Author's response to reviews

Title: Association between different measurements of blood pressure variability by ambulatory blood pressure monitoring (ABPM) and ankle-brachial index

Authors:

Estefânia Wittke (wittke@ibest.com.br)
Sandra C Fuchs (scfuchs@terra.com.br)
Flávio D Fuchs (fuchs@hcpa.ufrgs.br)
Leila B Moreira (lbmoreira@hcpa.ufrgs.br)
Elton Ferlin (eferlin@hcpa.ufrgs.br)
Fábio T Cichelero (dr.fabio1@gmail.com)
Carolina M Moreira (cm.moreira@terra.com.br)
Jeruza Neyeloff (jeruza_med@yahoo.com.br)
Marina B Moreira (marina.moreira@yahoo.com.br)
Miguel Gus (mgus@terra.com.br)

Version: 2 Date: 1 May 2010

Author's response to reviews:

April 30, 2010

Melissa Norton, MD
Editor-in-chief
BMC Cardiovascular Disorders

MS: 1243547668354845 - Association between different measurements of blood pressure variability by ambulatory blood pressure monitoring (ABPM) and ankle-brachial index

Dear Dr. Norton,

Enclosed is a revised version of our manuscript entitled. We offered a detailed response to all reviewer’s comments and some of them lead to modifications in the original, which are highlighted in red and bold. The recommendations were light but improved the interpretation of our findings. Additional analyses are presented in the response and cited in the Ms when applicable.

Sincerely yours,

Flávio Danni Fuchs, M.D., Ph.D.
Serviço de Cardiologia
Hospital de Clínicas de Porto Alegre
Ramiro Barcelos, 2350
Response to the reviewers comments:

Reviewer 1
Reviewer's report
Title: Association between different measurements of blood pressure variability by ambulatory blood pressure monitoring (ABPM) and ankle-brachial index

Version: 1 Date: 24 March 2010

Reviewer: Kouichi Tamura

Reviewer's report:

This study by Wittke et al. compared three different parameters of BP variability obtained by ABPM with respect to possible relationships with ABI values in hypertensive patients. They found that the 24-h time rate index was strongly associated with ABI but neither 24-h SD nor 24-h CV was associated with ABI, thereby suggesting that the time rate index is a sensitive parameter to estimate BP variability by ABPM. The following points should be addressed.

Major points:
1. Because previous studies reported that the magnitude of the nocturnal decline in BP, which is an index of circadian BP variation, was the strongest predictor of the SD of 24-h BP, indicating that the SD of 24-h BP is not an appropriate index of BP variability (Imai Y, et al. Am J Hypertens. 1997:10: 1281–1289; Ref. 12), it is not so surprising that 24-h SD or 24-h CV was not associated with ABI in this study. In order to estimate BP variability using SD or CV, the authors should examine possible relationships between ABI and daytime SD or CV and between ABI and nighttime SD or CV, separately as performed previously (Ref. 8; Sander D, et al. Circulation 2000:102:1536–1541; Shintani Y, et al. J Hypertens 2007:25:1704–1710; Mitsuhashi H, et al. Atherosclerosis 2009:207:186-190).

Response:

We proceeded to the analysis proposed by the reviewer (table below). The association of time-rate lost formal significance by period but kept the overall trend. In face of the absence of association by time period (despite the trend for SD), we included the following paragraphs in results and discussion:

In results: Standard deviation and coefficient of variability calculated separately for the daytime and nighttime periods were not associated with abnormal ABI also.
In discussion: It was previously demonstrated that blood pressure variability 
evaluated by the standard deviation and coefficient of variability using blood 
pressure of the nighttime period has a more intense association with 
cardiocascular outcomes (8, 34). This association was not evident in our study, 
but this may be potentially ascribed to statistical power.

<table>
<thead>
<tr>
<th>Normal ABI</th>
<th>Abnormal ABI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime SD</td>
<td>10.9 ± 3.7</td>
<td>11.8 ± 4.7</td>
</tr>
<tr>
<td>Nighttime SD</td>
<td>9.7 ± 4.3</td>
<td>10.8 ± 4.3</td>
</tr>
<tr>
<td>Daytime CV</td>
<td>8.2 ± 2.6</td>
<td>8.5 ± 3.1</td>
</tr>
<tr>
<td>Nighttime CV</td>
<td>7.9 ± 3.4</td>
<td>8.3 ± 3.0</td>
</tr>
</tbody>
</table>

2. Discussion, page 12, lines 13-22. Although the authors described that the time 
rate index is more powerful parameters than other parameters such as SD or CV 
(Refs. 11-13), the formula for BP variability (ARV, average real variability) 
described in Ref. 13 is likely to be the same with the formula described in this 
study as the time rate index. This paragraph is rather confusing and the authors 
should re-write this paragraph and clearly explain the similarities and/or 
differences between the time rate index and ARV for the readers to better 
understand exactly the obtainable parameters by ABPM.

Response:

The time-rate index is calculated considering the absolute blood pressure 
differences and the time intervals between each measure. As far as we 
understood the formula described by Meta et. al. (Ref 13 cited) the time between 
each measure is not included in calculation of ARV. This is an interesting point 
because our findings indicate that in the analysis of blood pressure variation it is 
important to measure not only blood pressure differences between each measure 
but how fast or how slow it occurs and to which direction the blood pressure 
changes. The following sentence was included in the paragraph:

Different parameters of BP variability derived from ABPM have been described 
(11-13), but the time-rate index embodies the concept that in the analysis of 
blood pressure variability it is important to measure not only blood pressure 
differences between each measure but how fast or how slow it occurs and to 
which direction the blood pressure changes.

3. While a previous study showed that high ARV of daytime systolic BP resulted 
in an independent predictor of cardiovascular risk in hypertensive patients 
population cohort study failed to show that ARV contributes much to risk 
stratification over and beyond 24-h BP. (Hansen TW, et al. Hypertension. 
2010:55:1049-1057). The authors should discuss the results of theses recent 

Response: we thank to the reviewer for this suggestion, the studies were not
cited because they came out after the preparation of our Ms. In fact, the studies evaluated other indexes and not the time-rate. We commented the negative results of Hansen et all including the following comment in discussion:

In a recent report from a large population cohort, BP variability assessed by standard deviation did not contribute for risk stratification beyond 24-hour BP (ref). The time-rate index may perform better, and should be also tested in large cohort studies.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
'I declare that I have no competing interests'

Reviewer 2
Reviewer’s report
Title: Association between different measurements of blood pressure variability by ambulatory blood pressure monitoring (ABPM) and ankle-brachial index
Version: 1 Date: 17 April 2010
Reviewer: Beth Weatherley
Reviewer’s report:
The authors examine which of three blood pressure variability measures derived from ambulatory blood pressure monitoring is most related to the ankle-brachial index, a marker of macrovascular atherosclerosis, in 425 hypertensive patients included in the MONITOR clinical study.

Major compulsory revisions:
1. In the introduction, the authors state that whether these variability measures add substantial information over BP values has not been shown, but analyses do not appear to directly address this question. The predictiveness (AUC or c index) for a model including, for example, only age, diabetes, and BP over 24 hours could be compared with the value for a model that further includes one or more measures of BP variability.

Response:
This is an interesting point, we agree that to investigate the additional explanation of any index would require to run a model with and without each index. But we have not done this and we did not conclude that the time-rate
index added explanatory power for cardiovascular prognosis. Our analyses of AUC just compared the indexes. We had not discussed this point either. In face of a suggestion also from the reviewer 1, we added the following paragraph in discussion, which put in perspective our findings:

In a recent report from a large population cohort, BP variability assessed by standard deviation did not contribute for risk stratification beyond 24-hour BP (35). The time-rate index may perform better, and should be also investigated in large cohort studies, including its capacity to increase the precision of prognostic estimation.

2. Modelling the association with ABI as a dichotomous variable assumes that both high and low ABI are associated with higher BP variability. Was this assumption checked? High ABI has not been consistently shown to represent high risk of cardiovascular outcomes (in the ARIC study it was not). High and low ABI values may represent differing underlying pathophysilogies, therefore, it would seem prudent to examine the associations separately with high and low ABI. For example, Table 1 could present characteristics of patients with low, normal, and high ABI. Logistic regression models could either exclude those with high ABI, and compare low with normal ABI, or include ABI as a 3-category outcome. A plot of BP variability versus ABI would show whether both low and high ABI values are associated with higher BP variability.

Response:
In our sample only three patients had abnormal high ABI because of high values and therefore most recommendations from the reviewer could not be followed (distributions by just three guys). We kept them in most analyses because of the definition of abnormality of the ABI. In the specific evaluation by multiple linear association, however, we excluded these guys. This was already informed in the end of the first paragraph of pg 10.

3. Modelling the association with ABI as a continuous outcome and, presumably, each measure of BP variability as a linear predictor, assumes that the association is linear, e.g., BP variability increases with decreasing ABI. This would seem contradictory to considering both high and low ABI as 'abnormal' in the logistic regression models, with the expectation that increased BP variability is related to both low and high ABI. This relationship could be explored by modelling the BP variability as a non-linear function of the ABI, to see if indeed both low and high ABI values are associated with increased BP variability.

Response:
This point is a corollary of the previous. Any modeling with just three guys at one side would be difficult to fit. Spline statistics would theoretically be applied for such non-linear association, but it is limited by power. We therefore decided to maintain our analyses excluding high ABI from the multivariate models. In order to explore the shape of the association we run a plot of ABI by time-rate with and without these guys. Below is plot for one leg without the subjects. Including them there was not any major change.
4. The BP variability may reflect arterial compliance. The addition of pulse pressure to the models might clarify the independence of effects of the BP variability itself from compliance.

Response:

The introduction of 24-ABPM pulse pressure in the models instead of systolic blood pressure didn’t change the independent association between the time rate index and ABI

Right lower limb: Beta:-0.15; P value: 0.003
Left lower limb: Beta:-0.14; P value: 0.007

The following sentence was introduced in pg 10, first paragraph:

The introduction of 24-ABPM pulse pressure in the models instead of systolic blood pressure did not change the independent association between the time rate index and ABI"

Minor essential revisions:

We thank to the reviewer for the careful review of our Ms, we corrected all the points below.

1. ABPM should be spelled out at first occurrence in abstract, and should be noted following first full reference in the introduction: done.

2. In table 1, the row label ‘No antihypertensive’ should be clarified, as it is not clear what the numbers represent: done.

Discretionary revisions:

1. Is there a theoretical reason why the time rate index should be more highly correlated with abnormal ABI than the other two measures? If so, this should be included in the discussion.

The following sentence was introduced in the discussion

Pg 12, second paragraph

Different parameters of BP variability derived from ABPM have been described (11-13), but the time-rate index embodies the concept that in the analysis of blood pressure variability it is important to measure not only blood pressure differences between each measure but how fast or how slow it occurs and to which direction the blood pressure changes"
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests.