

Is Integrative Medicine Missing Something?

by

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ABSTRACT

Here we review Integrative Medicine, a conventional and well-researched, evidence-based complementary medicine approach, from the point of view of autonomic, specifically, Parasympathetic and Sympathetic (P&S) nervous system monitoring. The basis is the five-domain concept for achieving wellness, to normalize morbidity and mortality risk, and improve quality of life and productivity, [the National Center for Complementary and Integrative Health (NCCIH), 2017]. Given that the P&S systems control or coordinate all other systems and organs of the body, the more information from P&S Monitoring simplifies and quantifies the efficacy of the multidomain approach.

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INTRODUCTION

Integrative Medicine is a form of medical therapy that combines the most well-researched conventional medicine with the most well-researched, evidence-based complementary therapies to achieve the appropriate care for each person. It includes four pillars believed required to achieving optimal health and wellness: food, movement, relaxation, and community. From these pillars, the National Center for Complementary and Integrative Health (NCCIH) developed a five-domain concept [1]: 1) manipulative and body-based methods, 2) mind-body medicine, 3) alternative medical systems, 4) energy therapies, and 5) biologic-based therapies (see “The 5 Domains of Complimentary and Alternative Medicine” Figure below). The regimen to achieve wellness includes: 1) Diet and Exercise, 2) a healthy environment, 3) healthy relationships, and 4) detoxification. Integrated Medicine works

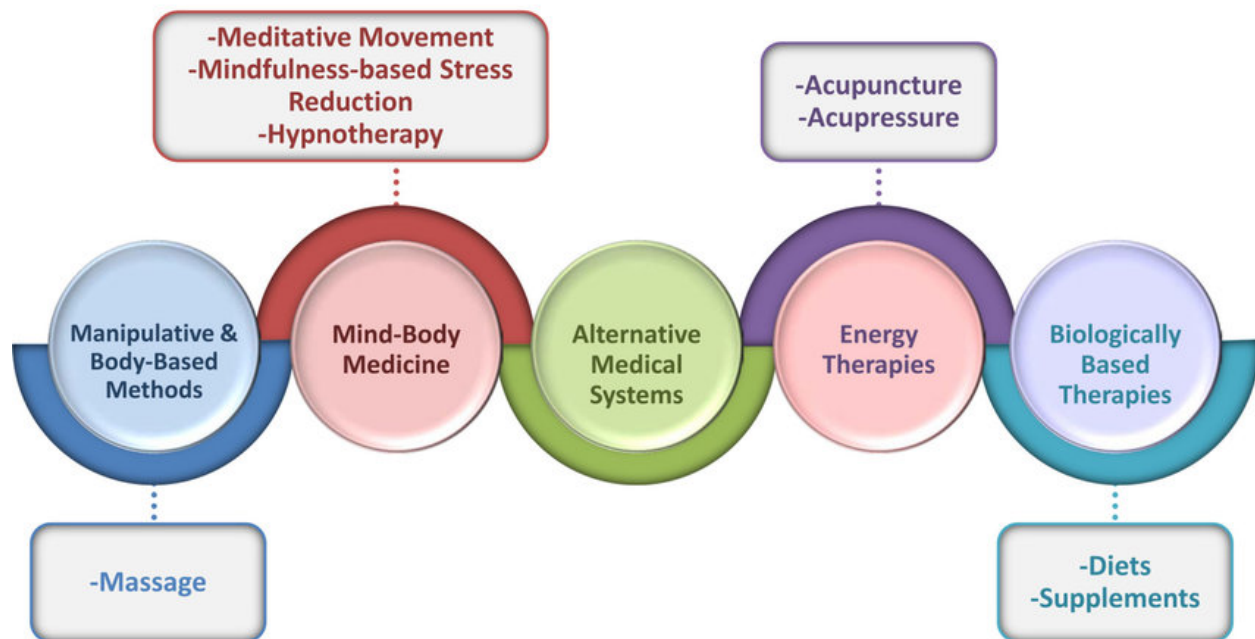
to find optimal health and wellness by understanding the individual’s need for achieving balance and harmony, internally and externally.

In these terms we differentiate optimal health from wellness based on pharmaceutical treatment versus natural medicine treatment. There are those that, due to organ or system deficits, will require pharmaceutical treatment for life to restore functionality lost. However, there are many who experience dysfunction, even though the organs and systems remain healthy. For example, without blockages or holes in the GI system, the GI system is essentially healthy, but there are symptoms. These symptoms may be due to dysmotility which is a nervous system dysfunction (autonomic imbalance, primarily Parasympathetic). To restore proper motility and not only health but wellness, treatment should be focused on the Parasympathetic and Sympathetic (P&S) nervous systems and not the GI system. Of

course, with dysmotility, blockages or holes become a self-fulfilling prophecy due to resulting inflammation, and long-term

pharmaceutical treatment is often required leaving optimal health as the alternative.

The 5 Domains of Complementary and Alternative Medicine



As another example, dysfunction in one P or S system may be compensatory for dysfunction in another system. Consider Hypertension or Tachycardia. With a full understanding of the dangers of Hypertension and Tachycardia, they may not always be a primary dysfunction. It may be compensating for some other dysfunction and in that sense may be merely a symptom. In the case of Hypertension, consider Orthostatic Hypotension (OH). If BP drops upon standing, to levels that cause poor cerebral perfusion, the brain will trigger mechanisms to compensate to ensure proper perfusion and prevent lightheadedness (Orthostatic dysfunction or Syncope). As a

result, resting BP may enter the realm of Hypertension, depending on the drop in BP upon standing, so that even after the drop the brain is remains properly perfused upon standing. Unfortunately, a typical cardiology exam for Hypertension only documents the high resting BP and not the Orthostatic BP response and therefore Hypertension is assumed to be the problem. Yet in these individuals, treatment often makes them feel worse due to the body working to defeat the treatment or the therapy causing exercise intolerance or more fatigue.

Similarly in Postural Orthostatic Tachycardia Syndrome (POTS), the Tachycardia is another compensatory mechanism for the Orthostatic dysfunction (blood pooling in the lower extremities). As with OH and anti-hypertensive treatment, the clinician's response to POTS may again turn to long-term beta-blocker treatment to limit the Tachycardia. However, as a long-term solution without restoring proper perfusion of the heart, by relieving the Orthostatic dysfunction, but this just makes the situation worse. Because, it is not addressing the underlying cause, a disequilibrium in the P&S systems. Note, it typically takes up to nine months or more, depending on history, to relieve the Orthostatic dysfunction. Therefore, during this up to 9 month time, short-term use of anti-hypertensive treatment or beta-blockers, may be needed and is recommended to protect the patient from the continued Tachycardia and any significant increases in BP as the Orthostatic dysfunction is being relieved. Ultimately, the better way to restore quality of life is by relieving the underlying cause of OH or POTS: Orthostatic dysfunction (the 'O' in both disorders), and that involves separating out the measurements of the P&S nervous systems in heart rate measurement rather than summarizing them which doesn't allow you to see excess and withdrawal phenomena of the two nervous systems.

In many cases, more information is required to understand and document these underlying conditions. This more information also helps to specify the patient's individual response to disease or disorder, as well as to treatment and therapy. One such source of information is the P&S (autonomic) nervous systems, given that

they control and coordinate all systems of the body and virtually every cell of the body.

More specifically, the source of information must include directly measuring the activity of both the Parasympathetic and Sympathetic (P&S) branches of the autonomic system, directly (*e.g.*, mathematically independently) and

simultaneously.

Figure 1 depicts how to measure P&S activity in comparison to how autonomic activity is currently measured. It is based on spectral domain analysis. The current spectral analysis method of measuring autonomic activity (resulting in Low frequency (LF), dark gray, and High Frequency (HF), light gray) [2,3] is truly a measure of only total autonomic activity and

requires assumption and approximation to theorize P&S activity. If instead the Cardio-Respiratory method [4] is used as depicted in Figure 1, there are separate direct measure of P&S (blue Parasympathetic-RFa) and red Sympathetic, LFa⁵) and there are no assumptions and approximations of the P&S systems .

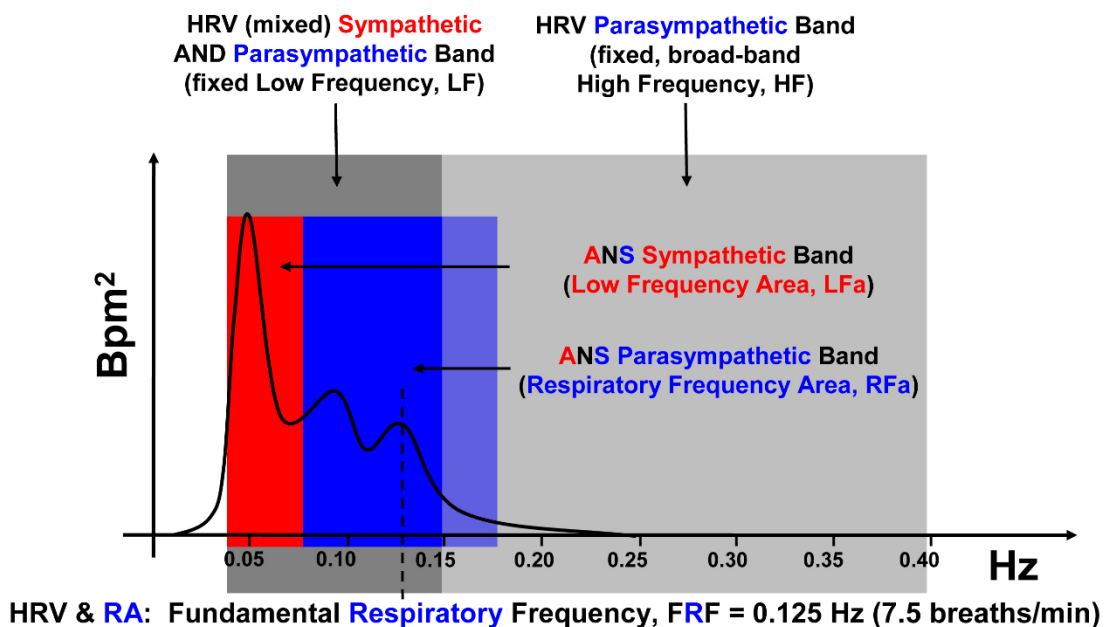
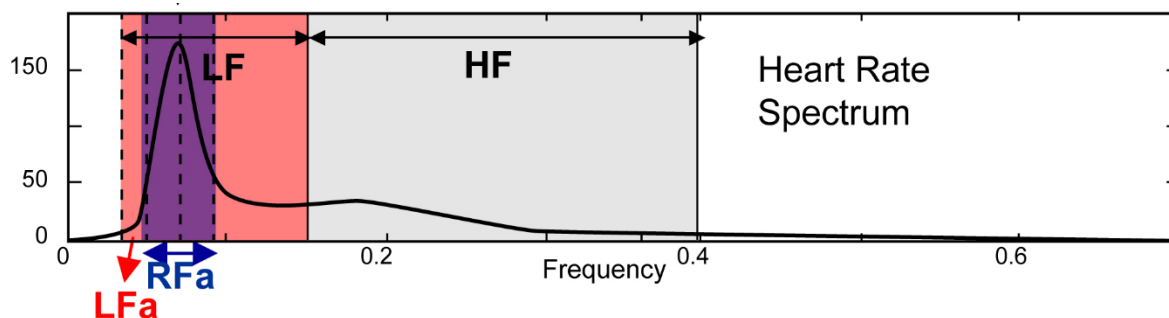


Figure 1: Comparing the standard spectral analysis process (using grey tones) to the Cardio-Respiratory Method used to compute P&S activity blue and red areas, respectively; [2] Note the difference, with the standard spectral analysis process used to compute autonomic activity one must “assume” the roles of Sympathetic and Parasympathetic activity (dark gray and light gray) which is much less informative [2,3].



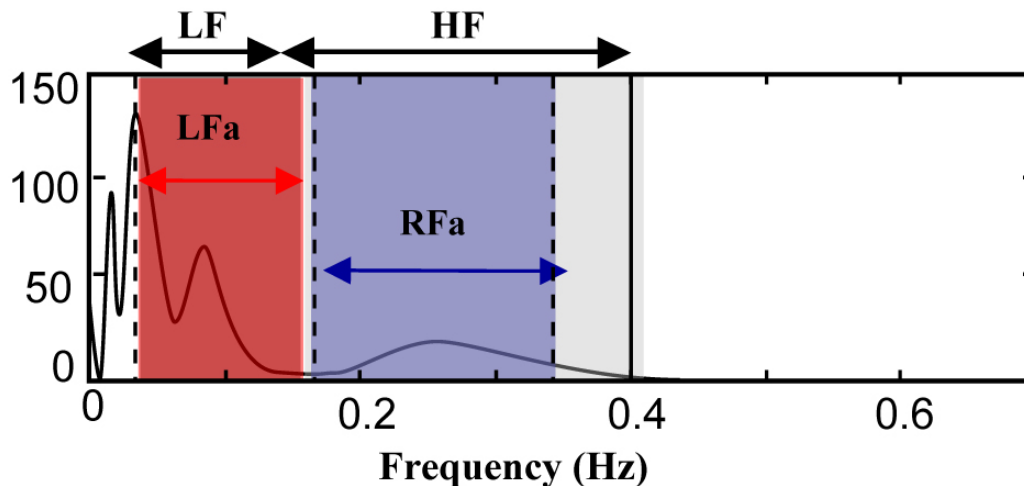


Figure 2: The effect of different breathing rates on P&S activity as computed by the Cardio-Respiratory Method (P&S, blue and red or RFa & LFa; respectively) [4] and the Standard HRV method (LF & HF, dark gray and light gray, respectively) [2,3]. Top graph displays the results of the Deep Breathing (Parasympathetic) Challenge (respiratory frequency of 0.1 Hz which is 6 breaths per minute) from the standard autonomic challenges known as the Ewing Challenges [6,7,8]. Note that all of the Parasympathetic activity is within the Low Frequency, which is assumed to be a measure of Sympathetic activity. The bottom graph displays the minimum respiratory frequency needed to separate P&S activity into the LF red sympathetic and HF blue parasympathetic regions. This frequency is 0.26 Hz or 15.6 breaths per minute, which is rather high for many patients. Even at this breathing rate there is still some light gray area not covered by the blue amplifying the measure of Parasympathetic activity using the standard HRV method/

In the current method [2,3], the spectral domain analysis, is based on HR variability (HRV) as the signal source and short-term Fast Fourier Transform (stFFT) as the spectral analysis method. Both the HRV and stFFT are sources of assumption and approximation in this method. HRV is only one mathematically independent measure of the autonomic system which has two mathematically independent components (the P&S systems). Therefore, HRV is truly a measure of total autonomic activity and requires assumption and approximation to theorize P&S information. As shown in the gray areas of Figure 1, darker gray area, the

Low Frequency (LF) area is well known as a mix of Sympathetic activity (the lower frequency component of the autonomic system – it reacts only as fast as in 2 to 5 heart beats⁹⁾) and Parasympathetic activity (the higher frequency component of the autonomic system – it may react in 1 to 3 heart beats). The lighter gray area of the top graph in the above Figure 2, is the High Frequency (HF) area and is well known to include Parasympathetic activity and what is assumed to be noise.

Often the assumptions and approximations required by the standard HRV method to theorize P&S activity, instead of the Cardio-

Respiratory method we are proposing, are buried P&S activity in the patient population selected to be studied. For example, in study being done on older, more severely symptomatic patients such as patients diagnosed with advanced diabetes, advanced Parkinson's, Multiple System Atrophy, or Primary Autonomic Failure it seems reasonable to assume that the Parasympathetics are significantly depleted compared with the Sympathetics; therefore, the LF includes Sympathetic activity (any Parasympathetic is insignificant) and the HF may be ignored or assumed to be the sample of Parasympathetic activity. A result of these assumptions is evident in the COMET studies comparing the benefits of Carvedilol ('CReg') with 'METoprolol' in patients diagnosed with advanced diabetes, type 2 using standard HRV methodologies [10,11]. No statistical difference in benefit was reported; yet it is well known that Coreg is the preferred beta-blocker for patients with diabetes. If no difference, why the preference? When a repeat of the COMET studies [12,13] is done with the Cardio-Respiratory method we get our answer! The Cardio-Respiratory method demonstrated a small, but statically significant rebound in Parasympathetic activity with Coreg, not found with Metoprolol. The Parasympathetic system was not depleted or insignificant! More Parasympathetic activity is known to be cardio-protective [14] (actually protective of all organs). By assuming the Parasympathetics are depleted, this rebound is assumed away and missed.

The stFFT also requires assumption and approximation. This is the well-known time-frequency trade off inherent in the stFFT. If time domain specificity is

required, frequency domain specificity is sacrificed and vice versa. This is because FFTs assume an infinitely long signal (in time) to ensure that all frequencies are captured. STFFTs, necessarily, limit the time duration of the signal and analyze it any way. Examples of the results are depicted in Figure 2 in the time domain and Figure 3 in the frequency or spectral domain.

In the left panel of Figure 3 two different analysis "window lengths" (WL) are selected. The WL limits the temporal information retained in the signal. Shorter WLs retain less time information but offer more frequency (spectral) information. Longer WLs retain less frequency information but offer more temporal (time) information. As depicted, the shorter WL more severely compromises temporal accuracy. When the time domain signal is regenerated, temporal details would be omitted. This is implicit in the appearance or lack of appearance of the little, high frequency, circle seen in the WL = 32 spectrum and not in the WL = 64 spectrum. Regenerating the time domain representation of the shorter WL spectrum, the high frequency event in the middle of the sample waveform depicted at the top of Figure 3 would be omitted. Whereas, with the longer window length, that temporal event would be retained, but as is depicted, the high frequency content as shown in the longer WL spectrum is missing. But look what happens if we combine these limits into a CWT (Continuous Wavelength Transformation). Let's return to figures 1 and 2 to explain CWT.

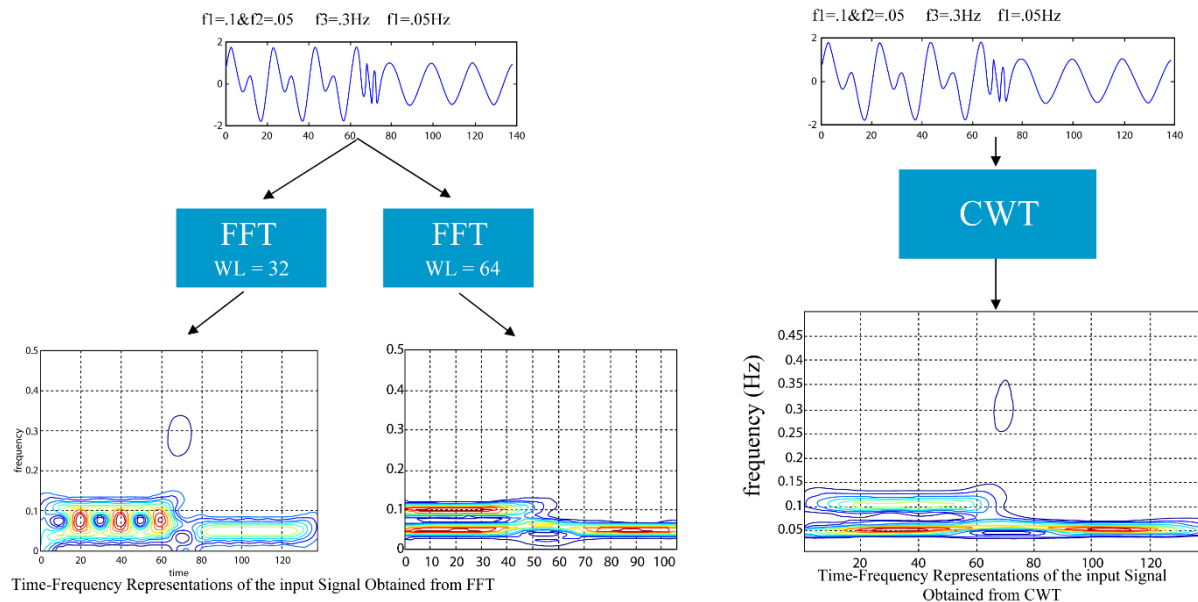


Figure 3: Comparing Fast-Fourier Transform (FFT) spectral analyses of the same signal with a Continuous Wavelet Transform (CWT) spectral analysis of that signal. The FFT method requires assumption and approximation based on the window length utilized which changes what spectral information is retained. The CWT method captures all of the spectral information without assumption and approximation.

The results of the Cardio-respiratory method of P&S monitoring are depicted in Figure 1 in red (representing Sympathetic activity only) and blue (representing Parasympathetic activity only). In the top graph, the mix of P&S activity in the LF region is shown with a common respiratory rate of 7.5 breaths/minute. It demonstrated how, in this case, the LF region is more Parasympathetic than Sympathetic, and the HF region includes very little Parasympathetic activity (so what else is being measured – the “what-else” is considered “noise”).

Other examples of the effects of these assumptions and approximations are shown

Figure 2. The top graph depicts the spectral results of the standard Deep Breathing Ewing challenge [5,6,7]. The Deep Breathing challenge is well known to be one of the most powerful Parasympathetic stimuli available. Note, all of the Parasympathetic (blue) activity region is fully within the LF region, and no Parasympathetic activity indicated in the HF region. So, what is being measured in the HF region in this case. This is why standard autonomic (HRV) practitioners do not look to the spectral results from deep breathing challenges, only time domain or statistical results (*e.g.*, E/I Ratio [5,6,7]).

The bottom graph of Figure 2 shows another example. In this case the breathing frequency of the patient is 15.6 breaths per minute, which is near hyperventilation. Hyperventilation is well known to be a Sympathetic challenge. Given the assumption that LF measures Sympathetic activity, this is justified. As depicted, the LF region (dark gray) and the Sympathetic (LFa, red) region match. The Parasympathetic (RFa, blue) region is full captured in the HF (light gray) region, but does not match, there is still light gray area left that include spectral content from the patient. What is this extra spectral content? This is considered noise and would artificially exaggerate the Parasympathetic measure in the standard method, when this is a Sympathetic challenge and less Parasympathetic activity is expected.

Some of the “noise” as described above is added by the time-frequency trade-off inherent in the stFFT method. This is corrected by using a more appropriate spectral analysis method such as the Continuous Wavelet Transform (CWT). As depicted in the right panel in Figure 3, all of the frequency content depicted in both spectra in the left panel are included in the single spectra in the right panel. This is due to the fact that the CWT method is a three-dimensional spectral analysis method, including as independent measures amplitude, frequency, and time; therefore, no assumption of approximation is required.

Clinically, a way to think of this is HRV, as a single measure of P&S activity (both autonomic branches control the heart at all times) provides only one number, call it ‘T’. If T changes it is not possible to determine which changed ‘P’ or ‘S’ nor is it possible to determine by how much. The assumptions and approximations combine to assume that ‘T’ equals ‘S’. However, with Cardio-Respiratory Monitoring both the heart (including HRV) and the lungs (and independent organ) combine to measure P&S. From the heart, as in HRV, ‘T’ is measured. From the lungs (*e.g.*, Respiratory Sinus Arrhythmia, which is well known to be a result of purely Vagal, Parasympathetic, activity), ‘P’ is measured. It is well known that $T = P + S$. In the Cardio-Respiratory Method, T & P are known. Therefore, solving for S ($= T - P$) the Sympathetic activity is calculated, without assumptions or approximations, and without or much less noise. This provides the missing information to complete the Mind-Body Medicine component of the Integrative Medicine paradigm, which inherently influences and affects the other domains, and enables P&S measurements to quantify the efficacy of the other domains. It can change the typical, often straight pharmacologic, treatment profile that the clinician pursues with a patient, If not in every patient at least in those who do not respond well to typical treatment. Cardio-Respiratory Monitoring should be pursued beyond the standard spectral analysis.

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