**Reviewer's report**

**Title:** Obesity and statins are both independent predictors of enhanced coronary arteriolar dilation in patients undergoing heart surgery

**Version:** 1  **Date:** 15 November 2012

**Reviewer:** Shawn Bender

**Reviewer's report:**

This study by Cassuto et al was designed to examine the impact of obesity, adjusted for co-morbidities and pharmacological interventions, on the dilator function of human coronary arterioles. Endothelium-dependent dilation to bradykinin was determined in atrial coronary arterioles from 64 patients and various statistical analyses were utilized to interrogate the data set. A strength of this study is the use of human tissue, however, the findings are largely confirmatory of previous work by this group. Furthermore, the physiological relevance of the findings is difficult to discern given the mild functional effects described and the lack of patient follow-up.

**Comments:**

1. This group reported in 2007 (citation 11) that obese hypertensive patients have increased coronary vasodilator responses compared to lean hypertensive patients. The patient population utilized in this study largely mirrors these groups as 89% of non-obese and 86% of obese patients studied were hypertensive. Thus, the results presented in Figure 1 are confirmatory of this previous work and no additional experiments are presented to provide additional mechanistic insight into coronary arteriolar function in these patients.

**Major Compulsory Revisions:**

1. This group's previous work (citation 11) demonstrated that the increased dilation in obese hypertensives (compared to lean hypertensives) was due primarily to enhanced endothelium-independent dilation since BK responses were not different but those to SNP were enhanced. Why were SNP responses not determined in this study? The results of the present study should be more clearly discussed in the context of the previous report by this group (citation 11) in the Discussion. Furthermore, in the absence of SNP responses, the conclusion at the beginning of the Discussion that ‘obesity and statins are independent predictors of enhanced endothelium-dependent dilation of coronary arterioles’ is not supported as these results could be explained entirely by enhanced smooth muscle endothelium-derived vasodilators as reported in citation 11.

2. The text regularly refers to ‘enhanced dilator function of coronary arterioles from obese patients’. This statement is not supported by the data since ‘maximal’ dilation to BK is similar between obese and non-obese and with and without statin use. These statements must be amended to refer to the noted differences in arteriolar sensitivity (ie, EC50) among the various groups. The title must also
be similarly amended to accurately reflect the data set.

3. The Discussion is currently too long. The attempt to clearly describe the cited studies is appreciated; however, these descriptions should be shortened and more time should be spent integrating the present results with the groups previous work (see comment 1).

4. Presentation of the data as 'trends' is inappropriate, particularly with p values of 0.2 and above as reported. This is done in the text in reference to the difference in BK dilation between obese and non-obese patients and to the effect of ACE inhibitors on coronary dilation. These are not significant differences and should be addressed accordingly.

5. It is not clear to this reviewer if the use of complex statistical analysis on such a small patient population is appropriate. Thus, I am recommending further statistical review.

6. Please report the percent development of spontaneous tone for the coronary arterioles used in the study in the Results.

7. It is unclear why BMI was correlated with % Dilation to BK in Figure 1B when the percent dilation curves were not different between groups. It seems more appropriate that such an analysis be done between BMI and the EC50 for BK since this variable is significantly different between the groups. Figure 1B is not necessary in its current form.

8. Discussion of the results with regard to their specific physiological relevance is inadequate. Specifically, what potential relevance is a modest increase in coronary arteriolar sensitivity to BK (with obesity or statin treatment) in heart disease patients? The discussion of the obesity paradox is appreciated but does not address mechanisms underlying the control of coronary blood flow. Since BK stimulates the release of endothelium-derived dilators and it can be assumed that most of the patients have ischemic heart disease (given the large percentage of CABG patients) it would be pertinent to discuss the increased role for endothelial-derived dilators like NO in the control of coronary flow in ischemia compared to non-ischemic states where NO plays little role.

9. Given the worsened clinical outcome of patients who are morbidly obese and underweight (presented in the Discussion), do the noted differences in BK sensitivity remain after the 7 patients who fall into these categories are removed from the data set? Inclusion of these patients appears somewhat confounding in the analysis of obese vs non-obese, especially in light of the obesity paradox.

Minor Essential Revisions:

1. In the Abstract, it appears that the SD or SE reported for the BK responses in obese and non-obese patients is incorrect as it does not correspond to that shown in Figure 1A. The Abstract values are 25% and 27% while in the figure these appear to be ~5%.

**Level of interest:** An article of limited interest
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