Title: Finger volume pulse waveforms facilitate reliable assessment of heart rate variability, but not blood pressure variability or baroreflex function

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Author's response to reviews: see over
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Editorial Board
*BMC Cardiovascular Disorders*

Dear Editor,

Please consider our re-submission: “Finger volume pulse waveforms facilitate reliable assessment of heart rate variability, but not blood pressure variability or baroreflex function” for submission in *BMC Cardiovascular Disorders*. The article validates the use of this methodology, one which may find broader use, for the assessment of heart rate variability. We have responded to the Reviewer’s concerns which are included in our item-by-item response to review appended to this letter. The manuscript presents original work, which has not been submitted elsewhere. The authors have no conflicts of interest or competing interests related to this work.

I am currently an Associate Editor for the Biomed Central journal *BMC Psychiatry* and my institution, University of Iowa, is a Supporter Member. I subsequently request the corresponding discounts in the article processing charges.

Thank you for your time and any consideration.

Sincerely,

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Reviewer 1:

Concern 1.0: One of the confusing matters for me is that BPV is usually interpreted as SD, CV, ARV (average real variability) etc… (Rothwell PM. Lancet. 2010;375:938-948.). How can you draw a distinction for this confusion? In addition, how to calculate BPV in the present study?? Please add some explanations specifically.

Response 1.0: We acknowledge the source of the stated confusion. Our study was designed to investigate the derivation blood pressure variability from a continuous 30-minute reading instead of variability between single measurements from multiple office visits. To clarify, we have added the following to paragraph 5 of the discussion:

“Similarly, our study is not applicable to the calculation of variability between routine BP readings in the clinic (Rothwell et al., 2010).”

Abstract

Concern 1.1: Please spell out “HF” and “LF.”

Response 1.1: We have corrected this in the abstract:

“… was excellent [High Frequency (HF)=0.80, Low Frequency (LF)=0.81], with …”

Methods

Concern 1.2: Page 6, blood pressure (BP) was already used in previous sentences.

Response 1.2: We have corrected this accordingly:

“For all participants, BP waveforms were recorded …”

Reviewer 2:

Introduction

Concern 2.0: The review of literature is incomplete and does not provide the reader with an appropriate accounting of the prevailing knowledge for the reliability of HRV and BPV parameters. Some of the references for the respective components (Akselrod, etc.) were formative studies that identified the presence of oscillations in heart rate, that when analyzed in different ways, yielded an objective reflection of autonomic control (Note: Pagani 1986, one of the gold standard papers for spectral analysis was omitted). The authors use the term “reliably” when describing the methods that “quantify” time or frequency domain parameters, but the references used do not report or support reliability of the outcomes. There are several empirical reports and a few review articles on the topic of test-retest reliability for HRV (for a well-articulated review on the topic see Sandercock G, 2004; Int J Cardiol).

Response 2.0: We appreciate the suggestions to supplement our background and have added the following on page 1:

“… of cardiac function (Cavalcanti et al., 1997, Ewing et al., 1981, Pagani et al., 1986, Sandercock et al., 2004), while …”

Concern 2.1: Current dogma for HRV reliability states that time domain parameters from
both short (< 10 minutes) and long (30 minutes to 24 hours) term recordings have high intra- and inter-visit reproducibility across numerous clinical and able-bodied cohorts. Linear measurements of HRV (i.e., HF, LF, VLF) have poor to moderate levels of reproducibility within and between visits; VLF and ULF measures are not commonly reported unless the data signal is obtained from a continuous holter monitor recording of up to 1 day (as an aside, the reviewer cannot recall a reference where VLF oscillations from HR alone represent baroreflex function. Please confirm your source; Line 101).

Response 2.1: Our mention of VLF HRV relating to baroreflex function has been removed from page 4, as it was only mentioned in passing and is not supported in the literature. Regarding the comment on intra- and inter-visit reproducibility of HRV measurements, we added the following text to our discussion of study limitations on page 12:

“While time domain parameters for HRV are generally accepted to have high inter- and intra-visit reproducibility, spectral measurements have been shown to be less reproducible between visits (La Fountaine et al., 2010), and may thus be less useful clinically.”

Concern 2.2: More recent advances in non-linear assessments (i.e., entropy, complexity, fractal scaling dimensions, etc) have bridged the gap, and routinely demonstrate very good reproducibility, but they are difficult to interpret. HRV is emerging as one of the most widely used and abused outcomes in health. A snapshot data collection is often used and interpreted to reflect a state of psychophysiological health. While inter-group comparisons frequently yield statistical differences, individual subject outcomes may lie well within the standard deviation of the other group. Because of this, there exists no threshold values for which normal/abnormal can be defined. Thus, a relative increase or decrease in HRV is often reported (compared to the control or ideal group). HRV reliability is confounded by the psychophysiological state, respiration rate and depth, and numerous other reasons. Thus, the technical aspects of the data collection and processing must be iron-clad. On the other hand, BPV is less well described and is extremely difficult to obtain. The dearth of empirical evidence for BPV is not an accident.

Response 2.2: While certainly a thorough account of clinical and academic use of HRV and BPV in health, this discussion lies outside of the scope of our current manuscript. This issue has been addressed elsewhere in the literature, and while it undoubtedly impacts the future application. To avoid adding greater complexity to our presentation, we have elected to defer such discussion though are nonetheless willing to add such discussion if deemed necessary for the reader by the Reviewer or Editor.

Methods

Concern 2.3: The customary period to abstain from food, caffeine and tobacco is a minimum of 6 hours. In addition, please verify if subjects abstained from exercise for a period of at least 24 hours. Vigorous exercise may confound HRV parameters, too.

Response 2.3: Exercise in the previous 24 hours was not assessed in our study, but the issue of confounding with this and other listed factors (smoking, food, caffeine) was mitigated by the study design. We were not assessing the relationship between these measures as other outcomes. Our study aim was to compare the performance of two devices. Participants served as their own control and both machines collected data
concurrently on each patient. Abstaining from food, caffeine, etc. was recommended so that patients might feel more comfortable during the 30-minute recording period, when they could not get up to go to the bathroom.

**Concern 2.4:** Simultaneous recordings of each device were performed with the Finapres cuff on the middle and EndoPAT on the index finer. This is a potentially problematic design because pulses may differ slightly from digit to digit.

**Response 2.4:** In considering the design, we believed adjacent fingers would be preferable to the same finger on opposite arms. Nonetheless, this limitation should be rendered more explicit. We have expanded our discussion of these limitations with the following on page 12:

> “Pulses may differ across digits... These design issues might contribute to discrepancies between recordings from the two machines, which if anything would bias the observed correlation to an underestimate. Thus, the correlation between measures can be assumed to be at least as strong as our study indicates.”

This concern leads into further discussion of the impact of study design on correlation, which we address in our response to Concern 2.6.

**Concern 2.5:** Finapres data were collected at 200 Hz, but there in mention of the sampling frequency of the EndoPAT. The Task force recommends that autonomic collections be performed within a 250-500 Hz sampling range. Is is almost universal that data are sampled at 500 Hz, while many investigators opt for 1000 Hz. It is easy to downsample your data after collection, but upsampling is not possible. Please provide clarification on the EndoPAT sampling rate and why Finapres sampling was below the recommended data collection standards. It may be possible that there is little or no agreement in the data between the devices because they were sampling data at different frequencies. This may seem like parting hairs, but if each device is doing this, then you are effectively biasing your results toward an unfavorable outcome because you are not comparing apples to apples.

**Response 2.5:** Signals from both machines were spline interpolated to a frequency of 10 Hz (as mentioned in our manuscript) to allow for accurate spectral comparison. We appreciate the suggestion to include EndoPAT sampling rate, and have made the following addition to page 6:

> “…EndoPAT device, sampling at a frequency of 128 Hz.”

**Concern 2.6:** Were data signals lined up during analysis so that each device was recording the same pulse at the same time? There was not a continuous, digital EKG obtained during this investigation. HRV was derived from the beat-to-beat blood pressure signal. It is not customary to use an indirect measure of a primary outcome in the determination of reliability. Why did authors elect to not obtain EKG for HRV? Also, if the signals were not lined up, collected at the same sampling rate, and used different processing filters, there will be dramatic differences that emerge. Also, if HR is exclusively defined by the BP device on 2 different fingers, then the pulse arrival time may differ between devices/fingers. When dealing in milliseconds, every potential source of delay adds up.
Response 2.6: These are important points and again could bias toward underestimating reliability. We have added the following statement to our discussion of study limitations:

“…Additionally, signals for both machines were not recorded in unison and were sampled at different frequencies. These design issues might contribute to discrepancies between recordings from the two machines, which if anything would bias the observed correlation to an underestimate. Thus, the correlation between measures can be assumed to be at least as strong as our study indicates.”

In hindsight, we regret not including EKG as a gold standard for HRV. This too is mentioned in our discussion of limitations where we also notes that HRV measures from both instruments were highly consistent with each other. Heart rate can additionally be readily discerned with each device.

Concern 2.7: What filters were used on the data, if any?

Response 2.7: We did not use filters during our study protocol, or in subsequent data analysis. We amended the Methods section as follows on page 6:

“No filters were used during data acquisition or subsequent data analysis.”

Concern 2.8: If data were collected for 30 minutes, why was only 5 minutes of data used for time domain parameters, and 30 minutes for frequency domain? There is inconsistency, which makes it difficult to figure out what was done and why. The confusion I have as a reader makes the results not at all surprising, which could prove detrimental if the EndoPAT is truly a useful device at satisfying the intended aims.

Response 2.8: We agree, clarification of this section reduces potential issues of confusion for readers. We have added the following explanation on page 7:

“Time-domain analysis was limited to 5-minute segments, as recommended (Task Force Report, 1996), because duration affects the size of the results in time-domain analysis. Results from frequency-domain analysis, on the other hand, are not affected by duration of the segments analyzed.”

Concern 2.9: Although providing the link to the analysis program used in the study, every manuscript must provide sufficient detail so that it functions as a stand-alone entity. The reader should not have to go to a source to obtain primary information on how measurements were calculated.

Response 2.9: We thank the reviewer for bringing this concern to our attention. We have added the following passage to improve clarity:

“HR and systolic BP were derived from the calibrated EndoPAT waveform. From this signal, beat-by-beat trends in heart rate and systolic BP were derived in the HemoLab software analyzer module. The Finometer provided an automatically derived trend for both HR and BP.”

We also added the following passage to supplement the explanation of baroreceptor-heart rate reflex analysis.

“… HemoLab software. The entire recording was selected for analysis of each device, separately. Systolic BP was analyzed using the “Calculate-Baroreflex” function with an “R for inclusion” of 0.8. A delay of three heartbeats was selected between the beat-by-beat systolic BP and pulse interval values.”
Concern 2.10: Baroreceptor heart rate reflex sensitivity was calculated using the arterial waveforms. Similar to my previous comment, it is not common practice to calculate baroreceptor sensitivity from one device alone. A majority of the respected literature on baroreflex sensitivity use signals from 2 devices (i.e., EKG and Finapres or equivalent). Please clarify.

Response 2.10: As mentioned before, EKG recording was not available at the time of participant intake. We feel confident in values obtained from the Finometer on a beat-by-beat basis (Schutte et al., 2004), being an accurate standard against which to compare the EndoPAT for baroreflex analysis. As with BPV, the baroreflex results are consistent with what one would expect when considering the poor coherence values seen between the machines with respect to derived BP signals.
References:


