysis of systolic pressures and R-R intervals in two studies (7, 20), the results of which are summarized in Fig. 1.

Data in Fig. 1, A and B, were recorded during fixed-frequency breathing at progressive angles of passive upright tilt (7). The average phase angle was minus 53° at the low frequency (A) and did not change significantly during tilt (P = 0.48, linear regression). Such analyses do not indicate whether systolic pressure changes precede R-R interval changes [by 1.6 s (53°/360°–11.1 s)] or follow R-R interval changes [by 9.5 (11.1 – 1.6) s]. A latency of 9.5 s is not consistent with baroreflex mechanisms; systolic pressure returns to usual levels within 3 s after transient reductions of arterial pressure (30). Therefore, it is likely that low frequency R-R interval changes follow systolic pressure changes, with an average latency that is consistent with arterial baroreflex physiology (2).

Figure 1B shows an entirely different picture for respiratory-frequency systolic pressure—R-R interval phase angles. The phase was positive in the supine position (extreme left) and declined systematically (P = 0.001) to negative levels, in proportion to the tilt angle. Average calculated latencies between systolic pressure and P-P intervals (subtracting an assumed P-R interval of 0.15 s) from these data were plus 0.3 s in the supine position and minus 0.1 s at the 80° the tilt position. Other studies (8, 23) document similar latencies for both low- and respiratory-frequency systolic pressure-R-R interval cross-spectra in supine subjects.

Data shown in Fig. 1, C and D, (20) were recorded from supine subjects during controlled-frequency breathing and conventional mechanical ventilation (both at 0.25 Hz). Calculated latencies averaged −2.7 and −3.0 s at low frequencies (P = 0.88, Mann-Whitney Rank Sum, Fig. 1C) and −0.28 and 0.53 s at respiratory frequencies (P = 0.001, Fig. 1D) during spontaneous breathing and mechanical ventilation. One point that stands out in this figure [and in other studies (4, 7, 10, 24)] is that systolic pressure-R-R interval phase angles at respiratory frequencies vary greatly.

Therefore, if respiratory frequency R-R interval fluctuations are baroreflex-mediated, baroreflex latencies—mainly reflecting the kinetics of acetylcholine effects on the sinoatrial node—vary systematically, according to the physiological cir-
cumstances of the moment. Saul and coworkers (24) proposed a vastly simpler explanation: R-R interval changes follow breathing, not pressure, with a nearly fixed time delay of \(0.3\) s.

Although I emphasize baroreflex latencies, other types of evidence point to a respiratory, non-baroreflex causation of respiratory R-R interval changes. In anesthetized dogs, R-R interval fluctuations follow phrenic nerve activity and persist when intrathoracic pressure fluctuations are abolished (26). Thoracotomy increases respiratory blood pressure changes but decreases R-R interval fluctuations (17). Fixed-rate atrial pacing reduces respiratory frequency blood pressure fluctuations (28); if baroreflex responses buffer blood pressure fluctuations, blood pressure oscillations should be greater, not less, during fixed-rate pacing. Conventional mechanical ventilation, which presumably silences phrenic motoneurons, augments respiratory blood pressure fluctuations, but nearly abolishes respiratory R-R interval fluctuations (20). Removal of respiratory influences on systolic pressures and R-R intervals by partialization reduces coherence between the latter signals from close to 1.0 to \(<0.5\) (1).

I subscribe to the view that blood pressure changes provoke parallel R-R interval changes—a cause-and-effect baroreflex relation. However, in this physiology, timing is everything. Before I accept the view that R-R interval fluctuations at respiratory frequencies are baroreflex responses, someone must explain 1) how an arterial pressure change can, within \(0.1\) s, speed or slow the appearance of the next P wave; 2) how the kinetics of sinoatrial nodal responses to acetylcholine are modulated systematically by body position and breathing frequency; and most difficult of all, 3) how baroreflex R-R interval responses can occur before the arterial pressure changes that provoke them. I submit that the last possibility, that effects can precede causes, turns logic on its head.

REFERENCES

COUNTERPOINT: RESPIRATORY SINUS ARRHYTHMIA IS DUE TO THE BAROREFLEX MECHANISM

In healthy humans blood pressure and heart periods fluctuate at respiratory and other frequencies. The extent of these fluctuations is situation and age dependent. Although literature concurs that most of these fluctuations are reflex driven, some insist on an explanation for the respiratory oscillations. In view of the widespread central nervous activity related to respiration, it is reasoned that in the course of evolution the cardiovascular system has, centrally, become entrained to the respiratory drive. This would, teleologically, improve oxygen uptake by increasing heart rate in the inspiratory phase. Here I make the case that respiratory sinus arrhythmia is mainly a reflex phenomenon, driven by incoming information from baroreceptors. I will base this argument on well-established physiological facts and insight that can be gained from simple computational models.

This will not refute animal experiments that show respiration to modulate centrally the blood pressure to heart period reflex. However, I intend to demonstrate that in awake humans this phenomenon is insufficient to explain respiration-to-heart rate relations.

The beauty of modeling is that it puts physiological insight to the test: does my interpretation of experimental findings fulfill all the requirements; can it describe what has been measured; and, still better, does it correctly predict findings that have not yet been obtained? The problem of modeling is the complexity of most models: they require so many parameters and mathematical formulas that, to the non-expert reader, any desired outcome might be obtained. In this essay I will try to simplify and restrict modeling to the bare minimum; more complex reasoning and models can be found in the literature.

First, let us look at a picture of common baroreflex physiology (Fig. 1A): baroreflex afferent information is in the brainstem relayed to cardiac vagal efferent traffic, leading to sinus node slowing, be it by a full reset of the diastolic depolarization (5) as depicted, or to a slowing of depolarization (2). In any case, this acts sufficiently fast, the next heart beat will be delayed after a systolic pressure increase, thereby stabilizing diastolic pressure (Fig. 1C). As has been argued by Dr. Eckberg in his Point preceding this Counterpoint, we may assume that this can, in humans, occur within one beat, in view of the latencies involved. Also the founding fathers of the “gold standard” of baroreflex sensitivity (BRs) measurement came to this insight in a later publication (6): if resting heart rate in humans is below ~75 beats/min the best correlation between (increasing) systolic pressures and heart periods is found for the heart period in which a specific systolic pressure occurs, rather than for the next heart period. It is strange to see that this insight did not make it into practice.

Now suppose that in a sequence of beats as depicted in Fig. 1A, suddenly the central nervous system decides to command the heart period to modulate centrally the blood pressure to heart period reflex. How does the baroreflex mechanism participate in this process? We will see that the respiratory sinus arrhythmia is the reflex component in the respiratory drive. This would, teleologically, improve oxygen uptake by increasing heart rate in the inspiratory phase. Here I make the case that respiratory sinus arrhythmia is mainly a reflex phenomenon, driven by incoming information from baroreceptors. I will base this argument on well-established physiological facts and insight that can be gained from simple computational models.

The jumping between frequency and time domain should be done with caution. In treating blood pressure and heart period recordings, it is common practice to reduce the amount of data