Author's response to reviews

Title: Obesity & hypertension are determinants of poor hemodynamic control: A retrospective review

Authors:

Benedict U Nwachukwu (benedict_nwachukwu@hms.harvard.edu)
Jamie E Collins (jcollins13@partners.org)
Emily P Nelson (emilypagenelson@gmail.com)
Mercedes Concepcion (mconcepcion@partners.org)
Thomas S Thornhill (tthornhill@partners.org)
Jeffrey N Katz (jnkatz@partners.org)

Version: 2 Date: 9 December 2012

Author's response to reviews: see over
December 4th, 2012

Obesity & hypertension are determinants of poor hemodynamic control during total joint arthroplasty: A retrospective review

Authors: Benedict U Nwachukwu, Jamie E. Collins, Emily P. Nelson, Mercedes Concepcion, Thomas T. Thornhill, Jeffrey N. Katz

Dear Editors,

My Co-authors thank you for your review and insightful comments. We have revised the manuscript based on reviewer comments and concerns and we have included as part of this letter a point-by-point response to reviewer comments.

We look forward to your response.

Benedict U. Nwachukwu
**EDITORIAL COMMENTS:**

*Editor Comment:* Please include a 'Competing interests' section between the Conclusions and Authors' contributions. If there are none to declare, please write 'The authors declare that they have no competing interests'.

*Author Response:* We have included this section as requested

*Editor Comment:* Please include an 'Authors' contributions' section before the Acknowledgements and Reference list.

*Author Response:* This section is included in the revised manuscript

*Editor Comment:* We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

*Author Response:* Please see below for a point-by-point response to the reviewers. We have revised our manuscript accordingly and have highlighted changes in the revised manuscript.
REFEREE 1:

Referee Comment: Duration of surgery over 3 hours led to a poorer blood pressure control. This is more likely due to the fact these cases were bilateral, rather than the duration of surgery. Is this the case?

Author Response: We re-analyzed the data to investigate the significance of bilateral procedures. The vast majority of cases over 3 hours were bilateral (17/18). Of the cases that were under 3 hours, 28% were bilateral. We examined the effect of bilateral surgery on outcome by including bilaterality as a covariate in our multivariable model. The inclusion of bilaterality in our multivariable model did not change results appreciably. The risk associated with surgery over 3 hours vs surgery under 3 hours increased from 1.64 (1.05, 1.47) to 1.79 (0.94, 3.42), but the uncertainty around the estimate also increased.

We also examined the relationship between duration of surgery and hemodynamic control in only bilateral surgeries using a similar multivariate model as our original analyses (adjusted for sex, bmi, and hypertension) and found a non-statistically significant risk associated with surgery greater than 3 hours.

Based on these analyses it appears that surgery over 3 hours does have an effect on outcome. However duration of surgery and procedure performed appear to be strongly related and our sample size does not allow us to independently distinguish with certainty the effects on outcome of duration vs procedure (i.e. bilateral vs unilateral). Given the uncertainty we have removed duration of surgery from our multivariable models, and have added text addressing this issue. We have also revised our results to reflect our new multivariate analysis.

Revised Text (1): Duration of surgery greater than 3 hours increased the risk for poor hemodynamic control (relative risk- 1.5), however given the strong and indistinguishable association between duration of surgery and procedure (bilateral vs unilateral) in our series, we did not include duration of surgery in multivariable models. (Line 216-220)

Revised Text (2): Patients with duration of surgery greater than 3 hours were at increased risk for poor hemodynamic control (RR 1.5; 95% CI 0.9 – 2.4). The vast majority of cases over 3 hours were bilateral (17/18). (Line 256-258)

Revised Text (3): Our results suggest that duration of surgery increases the risk for poor hemodynamic control. However duration of surgery also appears to be strongly related to procedure performed and 17/18 surgeries greater than three hours in duration were bilateral in nature. Understanding the potential risks associated with bilateral and/or lengthy procedures is important and should be addressed in future investigations. (Line 324-328)

Referee Comment: What do they mean by blood products in table 2 does it mean transfusion?

Author Response: Blood products as presented in Table 2 (and the manuscript) refers to the transfusion of packed RBCs in patients with difficult intra-operative hemodynamics. This was performed at the discretion of the anesthesiologist with the hope of increasing the oxygen
carrying potential of patient’s circulation in order to prevent an ischemic event. We have clarified this in our methods section.

**Revised Text:** An intra-operative blood product refers to intra-operative transfusion of packed red blood cells. Utilization of intra-operative blood products signified sub-optimal hemodynamic control as these agents were utilized at the discretion of the anesthesiologist in cases where the patient had difficult hemodynamics and there was concern for adequate tissue perfusion. (Line: 194-200)

**Referee Comment:** Was there a difference in transfusions between the 2 groups?

**Author Response:** Of the 6 patients that received blood products, three patients had poor hemodynamic control and 5 out of the 6 patients had pre-operative hypertension. This suggests that hypertension is increases the risk for requiring intra-operative blood products.

**Referee Comment:** I presume the bilateral cases had no effect of blood pressure control as most of these were total knees which would have been done under tourniquet. Was the tourniquet inflated on both knees at the same time?

**Author Response:** Bilateral cases did not have an effect on blood pressure beyond the association with surgery of duration greater than 3 hours. In cases of bilateral knees the knee replacements were performed consecutively and not simultaneously and thus the tourniquet was never inflated on both knees at the same time. We have clarified this procedural point in the text.

**Revised Text:** Tourniquets were used in all TKAs. During bilateral TKA cases, knees were operated on consecutively and thus tourniquets were never insufflated in both knees at the same time. We believe that the use of tourniquet has minimal effect on intra-operative blood pressure assessment in our study population. (Line: 146-149)

**Referee Comment:** It may be better to exclude the 9 bilateral hips as no tourniquet used on these cases and blood loss may be significant

**Author Response:** In the study population we did not formally record units of blood loss therefore we are unable to predict the effect of blood loss on hemodynamic control. However based on the experience of the anesthesiologists participating in these mission trips there does not appear to be a robust relationship between blood-loss and hemodynamic control. Further, for THR surgeries, the utilization of permissive hypotension in this cohort mitigated the risk of significant blood loss during bilateral THRs.

We analyzed the effect of bilateral hip procedures on hemodynamic control by re-running our multivariable model without the inclusion of bilateral hip procedure and this did not appreciably change the risks identified in our study: SEX 2.0 (0.79 – 5.1); Hypertension 3.4 (1.5 – 7.8); BMI 1.2 (0.99 – 1.4).

**Referee Comment:** It would have been ideal to do measurements in recovery as blood pressure can change once the tourniquet is released
**Author Response:** We agree with this suggestion and it should certainly be an area of continued investigation i.e. perioperative blood pressure control associated with TJA. We note this limitation in the Discussion.

**Revised Text:** This study focused on intra-operative blood pressure assessment during TJA. An area of further investigation is the perioperative blood pressure changes associated with TJA. In certain patient populations blood pressure control can be difficult immediately after the procedure and in the post-anesthesia care unit. (Line: 351-354)

**Referee Comment:** Were the hips cemented or not?

**Author Response:** The hips in this cohort were uncemented. We have added this detail in our study methods.

**Revised Text:** All THRs were uncemented. (Line: 146)

---

**REFEREE 2:**
Referee Comment: Methods: “a priori algorithm” What is the algorithm? Whether they are <65% of MAP or >135% of MAP defines the outcome. This is an a priori definition of poor hemodynamic control, not an algorithm

Author Response: We agree with this suggestion and have made the necessary revision in our abstract

Revised text: “We developed an a priori definition for poor hemodynamic control” (Line 51-52)

Referee Comment: Results: The prevalence of hypertension and the incidence of poor hemodynamic control are very high in the study population.

Author Response: We agree that the prevalence of hypertension is high in the study population. Our study population consisted of patients with limited financial resources from the Dominican Republic. Based on local diet and lack of access to primary care needs these patients are more likely to be hypertensive. Further, based on the association between hypertension and poor hemodynamic control found as part of our analysis it is logical that there would then also be a high prevalence of poor hemodynamic control in our study population. To highlight that our study population is from the Dominican Republic we add:

Revised text: We performed a retrospective cohort analysis of 118 patients receiving TJA in the Dominican Republic. (Line 50-51)

Referee Comment: Poor intraop hemodynamic control is going to be dependent on how many co-interventions are utilized by the anesthetist: fluids, anti-hypertensives /vasopressors, and even type of anesthetic used.

Author Response: Based on our a priori definition, poor intra-operative hemodynamic control is objective and based on mean-arterial pressure measurements. Co-interventions are a response to poor intra-operative hemodynamic control. Specifically the interventions mentioned in this comment (fluids, anti-hypertensives/vasopressors) are typically used by our anesthesia team to keep MAP within our pre-defined MAP range, thereby meaning that sustained pressures falling out of this range is highly significant and of great concern. Finally, the majority of patients in our cohort received spinal anesthesia (89%) thereby reducing the potential impact of anesthesia type on hemodynamic control. Further, based on our analysis there was no significant difference found in hemodynamic control based on anesthesia type (Table 3).

Referee Comment: Furthermore, this is not an area of interest to most orthopaedic surgeons with little control by the surgeon during the surgery.

Author Response: Poor hemodynamic control during orthopaedic procedures has the potential to adversely impact overall patient outcome after the procedure. As discussed in the introduction of the submitted manuscript, Mortazavi et al. found that intra-operative heart rate excursion and cardiac abnormality increase the risk for perioperative stroke. The authors caution that the
potential for non-orthopaedic complication after orthopaedic procedures is under-recognized by orthopaedic surgeons. We believe that orthopaedic surgeons and anesthesiologist can collaborate to attenuate the risk of perioperative complication by achieving good intra-operative hemodynamic control. The reporting of our study is an important first step in this direction. We emphasize this point in our discussion.

Revised text: The risk for complication due to poor intra-operative blood pressure control during TJA is under-appreciated by the orthopaedic community. There is evidence in the orthopaedic literature that poor intra-operative blood pressure control is associated with increased risk for complication after TJA. One prior study found that systolic blood pressures above 150.6±9 mmHg significantly increased the risk of myocardial infarction in a cohort of patients undergoing a variety of non-cardiac procedures (orthopedic procedures represented greater than 50% of procedures in this study). Another study found that an intraoperative arrhythmia or other alteration in heart rate during TJA increased the risk of perioperative stroke. To our knowledge no prior studies have systematically investigated risk factors for poor hemodynamic control during orthopedic procedures. Risk factors for poor blood pressure control identified in the primary care setting include: age, gender, obesity, race and presence of diabetes/impaired fasting glucose. (Line: 284-295)

Referee Comment: Conclusion: Do these patients warrant further attention and medical optimization prior to TJA? With 40% incidence and low complications in most series of primary TJA, I am not sure one can make this statement. What further optimization will occur preop and is there any evidence to suggest this will prevent the high incidence of poor intraoperative hemodynamic control or that this will have any effect on patient important outcomes?

Author Response: Our patient series is unique as it comprises a population at high risk for hypertension and poor hemodynamic control. The high prevalence of poor hemodynamic control although unrepresentative provides us a rich opportunity for analysis and identification of risk factors. We believe that if risk attenuation and medical optimization is applied on the at-risk population identified in this study (hypertensive and obese patients) we will have significant opportunity to decrease mortality and morbidity on a population level.

As discussed in the manuscript, further optimization comprises of pre-operative blood pressure control and possible weight loss. We concede that weight loss goals will likely be difficulty and thus pre-operative interventions should be largely medico-therapeutic.

We also understand that there is a great deal of uncertainty in this area of patient outcome and thus we have added:

Revised text: More work is required to elucidate the relationship between these risk factors and overall outcome. (Lines 67-68)

Referee Comment: Manuscript: What was the incidence of complications in your series?
**Author Response:** We are unable to report on the incidence of complication in our series as these data were not prospectively collected. We acknowledge in our revised manuscript that our study findings are limited by the lack of a reported complication rate.

**Revised text:** A potential limitation of the present study is that the small sample size precludes stable peri/postoperative outcome data such as deaths and cardiac and other complications. As such we do not report a complication rate. (Line: 340-342)

**Referee Comment:** Are all intraoperative rhythm disturbances indicative of sub-optimal hemodynamic control?

**Author Response:** In our study population, we define intra-operative rhythm disturbances as: atrial fibrillation, atrial flutter, atrial/ventricular premature contractions and abnormal rhythms. While rhythm disturbances cannot be definitively attributed to sub-optimal hemodynamic control, physiologic principles suggest that rhythm disturbances of the heart are related to hemodynamic control and tissue perfusion. Namely, poor hemodynamic control can lead to hypoxemia and end organ ischemia. An early manifestation of this is cardiac dysrhythmias. In addition, dysrhythmias (especially fibrillations and flutters) contribute to stasis of blood in the heart which in turn increases the risk of intra-vascular clotting and perioperative thrombo-embolic event. This concept is widely accepted and even finds support in the orthopaedic literature (Mortazavi et al-- increased stroke risk with cardiac dysrhythmias). We have clarified this in the methods.

**Revised text:** Similarly, intraoperative rhythm disturbance was considered a proxy for sub-optimal hemodynamic control as we considered this to be potentially related to inadequate tissue perfusion. (Line: 199-201)

**Referee Comment:** Similarly, blood transfusions can also occur in the absence of large hemodynamic changes.

**Author Response:** Specific to our mission trips to the Dominican Republic, packed red bloods were an expensive and precious resource and thus transfusions were strictly reserved for patient cases with difficult hemodynamic management. Thus, in our study population, blood transfusions signified sub-optimal hemodynamic control. We clarify this in our Methods.

**Revised text:** Intra-operative blood products refers to intra-operative transfusion of packed red blood cells. Utilization of intra-operative blood products signified sub-optimal hemodynamic control as these agents were utilized at the discretion of the anesthesiologist in cases where the patient had difficult hemodynamics and there was concern for inadequate tissue perfusion. (Line: 195-199)

**Referee Comment:** Descriptive data: please provide some measure of dispersion for the average MAP (line 216)

**Author Response:** We agree with this suggestion and have added:
Revised text: Average preoperative mean arterial pressure was 109.0 ± 13.4 mmHg [corresponding to an average SBP of 149 ± 22.1 mmHg and DBP of 89 ± 11.3 mmHg]. (Line 230-231)

Referee Comment: It is likely that patients with pre-op hypertension do not respond to intraop management as well because they are already on anti-hypertensive medications.

Author Response: Bivariate analysis (Table 3) shows that being on an anti-hypertensive does not significantly increase the risk of poor hemodynamic control. Further when the pre-operative use of anti-hypertensives was incorporated into multivariate analyses it did not elevate the risk of poor hemodynamic control in a meaningful way.

Referee Comment: How many patients did you have with RA? Saying that RA was protective with such a wide 95% CI that crosses 1.0 may be misleading, particularly if your sample size of RA subjects is relatively small.

Author Response: We had 18 patients (15%) with rheumatoid arthritis. We agree that our current phrasing is confusing and we have changed this to:

Revised text: Patients with rheumatoid arthritis (RA) had a non-statistically significant decreased risk for poor hemodynamic control (RR 0.6; 95% CI 0.3 – 1.4). (Line 255-256)

Referee Comment: Longer duration of surgery gives the patient more opportunity to have a period of uncontrolled hypertension and is not a clinically useful variable because the surgeon cannot change the duration of surgery and this is unlikely to be changed with pre-op optimization.

Author Response: We agree that because longer surgeries have more data points there are additional opportunities for subjects to experience poor hemodynamic control. Further, as explained earlier, we have investigated the association between bilaterality and duration of surgery and have excluded duration of surgery from our multivariable models. Given the close association between bilaterality and duration of surgery clinicians can potentially control whether surgery is bilateral or unilateral.

Referee Comment: While I appreciate large prolonged changes in intraoperative blood pressure likely adds physiologic stress, I do not feel we know enough to find a clinically useful definition of “poor control.”

Author Response: We agree with this assessment. In our “Methods” section on “Definition of hemodynamic control” we concede that there is no consensus in the literature on optimal intraoperative hemodynamic control and as such it is difficult to create a definition for poor control (Line 186-189). Our definition however is derived from observations of prior literature (although lacking), consultation with anesthesiologists that worked on this project as well as anesthesiologists at our institution. To further concede this point we have added to our discussion:
**Revised text:** Finally, given the paucity of clinical data on intra-operative blood pressure control and its relationship to outcome, we cannot advocate our a priori definition of poor intra-operative blood pressure control as a standard definition. (Line 348-351)

**Referee Comment:** Line 286: “unacceptable hemodynamic control” Is your definition of uncontrolled hypertension unacceptable for patients to experience when undergoing TJA? I don’t know, but given the high safety of TJA and the high incidence of uncontrolled hypertension in your series, I am not convinced this statement is true.

**Author Response:** We appreciate this suggestion and we have replaced the term “unacceptable” with “poorly controlled”. We also add a justification for using “poor hemodynamic control” as our primary outcome.

**Revised text:** …poorly controlled hemodynamic control…(Line 311-312)

**Revised text:** These data linking poor intra-operative hemodynamic control with adverse outcomes provide the justification for our use of poor hemodynamic control as the primary outcome variable in this study. (Line 280-283)

**Referee Comment:** Line 297: These patients should be medically optimized. What would you suggest?

**Author Response:** We expand on strategies for medical optimization:

**Revised text:** …patients selected for total joint arthroplasty are carefully optimized prior to admission for surgery. These efforts should include assessment of adherence to prescribed pharmaco-therapeutics as well as attention to non-pharmacologic approaches (dietary, lifestyle). (Line 336-339)

**Referee Comment:** The controlled hypertensive group also had an increased RR for poor hemodynamic control. I would think these patients would have met the definition for medically optimized.

**Author Response:** The data in our manuscript does not support this assertion. Patients with controlled hypertension had a RR 1.3 (0.3, 5.0) while the uncontrolled hypertensive group has a RR 3.7 (1.3, 10.7) [Table 3]. This supports our assertion that prior medial optimization attenuates the risk for poor hemodynamic control.

**Referee Comment:** Furthermore, I am still not convinced this would change the outcome for patients. Preop weight loss for patients with end-stage arthritis is very difficult and unlikely to occur.
Author Response: We concede that pre-operative weight loss for patients with end-stage arthritis would be difficult, however by elucidating the risk associated with obesity and hypertension, healthcare providers can seek to more aggressively control blood pressure given the difficulties associated with weight reduction. We hope to encourage debate thereby exhorting orthopaedic surgeons and anesthesiologist to further investigate this area of orthopaedics.

Revised text: Managing the risks associated with obesity will be particularly challenging for the orthopaedic surgeon given the difficulty of perioperative weight loss in the osteoarthritic population. (Line: 308-310)