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

RSA: NUMBERS AND BEYOND

TO THE EDITOR: Respiratory sinus arrhythmia (RSA) is a complex phenomenon whose physiological role is still a matter of debate (6). From a practical point of view, it is important to know whether RSA can be used to compute indexes of cardiac baroreflex sensitivity, hence the present Point:Counterpoint article (2, 4). A direct approach to the question of baroreflex involvement in the production of RSA is to examine whether it is attenuated in patients with baroreflex failure. I have been unable to locate such data in the literature, with the exception of one study where a short mention was made of the presence of high-frequency oscillations of heart rate in a patient with baroreflex failure secondary to neck surgery (3). In rats, it has been reported that chronic denervation of arterial baroreceptors increases the respiratory related fluctuations of heart rate (1). Overall, the divergence of opinion between Eckberg (2) and Karemaker (4) is mainly a quarrel about numbers. While I take the point of both authors, I would like to make a general comment about phase shifts. A positive phase (phase lead) does not necessarily mean that the effect precedes the cause. For example, the derivative term contained in some dynamic systems produces a phase lead, which at certain frequencies, offsets or even exceeds the phase lag introduced by other components (low-pass filters and fixed time delays; 5). In conclusion, considering the present state-of-the-art, I agree with Eckberg that RSA should not be used to assess cardiac baroreflex sensitivity.

REFERENCES


RSA: BOTH MAY BE INVOLVED

TO THE EDITOR: Four points might be helpful.

1) Both mechanisms are “central” in that both operate via the brain stem.
2) Both may contribute simultaneously (they are not necessarily mutually exclusive).
3) One support for a contribution from the central respiratory rhythm is that abolishing phrenic motoneuron activity nearly abolished RSA: “conventional mechanical ventilation [in normocapnia], which presumably silences phrenic motoneurons, augments respiratory blood pressure fluctuations, but nearly abolished respiratory R-R interval fluctuations” (5).
4) We (2) agree with this support but not with the interpretation of Koh’s data. Koh’s loss of RSA may be due to using fentanyl (5–10 μg/kg), which causes central apnea and possibly death if patients are not reminded to breathe (4). We (2) describe one mechanical ventilation regimen for conscious and unmedicated volunteers that did not silence phrenic motoneurons in normocapnia (rhythmic diaphragm EMG activity remained detectable from the body surface), did not augment respiratory blood pressure fluctuations and did not significantly change RSA. We did, however, show (2) that surreptitiously inducing hypocapnia (mean PetCO2 of 24 mmHg), without altering the rhythmic mechanical ventilation, did abolish body surface diaphragm EMG activity, did reduced RSA by ~70%, but had no effect on the presumed baroreflex stimulus (BP) nor on mean heart period.

5) Another support is the fact that during breath-holding rhythmic changes in lung inflation and presumably in venous return cease. Yet the central respiratory rhythm continues (1), some sinus arrhythmia continues and remains “respiratory” i.e., is CO2 dependent (3) and continues coinciding with diaphragm EMG activity (6).

REFERENCES


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SINUS ARRHYTHMIA AND BAROREFLEX SENSITIVITY: INTIMATE RELATIONSHIP OR SEPARATE IDENTITIES?

TO THE EDITOR: The computation of baroreflex sensitivity (BRS) using spontaneous blood pressure and cardiac cycle intervals fluctuations at the respiratory frequency is grounded on the assumption that respiratory sinus arrhythmia (RSA) is baroreflex mediated. The present debate indicates that this assumption remains unclear (1, 3). Given the breadth of evidence for both mechanistic proposals, the truth may lie somewhere in between. If we accept that RSA is generated by some amalgam of central and baroreflex processing, then spontaneous BRS based on the analysis of RSA can only partially reflect BRS. Here lies the concern: if an experiment obtains a change in BRS calculated from RSA,
how do we know that this is the result of a change in baroreflex activity as opposed to a change in nonbaroreflex activity? Thus spontaneous BRS should be interpreted with caution.

We have one additional remark concerning the use of spectral analysis. The decomposition of physiological signals into sinusoids eliminates important information, especially as neither RSA nor blood pressure fluctuations coincident with respiration are sinusoidal oscillations (4–6). Therefore, although a negative phase difference between cardiac cycle interval and systolic blood pressure might be consistent with baroreflex physiology, a single phase difference value cannot be taken as a fixed latency throughout all phases of the respiratory cycle. More mechanistic detail may be revealed with phase domain techniques, which portray RSA and blood pressure changes as a function of the respiratory cycle (2). Efforts should be directed toward developing a unified theory of RSA incorporating both central and baroreflex mechanisms.

REFERENCES

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IS RESPIRATORY SINUS ARRHYTHMIA A LINEAR OSCILLATOR?
TO THE EDITOR: The Point-Counterpoint (2, 4) about sinus arrhythmia opposed not only two experts in the field but also two approaches of integrative physiology. Modeling obviously suffers from limitations of oversimplification as Karemaker (4) acknowledges. Experimental approach should be complementary to modeling. However, the experiments presented by Eckberg (2) suffer from the same limitations as modeling since the cardiovascular system was experimentally forced (pharmacological or mechanical forcing of the baroreflex, breathe pacing and even heart pacing) to fit linear models (sigmoid baroreflex relationship, sinusoid like breathing, and steady heart rhythm; Ref. 2). The classical view of cardiovascular system as a steady-state linear system responding to environmental changes (internal or external) thanks to corresponding autonomies bursts in an on-or-off fashion should be revisited. The complexity of the cardiovascular system that includes at least 200 interacting variables (3) logically leads to complex nonlinear dynamics (5). Interacting variables are illustrated by the observation of sinus arrhythmia oscillations (a phenomenon mechanically generated by thoracic movements and/or mediated by the parasympathetic system) in laser-Doppler flowmetry of forearm skin microcirculation (that is free from direct mechanical influences of the thorax and from direct parasympathetic influences; Ref. 1). The cardiovascular dynamics, including respiratory sinus arrhythmia, results from constantly interacting nonlinear oscillators made from the numerous cardiovascular variables. Studies of the cardiovascular system have to take into account the complexity of the system and of its resulting dynamics.

REFERENCES

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ORIGIN OF THE RESPIRATORY SINUS ARRHYTHMIA: INSIGHTS FROM CAUSAL ANALYSIS

TO THE EDITOR: The Point:Counterpoint (1, 2) can be rephrased as: is respiratory sinus arrhythmia (RSA) causally linked to arterial pressure (AP) oscillations or is it a parallel phenomenon?

According to the formulation of Granger causality, the baroreflex origin of RSA should be proved by checking that at the respiratory rate: a) AP fluctuations occur before heart period (HP) oscillations; b) RSA is significantly linked to AP from AP to RSA; c) the inclusion of new signals does not allow to predict RSA better than using solely HP variability (HPV) and AP. In intact organisms the assessment of delays from measured signals is unreliable due to the ambiguity in input-output relationships and phase wraps. Therefore, the baroreflex origin of RSA should be tested according to points a and c.

Recent studies on causality support the hypothesis that baroreflex cannot be considered the unique origin of RSA: indeed, i) when a simple model, describing the AP as the sole result of past systolic AP (SAP) values plus a white noise, was used, the goodness of fit was very poor (4, 6) and became significant when sources of HPV, independent of SAP, were introduced (4, 6); ii) the fraction of RSA driven by SAP changes was decreased when introducing a respiratory signal as an exogenous signal (4, 6); iii) in resting humans, in presence of a high global correlation between RSA and SAP, the causal link from SAP variability to RSA is insignificant in 2 of 7 subjects in Ref. 5 and in 4 of 15 subjects in Ref. 3.

REFERENCES


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IS THE BAROREFLEX SIMPLY A REFLEX?

TO THE EDITOR: There might be no greater bias in choosing between central (2) versus peripheral (3) origin of respiratory sinus arrhythmia (consisting in a continuous wave of heat by beat oscillations in R-R interval) than the concept of the (baro)reflex, which implies an event occurring in a limited time window (impulse). The consideration that a reflex is “probably a purely abstract conception, because all parts of the nervous system are connected together” (1) and this “system certainly [is] never absolutely at rest” (1), would favor a central origin. Because, however, “[t]he main secret of nervous co-ordination lies . . . in the compounding of reflexes” (1), it might well be that also the periphery might matter: the baroreflex would thus be critical in modulating respiratory driven respiratory oscillations of R-R interval within a network of neuronal circuits and reflexes generating continuous oscillations. Indeed on one hand baroreflex denervation in conscious dogs profoundly reduces (but not abolishes) respiratory arrhythmia (6), conversely neural autonomic coding comprises both tonic and oscillatory components (5). Interpretation of experiments will be implicitly colored by the discontinuous nature of heart rhythm, through a Nyquist bias (depending on how many beats are present in the unit time to reconstruct the idealized heart rate waveform). In conclusion, the question could be rephrased into what are the respective roles of central respiratory neural networks and peripheral baroreflex circuits. We might add that cardiovascular neural networks comprise as well positive feedback sympathetic (4) reflexes, whose varying activity might modulate both respiratory arrhythmia and baroreflex regulation in a concerted fashion.

REFERENCES


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SINUS ARRHYTHMIA HAS MECHANICAL ORIGINS

TO THE EDITOR: In their Point:Counterpoint, Drs. Eckberg and Karemaker (1, 2) presented opposing views on the origin of respiratory sinus arrhythmia. It is hard to ignore the evidence presented from animal studies that respiratory gating occurs, but it is also difficult to see in human experimentation that respiratory gating has the same dominant effect. Various approaches have been taken to study the human cardiac baroreflex. Vagal baroreflex gain was less with the neck chamber method where subjects hold their breath (6) than in drug-induced pressure ramps applied during spontaneous respiration (5). We are left questioning whether this is a consequence of breath hold or pressure stimulus on the
carotid baroreceptors? The tangent of the drug-induced pressure-R-R-interval relationship was highly correlated with the spontaneous baroreflex from the beat-sequence method and the slope of the relationship was close to 1.0 (5). Modeling approaches to extract effects of respiration from those of arterial pressure on heart rate suggested that both factors might contribute to respiratory sinus arrhythmia (3), but while we apply these models they are only as good as the assumptions that underlie their development. What is clear though is that respiration does induce fluctuations in cardiac stroke volume that will reduce arterial pressure on inspiration potentially activating the arterial baroreflex (4). This relationship between inspiration and cardiac output is contrary, as Dr. Karemaker points out, to a teleological assumption linking heart rate acceleration to greater oxygenation that might enhance oxygen uptake with inspiration. The baroreflex works with or without respiration.

REFERENCES

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REASSORTY SINUS ARRHYTHMIA: ARE SIMPLE “MODELS” SUFFICIENT?

TO THE EDITOR: To refute any role for a central mechanism, the Counterpoint (1) relies on a “model” and the observation that the magnitude of diastolic pressure oscillations at the respiratory frequencies are small relative to that of systolic pressure oscillations. This difference is interpreted as an evidence for “stabilization” by baroreflex mechanisms. The model, however, is based on the (untested) assumption that the level of diastolic pressure is determined solely by the preceding systolic pressure. Furthermore, comparing the magnitudes of systolic and diastolic blood pressure oscillations is misleading. The relative magnitudes of oscillations do not provide insight into the mechanism(s) underlying respiratory sinus arrhythmia. (An analogy is that the systolic blood pressure oscillation is not “conspicuous” because its magnitude is smaller than that in R-R interval.) However, if the vagally mediated oscillation in R-R interval is augmented, its source can be inferred from the change in diastolic oscillations. For example, low-dose atropine augments respiratory sinus arrhythmia (2), and if the magnitude of diastolic pressure oscillations at the respiratory frequency are unchanged or lower, one can infer that the baroreflex control is “stabilizing” diastolic pressure; on the other hand, if it is larger, the model correctly predicts a prominent role for central modulation. In the absence of such experiments, however, the model awaits verification. The Counterpoint (1) is concluded by the remark that “too complex a model may become a belief on its own.” Oversimplification, however, is equally dangerous; particularly if the model is an illustration of a complex physiology, without adequate experimental tests of a models’ assumptions and predictions.

REFERENCES

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SINUS RESPIRATORY ARRHYTHMIA DEPENDS ON THE PONS

TO THE EDITOR: We have evidence in support of Eckberg’s position (2, 3) that respiratory sinus arrhythmia is due to a central mechanism. Recently, we reported that the respiratory sinus arrhythmia depends on the pons being intact in the in situ-perfused rat preparation (1). Respiratory sinus arrhythmia, respiratory modulation of sympathetic nerve activity (and Traube-Hering waves in arterial pressure), and postinspiratory discharges recorded from vagal efferents were prevalent with a ramping pattern of phrenic nerve activity and with pons and medulla intact. The respiratory modulation of sympathetic nerve activity and heart rate was not present after separating the pons from the medulla (1). Furthermore, although the sympathetic arterial baroreflex remained intact, the bradycardia elicited by baroreflex was attenuated after ponto-medullary transection. We conclude that pontine neural activity (probably from the rostral dl pons) is essential for physiological coupling of centrally generated respiratory and cardiovascular efferent activities including the respiratory sinus arrhythmia.

REFERENCES

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FEEDBACK FROM THE LUNG IS MANDATORY TO RSA IN HUMANS

TO THE EDITOR: Three mechanisms underlying respiratory sinus arrhythmia in humans have been revealed via experimental intervention and the use of organ transplant models. Heart denervated patients and double lung denervated patients with intact hearts both have significant RSA—but of a magnitude which is 1/100th that of controls on similar medications and with identical breathing patterns (1, 6). Furthermore, in intact subjects, eliminating the central respiratory motor output and diaphragm EMG via positive pressure ventilation eliminates most of the RSA (4, 6); but negative pressure mechanical ventilation does not eliminate RSA—implicating a right atrial reflex sensitive to filling during normal inspiration (3). These intervention data point to multiple, mutually dependent mechanisms underlying RSA in the intact human. However reflexive input from the lung is mandatory for RSA and, without it, synaptic input from central respiratory neurons and/or the heart to cardiovagal motoneurons are ineffective in modulating vagal efferent activity to the heart.

REFERENCES


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