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Heartbeat Synchronizes With Respiratory Rhythm Only Under Specific Circumstances

Evgeny Vaschillo, Bronya Vaschillo, Paul Lehrer, Fumihiko Yasuma and Jun-ichiro Hayano

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Monitoring the Adjustment of Antiasthma Medications With Adenosine Monophosphate Bronchoprovocation

To the Editor:

We would like to thank Dr. Proietti and colleagues for their interest and stimulating comments on our article.[1] We certainly agree with them that an alternative analysis utilizing a cut-off point of three doubling concentrations decrease in the provocative concentration causing a 20% fall in FEV_1 (PC_{20}) with adenosine 5′-monophosphate (AMP) 2 weeks after halving the dose of inhaled corticosteroids (ICS) would provide different results. However, only one of our patients showed a decrease in PC_{20} of three or more doubling concentrations 2 weeks after the dose of ICS was halved.

Dr Proietti states that, "by arbitrarily setting the cut-off values for PC_{20} AMP at baseline too high (400 mg/mL), there is the chance of including very mild asthmatic patients who are unlikely to develop exacerbations." We regret that our description of patient characteristics has led to misunderstanding. Our study examined the utility of the determination of airway responsiveness to AMP and exhaled nitric oxide levels as markers for safely reducing the dose of ICS. Thus, we selected patients with stable asthma in good control with ICS, but not subjects with mild asthma. Although asthma control is often used to define asthma severity, this assumption is incorrect.[2] A significant proportion of patients included in our study had moderate-to-severe asthma, but were well controlled with ICS at medium-to-high doses (beclomethasone, 500 to 1,000 μg or equivalent daily).

Finally, Proietti et al state that it could have been of critical importance to include methacholine provocation in the protocol. In a previous study,[3] we have shown that the detection of a plateau on the concentration-response curve to methacholine, but not the PC_{20} value, may be used as a marker for safely reducing the corticosteroid dose. However, it is clear that further studies are needed to clarify the potential value of the determination of the response to both methacholine and AMP as a means to identifying those asthmatic patients whose conditions will or will not deteriorate when the dose of ICS is reduced.

Luis Prieto, MD, PhD
Hospital Universitario Dr Peset
Valencia, Spain

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Correspondence to: Luis Prieto, MD, PhD, Seccion de Alergologia, Hospital Universitario Dr Peset, C/ Gaspar Aguilar 90, 46017 Valencia, Spain; e-mail: prieto_jes@gva.es

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Heartbeat Synchronizes With Respiratory Rhythm Only Under Specific Circumstances

To the Editor:

Yasuma and Hayano (February 2004)[1] have theorized that respiratory sinus arrhythmia improves respiratory efficiency by the pairing of increases in heart rate with inhalation, when the concentration of oxygen in the alveoli is maximal. However, this phase relationship only occurs under specific circumstances.

Saul et al[2] applied vagal and sympathetic blocking agents, and found that the phase lag from breathing to heart rate is near 0°, but only under pure vagal conditions. Under pure sympathetic conditions, the phase relationship varies from 180° at low frequencies to approximately −180° at high frequencies.

We asked eight healthy subjects to breathe at seven frequencies between 0.04 and 0.5 Hz for 2 min each, matching their strain-gauge respiration record to a computer-generated sine curve[3] to ensure a constant respiratory depth and a sinusoidal shape for respiratory curves. Using Fourier filtration,[3] we determined that the phase relationship between heart rate and respiration was 0° only at a respiratory frequency of approximately 0.1 Hz, in which the target frequency heart rate variability also was highest (Fig 1).

When healthy people breathe regularly at this resonant frequency for the cardiovascular system, we also found that the baroreflexes are systematically stimulated and baroreflex gain increases.[4] In addition, peak expiratory flow improves.[4] There also is preliminary evidence for an improvement in clinical asthma,[5] and for improvement in respiratory gas exchange efficiency and clinical function in COPD patients.[6]

Thus, the hypothesis of Yasuma and Hayani[1] would be specifically relevant for sympathetically medicated heart rate variabil-

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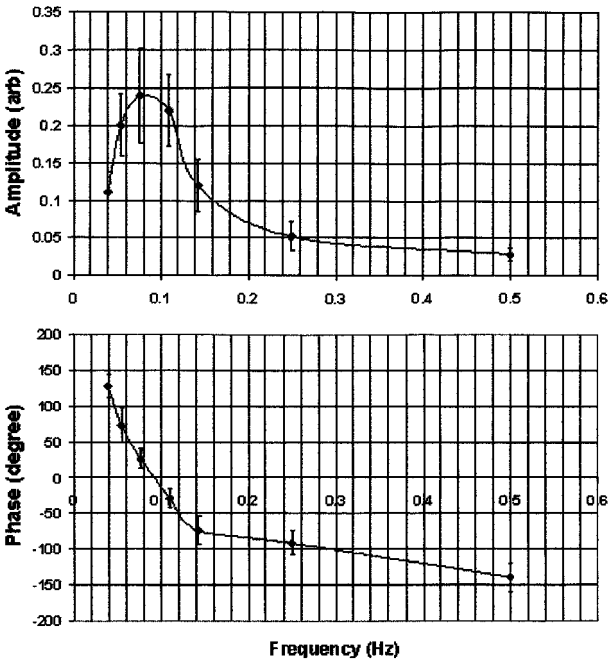

FIGURE 1. Transfer function of respiration (input) to heart rate (output). Values given as the mean of eight subjects.

ity, or for respiratory sinus arrhythmia associated with slow breathing at approximately 0.1 Hz.

Evgeny Vaschillo, PhD
Bronya Vaschillo, PhD
University of Medicine and Dentistry of New Jersey
New Jersey Medical School
Piscataway, NJ
Paul Lehrer, PhD
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
Piscataway, NJ

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Correspondence to: Paul Lehrer, PhD, Department of Psychiatry, D-335, UMDNJ-Robert Wood Johnson Medical School, 671 Hoes Ln, Piscataway, NJ 08854; e-mail: lehrer@umdnj.edu

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To the Editor:

We appreciate the interest by Drs. Vaschillo and Lehrer in our Opinions/Hypothesis article (February 2004)[1] on respiratory sinus arrhythmia (RSA). We agree with their comment that heartbeat synchronizes with respiratory rhythm only under certain conditions, so that the results of the physiologic experiment are only applicable to the model used in the study. In their well-organized investigation,[2] Vaschillo and coworkers[2] used healthy subjects who were strictly instructed to breathe in synchrony with the extrinsic pacemaker (*ie*, a metronome) at predetermined respiratory frequencies between 0.04 and 0.5 Hz for 2 min. As was noted in our Opinions/Hypothesis article,[1] humans are a species with a weak RSA compared with dogs. Moreover, a paced breathing that is in synchrony with the extrinsic rhythm generator might precipitate mental stress for subjects, and the equilibrium state of CO_2/O_2 metabolism through the paced breathing could not have been obtained in a very short period of time. Such factors as species, state of the subjects (*ie*, very alert, alert, relaxed, or asleep), and metabolism should always be considered in clinical/basic experiments on the synchrony of heartbeat with respiratory rhythm. Therefore, for this purpose we used trained dogs to lie down in a relaxed state under spontaneous breathing,[3–5] as dogs are a species with a strong RSA.

The phase relationship between heart rate and respiration shows frequency dependence, but the relationship is known to be nonlinear.[6] Eckberg[6] has reported that the phase analysis between heart rate and respiration shows a clear hysteresis, and that the prolongation of the R-R interval begins shortly after the onset of expiration independently of respiratory frequency. He has also demonstrated that the shortening of the R-R interval begins progressively earlier in reference to the onset of inspiration as respiratory frequency decreases. As a result, the timing of the maximum instantaneous heart rate occurs instantly after end-inspiration, with the maximal lung volume at least for a respiratory frequency of < 0.25 Hz. Although the phase of the maximum heart rate lags behind the phase of the maximum lung volume as respiratory frequency increases, the amplitude of RSA decreases progressively.[7] These facts seem to be consistent with the hypothesis that RSA is a function of physiologic respite for the cardiovascular and respiratory systems in resting animals and humans, because the phase relationship at a reduced respiratory frequency is optimal to cardiac and respiratory energy savings by reducing unnecessary heartbeats during expiration and unnecessary ventilation during the waning phase of the heart beat.[1,8]

Fumihiko Yasuma, MD, FCCP
Suzuka National Hospital
Suzuka, Japan
Jun-ichiro Hayano, MD, FCCP
Nagoya City University School of Medicine
Nagoya, Japan

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Correspondence to: Fumihiko Yasuma, MD, FCCP, Suzuka National Hospital, 3–2-1 Kasado, Suzuka, Japan 513-8501; e-mail: f-yasuma@mtb.biglobe.ne.jp

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Caregiving and Long-term Mechanical Ventilation

To the Editor:

We read with interest the recent research article by Im and colleagues,[1] and were particularly interested to note that they reported that it was difficult to compare their results to other studies of critically ill patients surviving mechanical ventilatory support. While we agree that such studies are rare, the similarity between the work of Im and colleagues and ours[2] is remarkable and warrants comparison.

While this study focused on caregivers, the eligibility criteria for patient subjects was different than in our study, and as a result the caregiving experiences most likely were different as well. Im and colleagues[1] defined prolonged mechanical ventilation as $\geq$ 48 h, while we defined it as $>$ 96 h of continuous mechanical ventilation. We selected our definition based on pilot work that identified a significant difference in morbidity and mortality between patients receiving ventilation for 48 h vs 96 h (B. Daly, PhD; unpublished analysis; December 1999). Thus, most likely the patients in the study by Im and colleagues[1] were healthier than the patients in our study,[2] and the caregiving experiences and expectations were different as well. It is this difference in eligibility criteria that may explain the differences reported in the two studies.

Another difference between the studies is that Im and colleagues[1] observed caregivers for 2 months after eligibility into the study; we followed caregivers for 6 months after hospital discharge.[2] Given the variability in hospital length of stay associated with this patient population, the data obtained 2 months after initiation of ventilation of the patient undoubtedly yielded varying postdischarge time points, and captured subjects at different points along the postdischarge continuum.

Like Im and colleagues,[1] we used the Center for Epidemiologic Studies Depression Scale (CES-D)[3] to assess depressive symptomatology and found similar average scores (6 months after discharge). We also obtained baseline CES-D scores at hospital discharge and tracked changes in depression over time, and found that 51.2% and 36.4% of caregivers had some depressive symptomatology (CES-D scores $>$ 15) at discharge and 6 months respectively. We found that 12.2% and 15.6% of caregivers were classified as having symptoms consistent with severe depression at hospital discharge and 6 months, respectively. The findings of Im and colleagues[1] confirmed ours[2] in showing that caregivers of patients residing in an institution had higher CES-D scores than did caregivers of patients residing at home. Unlike Im and colleagues,[1] we found those differences to be statistically significant ($p = 0.039$).[2] Of note is that a greater percentage of caregivers in our study were employed than in the study by Im and colleagues,[1] and that 70.1% of our caregivers received assistance in caregiving activities.

We agree with Im and colleagues[1] that little is known about caregiving needs and experiences after prolonged mechanical ventilation in the ICU. Caregivers of patients receiving prolonged mechanical ventilation are at risk for prolonged depression and poor health. Given the large percentage of caregivers who scored in the "severe" range of the CES-D, these families have needs for support and assistance, not only from family and friends, but from the health-care system as well. However, since patients receiving prolonged mechanical ventilation (and their caregivers) do not fall into any of the other well-studied groups (*eg*, cancer, Alzheimer disease), they remain unrecognized by the health-care system. In light of our work,[2] and the work of Im and colleagues,[1] it may be reasonable to consider assessment of these caregivers to identify those in need of referral for mental health services, and to design ways to provide additional support for their caregiving experience.

Sara L. Douglas, PhD, CRNP
Barbara J. Daly, PhD, RN
Case Western Reserve University
Cleveland, OH

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Correspondence to: Sara L. Douglas, PhD, CRNP, Frances Payne Bolton School of Nursing, Case Western Reserve University, 10900 Euclid Ave, Cleveland, OH 44104; e-mail: SLD4@po.cwru.edu

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To the Editor:

We would like to thank Drs. Douglas and Daly for their commentary on our article,[1] which was submitted prior to their article.[2] Although the two studies included slightly different caregiver populations due to different patient eligibility criteria and definition of long-term ventilation in the ICU, some of the results are very similar.

The mean levels of caregivers' depression (Center for Epidemiology depression scale [CES-D]) are remarkably similar, with similar variability, in these two studies: 13.9 (SD 12.8) and 13.2 (SD 11.0) for Douglas and Daly[2] and Im et al,[1] respectively. However, these results can not be compared directly because of the two distinctively different outcome time points, *ie*, 6 months after discharge from the hospital for the sample used by Douglas et al[2] and 2 months following ventilation for the sample used by Im et al.[1] We did collect CES-D data at 6 months and 12 months following intubation, but have not published these data yet.

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