PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Could the arm blood pressure measured with simultaneous bilateral arm method be used for hypertension diagnosis?
AUTHORS	Wan, Taixuan; Wu,, Yuan-hao; He, Zi-qiang; Su, Hai

VERSION 1 – REVIEW

REVIEWER	Chris Clark University of Exeter Medical School, England I have an active research programme concerning inter-arm blood pressure difference measurement
REVIEW RETURNED	10-Mar-2020

GENERAL COMMENTS	This study addresses the question of whether simultaneous measurement of BP in both arms leads to higher BP values than unilateral measurement. It was carried out using data measured in 295 subjects. The investigators found that overall average BP was 1.2/0.4mmHg higher using simultaneous measurement with two machines, compared the average right arm only BP measurements. The investigators claim novelty in this work which unfortunately is not justified. In 2013 van der Hoeven et al published an arguably more robust analysis of 240 subjects in J Clin Hypert; they found a remarkably similar mean difference of 1.3/0.4mmHg. This work must be acknowledged by the authors in the introduction, and their findings should be discussed in the context of this first report. Failure to fully acknowledge the previous literature is a major concern in this paper. I have noted a number of other problems, most of which are easily addressed, as follows: Introduction Paragraph 2 states that simultaneous arm BP measurement is widely used clinically. Although I am cited in this context I certainly didn't write that, in fact I continue find that there is poor uptake, at least in the UK, of checking both arms and have published data on this. Therefore this generalisation cannot, I think, be accepted. Methods 1. No sample size calculation has been reported, or the absence of one justified. 2. Participants gave verbal consent to the study. I would expect there to be a written record of consent. It may be that verbal consent is acceptable at the authors' institution but the editors will need to be satisfied about this. 3. We are not told who the participants are: were they out-patients (if so - attending what clinics) or in-patients (if so - what types)? Some more detail is need here. 4. Since one would normally standardise BP measurements to the higher reading arm (in keeping with hypertension guidelines) the

	logical comparison here would have been to compare the higher arm measured alone and simultaneously. In this study no determination of the higher reading arm, or the dominant arm, was made and the right arm was used throughout. This may have introduced bias by not confirming the arm dominance, and also by not knowing that the correct (i.e. higher reading) arm was being studied at all. We know that about 10% of the population are left arm dominant but more importantly about 50% will have a higher reading left arm compared to right. This design flaw needs to be carefully discussed and accounted for. Results 1. The results deal entirely with mean differences. The SD is > 20 suggesting that for some people there was a very larger difference between methods. Was this reproducible over the two stages of the protocol? Arguably these are the people who could really be helped to avoid mis-diagnosis and treatment of hypertension. They may well be people more prone to white coat effects anyway, and analyses designed to look at this, to look at how BP changes over the 4 measurements, and how it correlate with age sex and other parameters associated white white coat, would be informative and could add to this paper. We have published on the relationship between inter-arm difference and white coat effects. 2.It appears that the prevalence of a > 10mmHg systolic inter-arm difference was 3.5%. This is a single line in the results. It is not discussed despite being an important part of the introduction. No analyses incorporating IAD appear and so we don't know how IAD impacted the difference between RA1 and RA2. This seems an omission. Based on work from my group and others this prevalence of IAD seems low, so that at least needs some discussion. If we know more about the demographics of the study population that might help to understands this prevalence. Discussion 1. The statement that simultaneous BP measurement should not be used for diagnosing hypertension is not substantiated by the data. The small 1.2mmHhg systolic difference is negligible compared to the average accuracy of sphygmomanometers, indeed the published validation report (see dableeducational.org) for the HBP-1300 device reports a mean (SD) error between device and mercury standard of -2(4)/-4(4)mmHg and the authors should at least acknowledge this. Therefore the most obvious conclusion of this study is, in fact, that the difference between simultaneous and single arm readings is smaller than the diagnostic accuracy of the device used. This finding needs to be placed in a clear clinical context, and set against the known much larger effects of white coat, observer, rest, posture and the many other factors that affect a routine clinical BP measurement. The other thing that could be discussed is how much predicted cardiovascular risk changes with a 1.4mmHg difference. 2. The claim is again made that this is the first report of differences in BP according to method and as stated above must be retracted. 3. Paragraph 3 considers that BP may rise more in the act of undressing for people on combination antihypertensive therapy. This was not measured in the current study and seems to me to be highly speculative. 4. The authors conclude, slightly at odds with their study, that both arms should be measured to detect the reference arm, then this should be measured singly for diagnosing hypertension. Whilst this is logical the authors did not actually do this. They used the right

	arm throughout the study, and did not attempt to adopt the higher reading arm as reference (see above comments on the risk of bias inherent in this method). Therefore this is not a satisfactory concluding statement for this study as presented. CONSORT The editors have asked for comments on compliance with the CONSORT checklist. This was not an RCT so the comparison is limited – a STROBE statement would be more appropriate but I couldn't see one provided. I have mentioned the lack of sample size calculation and various other points above. Other STROBE points include: Lack of design in study title Setting and details of participants are lacking Insufficient consideration of risks of bias There is no mention of missing data handling – perhaps no data were missing? The flow chart is inadequate to help explain the study – did all participants complete the protocol?

REVIEWER	Pr Jean-Marc BOIVIN Lorraine University- General Practitioners Department CIC-P Inserm CHRU Nancy France
REVIEW RETURNED	30-Apr-2020

GENERAL COMMENTS	Given the extreme variability of BP, it is not certain that the results you observe will be the same on another occasion. I'm not even sure that this method even allows for comparison of results. The measurements should have been repeated using the RA-1 and RA-2 method, using a cross-over method. Each subject would then be his or her own control. There is no indication of when these measures took place? For hypertensive patients, before or after medication? How long after? You're not specific enough about the method. Were the measurements performed in the presence of the doctor or without the doctor being present (self-blood pressure measurement)? What is the correct method? You stipulate that one-armed measurement is the correct method. How can you claim that measuring with both arms overestimates BP? Isn't the single-arm measurement underestimating BP? Why didn't you choose the left arm instead of the right arm? How do you interpret the measurement differences between the two arms? Finally, what is the standard reference measurement?

VERSION 1 – AUTHOR RESPONSE

Reply to the Reviewer 1:
Reviewer: 1
Reviewer Name: Chris Clark
Institution and Country: University of Exeter Medical School, England
Please state any competing interests or state 'None declared': I have an active research programme concerning inter-arm blood pressure difference measurement
Response: We are very happy to contact you by this way. We read a lot of paper on IAD published by you and your team.

Please leave your comments for the authors below
This study addresses the question of whether simultaneous measurement of BP in both arms leads to higher BP values than unilateral measurement. It was carried out using data measured in 295 subjects. The investigators found that overall average BP was 1.2/0.4mmHg higher using simultaneous measurement with two machines, compared the average right arm only BP measurements. The investigators claim novelty in this work which unfortunately is not justified. In 2013 van der Hoeven et al published an arguably more robust analysis of 240 subjects in J Clin Hypert; they found a remarkably similar mean difference of 1.3/0.4mmHg. This work must be acknowledged by the authors in the introduction, and their findings should be discussed in the context of this first report. Failure to fully acknowledge the previous literature is a major concern in this paper. I have noted a number of other problems, most of which are easily addressed, as follows:

Response: According to your suggestion, we carefully read the paper of van der Hoeven et al. again. As the main purpose of that study was to compare inter-arm BP differences with simultaneous or sequential measurement, before we could not fully recognize that study also provided information that the mean arm SBP/DBP level from bilateral arm measurement was higher by 1.3/0.4mmHg than the unilateral (sequential) measurement (Niels V. van der Hoeven, et al. Simultaneous Compared With Sequential Blood Pressure Measurement Results in Smaller Inter-Arm Blood Pressure Differences. J Clin Hypertens (Greenwich). 2013;15:839–844.) In this revised manuscript, the data of Hoeven et al. were mentioned in the introduction and discussion sections. However, our study specially designed two BP measurement proposals to compare the difference from bilateral arm and the unilateral arm BP measurement, so that time interval for repeated BP measurement was shorter, therefore, our result may provide more accurate evidence.
Introduction
Paragraph 2 states that simultaneous arm BP measurement is widely used clinically. Although I am cited in this context I certainly didn't write that, in fact I continue find that there is poor uptake, at least in the UK, of checking both arms and have published data on this. Therefore this generalisation cannot, I think, be accepted.
Response: Several hypertension guidelines suggest bilateral arm measurement for the initial BP measurement. This concept is accepted by many physicians and bilateral arm measurement is used more in clinical practice. However, the bilateral arm measurement is fully performed even in the university hospital in China and other countries. Therefore, the statement in the prior paper was changed to “Therefore, simultaneous bilateral arm BP measurement (bilateral arm method) is suggested in clinical practice and epidemiological studies” in the revised manuscript.
Methods
1. No sample size calculation has been reported, or the absence of one justified.

Response: In fact, the existing data on the BP difference from bilateral arm and unilateral arm measurement is little. According a published paper that indicated the difference between the arm SBP levels from single arm BP measurement and four-limb BP measurement was 1.9 mmHg, assuming a standard deviation (SD) difference of 11 mm Hg, we calculated that 263 persons would be needed to demonstrate a 1.9 mm Hg difference with 80% power and a=0.05.

2. Participants gave verbal consent to the study. I would expect there to be a written record of consent. It may be that verbal consent is acceptable at the authors' institution but the editors will need to be satisfied about this.

Response: Indeed, a written record of consent is better than a verbal consent to the study. Unfortunately, we only had a verbal consent for this study as the BP measurement is a common clinical examination
3. We are not told who the participants are: were they out-patients (if so - attending what clinics) or in-patients (if so - what types)? Some more detail is need here.

Response: This study was performed in the Second Affiliated Hospital of the Nanchang University. All participants were outpatients attending our clinics. This information was added in the revised manuscript.

4. Since one would normally standardise BP measurements to the higher reading arm (in keeping with hypertension guidelines) the logical comparison here would have been to compare the higher arm measured alone and simultaneously. In this study no determination of the higher reading arm, or the dominant arm, was made and the right arm was used throughout. This may have introduced bias by not confirming the arm dominance, and also by not knowing that the correct (i.e. higher reading) arm was being studied at all. We know that about 10% of the population are left arm dominant but more importantly about 50% will have a higher reading left arm compared to right. This design flaw needs to be carefully discussed and accounted for.

Response: Your suggestion is very useful. The standard BP measurement is to identify reference arm by bilateral arm BP measurement and use the reference arm for getting final BP reading according to the hypertension guidelines. As the purpose of this study was to evaluate whether the arm BP level measured with simultaneous bilateral arm method is similar to that with unilateral arm method, we only selected the right arm for unilateral arm BP measurement. On this consideration, the title of the paper was change as “Is the blood pressure measured with simultaneous bilateral arm method similar to unilateral arm method”

Results

1. The results deal entirely with mean differences. The SD is > 20 suggesting that for some people there was a very larger difference between methods. Was this reproducible over the two stages of the protocol? Arguably these are the people who could really be helped to avoid mis-diagnosis and treatment of hypertension. They may well be people more prone to white coat effects anyway, and analyses designed to look at this, to look at how BP changes over the 4 measurements, and how it correlate with age sex and other parameters associated white coat effect, would be informative and could add to this paper. We have published on the relationship between inter-arm difference and white coat effects.

Response: In this study the SD of the RA-1 and RA-2 on SBP was about 20. The reasons for the large SD may be various as you suggested. A possible reason was the large range of BP of the studied population. Because the mean SBP and SD values of RA-1 and RA-2 were similar, and the SD of Dif-RA on SBP was 5, we could consider the reproducible of the two protocols may be well. Meanwhile, multivariate regression analyses showed that age and sex were not independent factor for Dif-RA on SBP.

2. It appears that the prevalence of a > 10mmHg systolic inter-arm difference was 3.5%. This is a single line in the results. It is not discussed despite being an important part of the introduction. No analyses incorporating IAD appear and so we don't know how IAD impacted the difference between RA1 and RA2. This seems an omission. Based on work from my group and others this prevalence of IAD seems low, so that at least needs some discussion. If we know more about the demographics of the study population that might help to understands this prevalence.

Response: As the aim of this study was on the difference of arm BP levels between bilateral arm method and unilateral arm method, we did not discuss fully about the IAD. The detection rate of systolic IAD > 10mmHg of 3.5% was lower than those reported by other researchers including your team. The main reason for the lower detection rate of sIAD may be from repeated bilateral arm measurement and different population. More discussion was conducted in the revised manuscript. The demographics of the study population were added. But the data were not complete as the participants were outpatients.

Discussion

1. The statement that simultaneous BP measurement should not be used for diagnosing hypertension is not substantiated by the data. The small 1.2 mmHhg systolic difference is negligible compared to the average accuracy of sphygmomanometers, indeed the published validation report (see dableeducational.org) for the HBP-1300 device reports a mean (SD) error between device and mercury standard of -2(4)/-4(4)mmHg and the authors should at least acknowledge this. Therefore the most obvious conclusion of this study is, in fact, that the difference between simultaneous and single arm readings is smaller than the diagnostic accuracy of the device used. This finding needs to be placed in a clear clinical context, and set against the known much larger effects of white coat, observer, rest, posture and the many other factors that affect a routine clinical BP measurement. The other thing that could be discussed is how much predicted cardiovascular risk changes with a 1.4mmHg difference.
Response: Your suggestion is very helpful for revising our manuscript. According to your suggestion, we changed the statement in the clinical implication section as “This study found that the arm SBP/DBP levels measured with bilateral arm method were higher by 1.2 and 0.4 mm Hg against the single arm method. In fact, the impact of various factors in routine clinical BP measurement, such as white coat effect, rest time, posture, observer, on SBP may be larger than 1.2 mmHg, meanwhile, this variation is within the permitted error range for certification of new BP device, meanwhile, even the error of BP measurement with oscillometric method may be about 5 mm Hg, thus, such a small difference may be negligible. However, this difference was systemic and statistically significant, we could consider that the BP readings with bilateral arm method overestimate the real BP.
Based on our data from 1540 community adults, a 2/1mmHg overestimation for SBP/DBP may increase hypertension prevalence from 33.4% to 37.3%, and decrease the control rate from 9.7% to 7.5%. For getting a more accurate result, we suggest that BP should be measured at first with simultaneous bilateral arm method to detect the reference arm, then, the BP reading measured on the reference arm with single arm BP method is used for hypertension diagnosis.”

2. The claim is again made that this is the first report of differences in BP according to method and as stated above must be retracted.
Response: This statement was changed in the revised manuscript.

3. Paragraph 3 considers that BP may rise more in the act of undressing for people on combination antihypertensive therapy. This was not measured in the current study and seems to me to be highly speculative.
Response: Sorry for our mistake. That sentence was deleted in the revised manuscript.

4. The authors conclude, slightly at odds with their study, that both arms should be measured to detect the reference arm, then this should be measured singly for diagnosing hypertension. Whilst this is logical the authors did not actually do this. They used the right arm throughout the study, and did not attempt to adopt the higher reading arm as reference (see above comments on the risk of bias inherent in this method). Therefore this is not a satisfactory concluding statement for this study as presented.
Response: According to your suggestion, we changed the conclusion as “The SBP and DBP of right arm measured with bilateral arm method are slightly, but statistically higher (1.2 and 0.4 mmHg) than those with the single arm BP method.” in the abstract section.
CONSORT
The editors have asked for comments on compliance with the CONSORT checklist. This was not an RCT so the comparison is limited – a STROBE statement would be more appropriate but I couldn’t see one provided.
I have mentioned the lack of sample size calculation and various other points above. Other STROBE points include:
Lack of design in study title
Setting and details of participants are lacking

Insufficient consideration of risks of bias
There is no mention of missing data handling – perhaps no data were missing? The flow chart is inadequate to help explain the study – did all participants complete the protocol?
Response: The information about the research question, study design and setting was added in the manuscript.
Reply to the Reviewer 2:
Reviewer Name: Pr Jean-Marc BOIVIN
Institution and Country:
Lorraine University- General Practitioners Department
CIC-P Inserm CHRU Nancy
France
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
Given the extreme variability of BP, it is not certain that the results you observe will be the same on another occasion.
Response: Although variability of BP is large, our result showed that the SBP measured with bilateral arm BP measurement s systemically higher than that with unilateral arm BP measurement. Previous study reported similar result. Niels V. van der Hoeven, et al. Simultaneous Compared With Sequential Blood Pressure Measurement Results in Smaller Inter-Arm Blood Pressure Differences. J Clin Hypertens (Greenwich). 2013;15:839–844.

I'm not even sure that this method even allows for comparison of results. The measurements should have been repeated using the RA-1 and RA-2 method, using a cross-over method. Each subject would then be his or her own control.
Response: As you suggested, using a cross-over method can get more reasonable result. However, that process needs more times to be conducted and repeated BP measurement may induce stress for the participants. Our result could provide an evidence to make that conclusion.
There is no indication of when these measures took place? For hypertensive patients, before or after medication? How long after?
Response: The information was added in the revised manuscript. This study was performed in the Second Affiliated Hospital of the Nanchang University. All the participants were outpatients. All the 33 hypertensive patients were treated. Unfortunately, we did not correct the data about the duration of treatment as the study purpose did not involve the evaluation of effectiveness.

You're not specific enough about the method. Were the measurements performed in the presence of the doctor or without the doctor being present (self-blood pressure measurement)?
Response: The method for BP measurement was stated in detail in the revised manuscript.

What is the correct method? You stipulate that one-armed measurement is the correct method. How can you claim that measuring with both arms overestimates BP? Isn't the single-arm measurement underestimating BP?
Response: According to hypertension guidelines, bilateral arm method should be used for the initial BP measurement to identify the reference arm (with higher BP value), then, the BP reading measured on the reference arm with single arm method as the final value. This is the correct BP method at present. On this way, the BP reading may be accurate.

Why didn't you choose the left arm instead of the right arm?
Response: Because the aim of this study was to compare the BP difference between the bilateral arm and unilateral arm BP measurement method, theologically, right arm or left arm may be used. In this study we used the right arm for unilateral arm BP measurement.

How do you interpret the measurement differences between the two arms?
Response: The BP difference between the two arms is named as the IAD. IAD≥10 mm Hg is a biomarker for asymmetric subclavian or brachial artery stenosis in the arm with lower BP. Meanwhile IAD is a useful predictor of cardiovascular events and all-cause mortality. More information was added in the revised manuscript.

This study found that there is BP differences between the two arms, that is, the IAD, which is a useful biomarker for diagnosis of disease and predicting the outcome.
Finally, what is the standard reference measurement?
Response: According to hypertension guidelines, the standard reference measurement should be bilateral arm method and bilateral method should be used for the initial BP measurement to identify the reference arm (with higher BP value), then, the BP reading measured on the reference arm with single arm method as the final value.

VERSION 2 – REVIEW

REVIEWER	Chris Clark University of Exeter Medical School, Exeter, Devon, UK
REVIEW RETURNED	19-May-2020

GENERAL COMMENTS	Thank you for giving me a second opportunity to review this paper. The revised manuscript seems to have addressed my comments adequately. There are a few typing errors and it would help if the authors could get an English language review to improve the readability - I can understand the paper but it would help to make it more accessible. I appreciate that this may not be possible. One tiny point - the authors refer throughout to multivariate analyses but I believe that multivariable is the correct term.

REVIEWER	Jean-Marc BOIVIN CIC-P Inserm CHRU de Nancy
REVIEW RETURNED	30-May-2020

GENERAL COMMENTS	The authors' answers are sufficiently informative. The manuscript has been improved and is now publishable.