Can short-term heart rate variability predict coronary artery disease in patients undergoing elective coronary angiography because of typical chest pain?

Ramaze Farouke Elhakeem, Mohamed Faisal Lutfi, Ahmed Babiker Mohamed Ali, Mohamed Yusif Sukkar

Corresponding author:
Mohamed Faisal Lutfi
Department of Physiology - Faculty of Medicine and Health Sciences - Al-Neelain University – Khartoum – Sudan

1st editorial decision
23-Jun-2020

Ref.: Ms. No. JCTRes-D-20-00035
Can short-term heart rate variability predict coronary artery disease in patients undergoing elective coronary angiography because of typical chest pain?
Journal of Clinical and Translational Research

Dear Prof Lutfi,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the

reviewers to rapidly verify all changes made.

Your revision is due by Jul 23, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: I make the following considerations and comments to the Authors:

1. A basic point of the study would be to characterize the anatomical findings in coronary angiography. There is a need to classify cases in terms of the degree of vascular involvement. Which coronary arteries were involved, in what degree of obstruction, in what location (proximal or distal), if diffuse or localized lesions, etc. What was the degree of myocardial impairment? (hypokinesias, dilations, etc.). Were the vessels tortuous?
2. Was the diagnosis based only on the typical precordial pain symptom? Did the patients not undergo exercise testing or myocardial scintigraphy?
3. What was the association found with the presence of diabetes mellitus?
4. The equipment used to collect the time series do not calculate non-linear variables?
5. Do the authors have access to the tachogram? How was the data filtering process done?
6. Were the patients on medication?
7. Why was used logarithmic notation?

Reviewer #2: General:
This is an interesting study where a challenging question was asked: "Can we tell apart the patients with 'true' anginal complaints from those with unspecific chest pain, but presenting as cardiac, just by a 5 minutes resting ECG-HRV measurement?"

The answer the authors came up with is 'no, we can't' but in my opinion there is more to be said about that given the data from the present study.

The study enrolled 150 patients of whom 108 turned out to have 'true' coronary artery disease (CAD), 42 did not. However, the definition of yes/no CAD is not specified in the paper. How much coronary stenosis was required for that diagnosis? The authors do not specify any other tests that might have been done before catheterization: exercise test, blood samples; was this 'stable' angina?

Then, after the dichotomy yes/no CAD, the CAD-group had 75% males. We do know, that the presentation of CAD in women is different from that in men. How was the selection of patients to undergo angiography made in the first place? This is a need-to-know question for others, using this study for their own purposes. When I did some calculations, using the data

from table 1, I found that 18/42 non-CAD were male and 81/108 CAD-
patients were. The study group consisted, therefore, of 99/150 males to begin with (i.e. 66%).
I don't understand the entry on the row "male gender% (95% CI)" in table 1, but an outcome
of 75% in the 'true-CAD'-group does not look strange to me. Moreover, to clarify this point,
the authors should have specified the numbers m/f in the study group from the beginning.
How were the 150 selected? Was this a number of consecutive, consenting patients? Were no
other factors involved that influenced the inclusion, like heart rate influencing medication
(e.g. propranolol or other ß-blocking agents, or anti-hypertensive drug therapy)? Was it not a
requisite that the patients were in sinus rhythm, how many extra-systoles were allowed, how
many patients did not meet the inclusion criteria?

Then, given the considerable differences between the two groups, the authors decided to
adjust for age, gender, BMI and heart rate using a general linear model, applying that to adjust
the HRV-results. Since the HRV-measures are most of the time highly correlated amongst
themselves, we are now in deep waters of Statistics, where the help from SPSS may be very
misleading if the wrong questions are asked. I consider it strange to use the HR in the to-be-
discarded differences between the groups, since HR is an outcome measure by itself in the
measurement of HRV. I hate to see a good study killed by poorly applied statistics; has a
trained bio-statistician been involved?

Detailed:
The opening statement needs adjustment, it now reads:
Variations in the RR interval of the ECG is the popular method used in the assessment of
heart rate variability (HRV),

Variations in RRI is not a method, Measurement of it is. But then we have the statement that
we measure RRI to assess HRV, which looks like a tautology to me.

The page on measurement of ECG and data evaluation reads like an advertisement for DM
systems: no specifics are given, it is all in the hands of the Chinese manufacturer. Not
everyone uses this system, some more clarification is necessary if others are to repeat the
study.

Start of the discussion:
Line 53: anginal pain is meant
Line 58: 'however' ?? Seems out of place, here. Probably it is meant to appear at the start of
the first sentence on the next page. On that page, in lines 9 and 21 we see 'heathy' where
healthy is meant; typo.

Conclusions:
Line 43: statistically significant differences is meant, not 'significance'

Reviewer #3: Authors investigated an important topic (HRV)
I suggest to perform the reliability test with AUC and ROC analysis

Author's response

The editor
Thank you for the valuable comments from the reviewers. Below are the point to point responses to the reviewers' comments:

Reviewer#1

Reviewer comment

1. A basic point of the study would be to characterize the anatomical findings in coronary angiography. There is a need to classify cases in terms of the degree of vascular involvement. Which coronary arteries were involved, in what degree of obstruction, in what location (proximal or distal), if diffuse or localized lesions, etc. What was the degree of myocardial impairment? (hypokinesias, dilations, etc.). Were the vessels tortuous?

Authors response

The diagnosis of CAD was made if ECT demonstrated one or more stenoses in ≥ half of the diameter of at least one major coronary artery, please see Marroquin, O et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the women's ischemia syndrome evaluation. Circulation 109, 714–721 and Lutfi MF et al. Zinc and copper levels are not correlated with angiographically-defined coronary artery disease in Sudanese patients. Front Physiol. 2015; 6:191). Case definition was added in the section of methods, please see the tack changes in the sixth paragraph in the section of methods.

Table 1 was modified and another table (table 2) was added to give more details about coronary arteries involved and the degree of myocardial impairment in the studied patients. Please see track changes in table 1 and 2.

Reviewer comment

2. Was the diagnosis based only on the typical precordial pain symptom? Did the patients not undergo exercise testing or myocardial scintigraphy?

Authors response

This study aimed to explore the possible HRV differences in patients with typical chest pain when classified according to ECA outcomes (normal vs. abnormal ECA). Accordingly, the study included patients who were selected by their cardiologist to undergo ECT because of the typical chest pain they presented with. Very few patients had stress ECG and none of them had myocardial scintigraphy.

Reviewer comment

1. What was the association found with the presence of diabetes mellitus? **Authors response**
Yes, the was significant association with diabetes mellitus. Please, see track changes in table 1.

Reviewer comment

4. The equipment used to collect the time series do not calculate non-linear variables? **Authors response**

The equipment used to collect the time series also calculate non-linear variables and other ECG derived values like QT dispersion, Ventricular late potential, vector analysis, …ect. However, we did not save them in the data collection sheets.

Reviewer comment

5. Do the authors have access to the tachogram? How was the data filtering process done? **Authors response**

Yes. Thank you very much for the comment. This was not mentioned in the previous manuscript and I have just added it in the section of methods. Screening for various types of abnormal ECG recording was performed manually. Abnormal ECG readings like ectopic beats, arrhythmias, and noise were deleted manually. Following visual inspection and manual

editing, the software was allowed to calculate HRV parameters from the rest of the ECG data. Please, see the track changes at the end of the second paragraph of the section of methods.

Reviewer comment

      6.   Were the patients on medication?

Authors response

Yes, both test and control groups were suffering from chronic diseases like HTN and DM and are expected to be on regular medications. Although some drugs can alter autonomic modulations and consequently HRV, use of these drugs by investigated patients is unlikely to bias study findings. This is because both test and control groups are equally exposed these drugs. Moreover, we adjusted for the variations in the heart rate while comparing for possible differences between the studied groups. I could not remember any researcher who adjusted for such drugs between the groups he/she investigated in all studies I reviewed in the discussion.

Reviewer comment

      7.   Why was used logarithmic notation?

Authors response

The HRV values are commonly expressed as the natural logarithm (Ln) of original units to achieve a more normal distribution.

Reviewer#2

Reviewer comment

This is an interesting study where a challenging question was asked: "Can we tell apart the patients with 'true' anginal complaints from those with unspecific chest pain, but presenting as cardiac, just by a 5 minutes resting ECG-HRV measurement?"

The answer the authors came up with is 'no, we can't' but in my opinion there is more to be said about that given the data from the present study.

The study enrolled 150 patients of whom 108 turned out to have 'true' coronary artery disease (CAD), 42 did not. However, the definition of yes/no CAD is not specified in the paper. How much coronary stenosis was required for that diagnosis? The authors do not specify any other tests that might have been done before catheterization: exercise test, blood samples; was this 'stable' angina? **Authors response**

The diagnosis of CAD was made if ECT demonstrated one or more stenoses in $\geq$ half of the diameter of at least one major coronary artery, as described before (please see Marroquin, O et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the women's ischemia syndrome evaluation. Circulation 109, 714–721 and Lutfi MF et al. Zinc and copper levels are not correlated with angiographicallydefined coronary artery disease in Sudanese patients. Front Physiol. 2015; 6:191). Case definition was added in the section of methods, please see the tack changes in the sixth paragraph in the section of methods. Table 1 was modified and another table (table 2) was added to give more details about coronary arteries involved and the degree of myocardial impairment in the studied patients. Please see track changes in table 1 and 2. This study aimed to explore the possible HRV differences in patients with typical chest pain when classified according to ECA outcomes (normal vs. abnormal ECA). Accordingly, the study included patients who were selected by their cardiologist to undergo ECT because of the typical chest pain they presented with. Very few patients had stress ECG and none of them had myocardial scintigraphy.

Reviewer comment

Then, after the dichotomy yes/no CAD, the CAD-group had 75% males. We do know, that the presentation of CAD in women is different from that in men. How was the selection of patients to undergo angiography made in the first place? This is a need-to-know question for

others, using this study for their own purposes. When I did some calculations, using the data from table 1, I found that 18/42 non-CAD were male and 81/108 CAD-patients were. The study group consisted, therefore, of 99/150 males to begin with (i.e. 66%). I don't understand the entry on the row "male gender% (95% CI)" in table 1, but an outcome of 75% in the 'true-CAD'-group does not look strange to me. Moreover, to clarify this point, the authors should have specified the numbers m/f in the study group from the beginning. How were the 150 selected? Was this a number of consecutive, consenting patients? Were no other factors involved that influenced the inclusion, like heart rate influencing medication (e.g. propranolol or other ß-blocking agents, or antihypertensive drug therapy)? Was it not a requisite that the patients were in sinus rhythm, how many extra-systoles were allowed, how many patients did not meet the inclusion criteria? **Authors response**

The present study included all patients who agreed to join the study and are not known to suffer from congenital or acquired heart diseases during the period of data collection. As you said, the 18/42 non-CAD and 81/108 CAD males were the numbers of consecutive, consenting patients during the period of data collection. Noteworthy, we adjusted for the gender differences in the studied groups during statistical analysis. Few words were added to the methods to make this clear. Please see track changes in the second paragraph in the section of methods.

ECG filtering process was not mentioned in the previous manuscript and I have just added it in the section of methods. Screening for various types of abnormal ECG recording was performed manually. Abnormal ECG readings like ectopic beats, arrhythmias, and noise were deleted manually. Following visual inspection and manual editing, the software was allowed to calculate HRV parameters from the rest of the ECG data. Please, see the track changes at the end of the second paragraph in the section of methods.

The test and control groups were both suffering from chronic diseases like HTN and DM and are expected to be on regular medications. Although some drugs can alter autonomic modulations and consequently HRV, use of these drugs by investigated patients is unlikely to bias the study findings. This is because both test and control groups are equally exposed these drugs. Moreover, we adjusted for the heart rate differences in the studied groups during statistical analysis.

Reviewer comment

Then, given the considerable differences between the two groups, the authors decided to adjust for age, gender, BMI and heart rate using a general linear model, applying that to adjust the HRVresults. Since the HRV-measures are most of the time highly correlated amongst themselves, we are now in deep waters of Statistics, where the help from SPSS may be very misleading if the wrong questions are asked. I consider it strange to use the HR in the to-be-discarded differences between the groups, since HR is an outcome measure by itself in the measurement of HRV. I hate to see a good study killed by poorly applied statistics; has a trained bio-statistician been involved? **Authors response**

Arguments that HRV is neither uniformly nor simply a surrogate for heart rate are available in the literature, please, see de Geus EJC, et al. Should heart rate variability be "corrected" for heart rate? Biological, quantitative, and interpretive considerations. Psychophysiology. 2019;56(2):e13287. doi:10.1111/psyp.13287. We gave the results of comparisons between the studied groups with and without adjustment for heart rate. This is to inform the reader if he/she believed that heart rate should not be adjusted for. We came across many studies in reputable journals that control for heart rate while comparing HRV measurements between the studied groups using SPSS, please, see Musa SM, et al. Heart Rate Variability and Autonomic Modulations in Preeclampsia. PLoS One. 2016;11(4):e0152704. Published 2016 Apr 4. doi:10.1371/journal.pone.0152704. We admit that there may be highly specialized

statistical packages better than SPSS, but we have no facility to access any of them. **Reviewer comment** Detailed:

The opening statement needs adjustment, it now reads:

Variations in the RR interval of the ECG is the popular method used in the assessment of heart rate variability (HRV),

Variations in RRI is not a method, Measurement of it is. But then we have the statement that we measure RRI to assess HRV, which looks like a tautology to me.

The page on measurement of ECG and data evaluation reads like an advertisement for DM systems: no specifics are given, it is all in the hands of the Chinese manufacturer. Not everyone uses this system, some more clarification is necessary if others are to repeat the study.

Authors response

The opening statement was rewritten. Please, see the track changes in the first two sentences of the introduction.

I described how I used Bluetooth ECG transmitter and receiver (DM systems (Beijing) Co. limited - China) to record ECG and evaluate of HRV. I tried my best to explain how I used this instrument so as to clarify the methods if others are to repeat the study. This may look like advertisement for DM systems; however, I was not intending to do so. The products of DM systems, including Bluetooth ECG transmitter and receiver, are available online for those who need more clarifications.

Reviewer comment

Start of the discussion:

Line 53: anginal pain is meant

Line 58: 'however' ?? Seems out of place, here. Probably it is meant to appear at the start of the first sentence on the next page. On that page, in lines 9 and 21 we see 'heathy' where healthy is meant; typo. **Authors response**

Thank you

The words "anginal" and "healthy" were corrected. The sentence containing "however" was modified. Please, see track changes in the first and second paragraphs in the section of discussion. **Reviewer comment** Conclusions:

Line 43: statistically significant differences is meant, not 'significance'

Authors response

Thank you The word "significant" was corrected. Please, see track changes in third line in the section of conclusion.

Reviewer #3

Reviewer comment

Authors investigated an important topic (HRV)

I suggest to perform the reliability test with AUC and ROC analysis

Authors response

Done. Please, see track changes in the last page in the section of the results and the first paragraph in the section of the discussion.

2nd Editorial response
26-Jul-2020

Ref.: Ms. No. JCTRes-D-20-00035R1
Can short-term heart rate variability predict coronary artery disease in patients undergoing elective coronary angiography because of typical chest pain?
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Aug 25, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: There is still a doubt related to the method of diagnosis of coronary disease. In two parts, the authors mention that:

1. ECA confirmed the diagnosis of CAD in 108 patients, who were considered as the test group. The diagnosis of CAD was made if ECT demonstrated one or more stenoses in ≥ half of the diameter of at least one major coronary artery, as described before [15,16]. The other 42 subjects were considered as a control group after exclusion of CAD

2. This study aimed to explore the possible HRV differences in patients with typical chest pain when classified according to ECA outcomes (normal vs. abnormal ECA). Accordingly, the study included patients who were selected by their cardiologist to undergo ECT because of the typical chest pain they presented with. Very few patients had stress ECG and none of them had myocardial scintigraphy

It was not clear what the meaning of ECT is. It is not mentioned in the text. Was it a typo wanting to mention ECA? (Elective Coronary Angiography).

Reviewer #2:
I thank the authors for their replies and the changes made to the manuscript. I trust they understand that comments were purely made to improve it. Since I only have received the red-lined version as pdf, without line numbers or even page numbers, please bear with me in my comments.

General:

A few details remain, cf. below, but one issue I want to stress, i.e. the number of participating males vs females in the study. I don't see what the problem is just to mention under results (since it was not something planned beforehand), in the very first sentence the following: Coronary artery catheterization of the studied subjects (N = 150, m/f: 99/51) revealed 108 patients (m/f: 81/27) with CAD (% (95% CI) = 72% (64.41-78.74%)) and 42 subjects (m/f: 18/24) with normal coronary arteries (28% (21.26-35.59%)).

Detailed:

Abstract:

Middle of the page: 'Bluetooth …. and receiver' were used (the subject is plural)

Under results I would have preferred 'Ln(pNN10) etc, using brackets to simplify reading. Whether one uses pNNx as a pure fraction or as % is immaterial when the logarithm is used in the statistics.

Under Introduction, bottom second page: ln(LF/HF) mathematics requires brackets for clarity here.

Results:

Table 1, diabetes mellitus, please correct.

Table 3: ln(pNNxxP) what is meant by P?

Abbreviations:

Forgotten: definition of CSX

Author's response

The editor

Thank you for the valuable comments from the reviewers. Below are the point to point responses to the reviewers' comments:

Reviewer#1

Reviewer comment

There is still a doubt related to the method of diagnosis of coronary disease. In two parts, the authors mention that:

1. ECA confirmed the diagnosis of CAD in 108 patients, who were considered as the test group. The diagnosis of CAD was made if ECT demonstrated one or more stenoses in ≥ half of the diameter of at least one major coronary artery, as described before [15,16]. The other 42 subjects were considered as a control group after exclusion of CAD

2. This study aimed to explore the possible HRV differences in patients with typical chest pain when classified according to ECA outcomes (normal vs. abnormal ECA). Accordingly, the study included patients who were selected by their cardiologist to undergo ECT because of the typical chest pain they presented with. Very few patients had stress ECG and none of them had myocardial scintigraphy

It was not clear what the meaning of ECT is. It is not mentioned in the text. Was it a typo wanting to mention ECA? (Elective Coronary Angiography).

Authors response

I am sorry. All ECTs mentioned in my response to your previous comments were typo mistakes. Please, see track changes in the sixth paragraph in the section of methods.

Reviewer#2

Reviewer comment

General:

A few details remain, cf. below, but one issue I want to stress, i.e. the number of participating males vs females in the study. I don't see what the problem is just to mention under results (since it was not something planned beforehand), in the very first sentence the following:

Coronary artery catheterization of the studied subjects (N = 150, m/f: 99/51) revealed 108 patients (m/f: 81/27) with CAD (% (95% CI) = 72% (64.41-78.74%)) and 42 subjects (m/f: 18/24) with normal coronary arteries (28% (21.26-35.59%)).

Authors response

OK, it was rewritten. Thank you for your help. Please, see track changes in the first paragraph in the section of the results.

Reviewer comment

Detailed:

1. Abstract:
   - Middle of the page: 'Bluetooth …. and receiver' were used (the subject is plural)
   - Under results I would have preferred 'Ln(pNN10) etc, using brackets to simplify reading. Whether one uses pNNx as a pure fraction or as % is immaterial when the logarithm is used in the statistics.
   - Under Introduction, bottom second page: ln(LF/HF) mathematics requires brackets for clarity here.
2. Results:
   - Table 1, diabetes mellitus, please correct.
   - Table 3: ln(pNNxxP) what is meant by P?
3. Abbreviations:
   - Forgotten: definition of CSX

Authors response

All were corrected. Please, see tract changes in the relevant sections.

1. Abstract
   - "Was" was replaced with "were" in the third line in the section of methods of the abstract
   - Ln(pNNx) and ln(LF/HF) were corrected in the abstract and the remaining part of the manuscript
2. Results:
   - Diabetes mellitus was corrected in table 1
   - ln(pNNxP) was replaced with ln(pNNx) in table 3
3. Abbreviations:
   - CSX was defined in the section of abbreviations

3rd editorial decision
27-Jul-2020

Ref.: Ms. No. JCTRes-D-20-00035R2
Can short-term heart rate variability predict coronary artery disease in patients undergoing elective coronary angiography because of typical chest pain?
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research