Author's response to reviews

Title: Predictor of Poor Coronary Collaterals in Chronic Kidney Disease Population with Significant Coronary Artery Disease

Authors:

Po-Chao Hsu (pochao.hsu@gmail.com)
Suh-Hang Juo (hjuo@kmu.edu.tw)
Ho-Ming Su (cobeshm@seed.net.tw)
Szu-Chia Chen (scarchen@ms57.url.com.tw)
Wei-chung Tsai (azygo91@gmail.com)
Wen-Ter Lai (wtlai@cc.kmu.edu.tw)
Sheng-Hsiung Sheu (sheush@kmu.edu.tw)
Tsung-Hsien Lin (lth@kmu.edu.tw)

Version: 2 Date: 9 July 2012

Author's response to reviews: see over
Dear editor:

The authors revised an original article entitled ‘Predictor of Poor Coronary Collaterals in Chronic Kidney Disease Population with Significant Coronary Artery Disease’ to BMC Nephrology. We provided a point-by-point response to editorial and each of the referees’ concerns as follows:

To editorial:
- Ethical Committee
Can you please include the full name of the ethical committee that granted approval for your study.

Ans:
We already included the full name of the ethical committee in our revised manuscript. The full name is ‘Kaohsiung Medical University Hospital- Institutional Review Board’

(added in line 16-18 on page 6, revised manuscript)

To Reviewer 1

1. Overall patient characteristics (Including hemoglobin level, smoking habits, previous coronary events etc.) should be provided in a separate table.

Ans:
We divided the data including hemoglobin level, smoking habits, previous coronary events etc. into 2 tables. Table 1 is baseline characteristics and table 2 is angiographic characteristics in patients with poor and good collateral.

(added in Table 1 & Table 2 revised manuscript)

2. Severity of coronary artery disease should be described more precisely. Assessment of coronary narrowing by using quantitative coronary angiography and including patients with more than 70% narrowing in a coronary artery is not enough for this study population. a) How many patients had multivessel disease? Please clarify, b) Severity score of the coronary artery disease should be calculated with using a known index such as Gensini Index.
Ans:
a). We already revised these data in the table 2. There are totally 143 patients with significant multi-vessel disease (>=2 vessel disease).

(added in table 2, revised manuscript)
b). We also showed the severity score of CAD in Table 2. There are several scoring methods such as "vessel score", "diffuse score," and "Gensini score" used to evaluate the extent and severity of coronary atherosclerosis. Because we ever used "diffuse score" to evaluate the severity score of CAD in previously published paper (Am J Hypertens. 2010 Sep;23(9):960-6.), we also used "diffuse score" in our Table 2 and text.

(added in lines 15-19 on page 8, lines 1-6 on page 9, and table 2, revised manuscript)

3. As Authors stated in limitation section, Rentrop classification system is a semiquantitative angiographic grading systems for the assessment of coronary collateral development. Moreover, Rentrop scoring had been originally defined by double injection into both main coronary arteries and by balloon occluding collateral receiving artery. Therefore, this scoring has important inherent limitations and in order to cope with its deficiencies, spontaneously visible collaterals could have been described with more details. For instance, describing angiographic collateral connection grades and pathways (angiographically) would have been very helpful

Ans: We also evaluated the collateral connection grades and pathways and showed the data in our methods and results section.

(added in lines 5-14 on page 8, lines 16-19 on page 10, lines 1 on page 11, revised manuscript)

4.

In the presence of multivessel disease (more than one significant lesion), it is not clear why collateral scoring had only been performed by choosing the vessel receiving highest degree of collateral flow. Instead of this, collateral score could have been calculated by summing the Rentrop numbers for each patient.

Ans: According to the previous literatures, there were several papers using different methods to classify the collateral vessels. Some literatures also used the collateral grading methods as shown in our paper. Dincer I et al. (Am J Cardiol. 2006 Mar 15;97(6):772-4) and Kocaman SA et al. (Atherosclerosis. 2008 Apr;197(2):753-6) also dichromized collateral grade into poor and grade, Gulec S et al. (Eur J Clin Invest. 2006 Jun;36(6):369-75) also used the higher collateral grade to analyze their data.
However, there were also some literatures summing the Rentrop numbers of every patients to calculate the collateral score. In our paper, we used the former methodology to evaluate the collateral scoring.

5.
How many patients had more than one collateral receiving artery? In other words, how many patients had multivessel disease?

Ans: We already revised these data in our Table 2. There are totally 143 patients with significant multivessel disease (≥2 vessel disease).
(added in table 2, revised manuscript)

6.
It is hard to explain/understand the difference found between the number of disease vessel and collateral development. In Table 1, it seems patients with poor collateral vessel had numerically fewer vessel disease with compared to those with good collaterals. If the authors had calculated collateral score by summing Rentrop numbers of each collateral receiving artery, this finding would have been expected. Nevertheless, they calculated collateral score based on the vessel, which was receiving highest degree of collateral flow. Furthermore, in the presence of severe multivessel disease, it has been expected that the collateral supplying vessel could also be affected from the atherosclerotic process (as a part of multivessel disease), which eventually turn out to be poor collateral flow quality toward the collateral receiving artery. At this point, knowing the number of the patients who had multivessel disease and the disease status of the collateral-supplying vessel became more critical.

Ans:
We fully understand Reviewer’s concern. However, the development of coronary collaterals is an adaptive response to chronic myoischemia and serves as a conduit bridging the significantly stenotic coronary vessels. More severe and extensive myocardial ischemia such as multi-vessel diseases may further stimulate the development of coronary collateral circulation. Hence, patients with good coronary collaterals appear to have a more extensive CAD. In previous studies, number of diseased vessels is also found to be a significant predictor of good collateral formation such as Gulec S et al ’s (Eur J Clin Invest. 2006 Jun;36(6):369-75) and Resar JR et al’s studies (Chest. 2005 Aug;128(2):787-91.)
We also showed the angiographic characteristics in patients with poor and good collateral in Table 2 (Including number of diseased vessels & severity score of CAD).

In our study, severity score evaluated by diffuse score was also significantly different between the 2 groups, which is similar to the results of number of diseased vessels.

(added in table 2, revised manuscript)

7. Were there any differences between collateral grades in different CKD stages?

Ans: No, we already added the data in our manuscript.
(added in lines 1-3 on page 11, revised manuscript)

8. Please include age as a variable in regression analysis.

Ans: We already added other variables such as age, BMI, dyslipidemia in the univariate regression analysis.
(added in lines 12-16 on page 11, and table 3, revised manuscript)

9. Since the effects of diabetes and hypertension on collateral vessel development could have only been analyzed in CKD population, we cannot discriminate their effects from the effect of CKD. In other words, effects of hypertension and diabetes might have potentiated (exaggerated) by the CKD?

Ans: We totally agree with reviewer’s comments. Hypertension is both a cause and consequence of CKD. Blood pressure in CKD patients is increased due to fluid overload and production of vasoactive hormones via renin-angiotensin system which might aggravate hypertension. Diabetes is also another leading cause of CKD. Insulin and glucose homeostasis are altered in the patients of end stage renal disease and even in the early stages of CKD, leading to insulin resistance by a variety of pathways. Insulin resistance is reported to increase with the progression of CKD, which also plays an important role in the pathogenesis of hypertension. Hence, CKD might further potentiate hypertension and diabetes and cause poor coronary collateral formation. Our paper found that in the CKD subjects hypertension and diabetes is really a negative predictor of coronary collateral development. This conclusion is only applied in the CKD population.
To Reviewer 2:

Major Compulsory Revisions:

1- Statistic section:
(a). authors should also show univariate analysis and list predictors of poor collaterals (even in a table) as well as explain the selection criteria for entering variables in multivariate analysis.
(b). Therefore, in statistical section, they should mention which kind of test they performed to assess OR for combined risk. It would be interesting to know (and to discuss) why they selected the combination of diabetes mellitus and hypertension rather than the other combinations.

Ans:
(a). We already revised our tables to show the both of univariate and multivariate analysis.
In our statistical section we add “Subsequently, significantly correlated variables in the univariate analysis or relevant variables were further analyzed by multivariate logistic regression analysis to predict the collateral development (poor vs. good).”
(b). In our study, only hypertension, diabetes and number of diseased vessels were significant predictors of poor coronary collaterals in multivariate logistic regression analysis. In the real world practice, physicians usually evaluate patients’ risk based on clinical parameters. It’s difficult to know the number of diseased vessels without tests such as invasive angiography. In contrast physician can easily know patients’ comorbidity such as hypertension and diabetes by history taking. Our paper showed that hypertension and diabetes had negative synergistic effect on coronary collateral development, which can be practically used in clinical setting.
(C) We used linear-by-linear association analysis to test their interaction on the collateral development and binary logistic regression to test their combined risk.

2-Furthermore, the aim of this paper appears to be more clinical than insight to pathophysiology. There are a number of mechanisms of signal transduction hypoxia-related, which have been demonstrated involved in collaterals development
(e.g. hypoxia-inducible factor, HIF-1). It could be interesting if authors could highlight more this issue in the discussion, with regard to the particularly critical subset of CKD patients.

Ans: We already added the issue in our revised manuscript.  
(added in lines 9-16 on page 13, revised manuscript)

3-
(a) Authors stated that "gender, age, duration of chest pain, history of diabetes mellitus, hypertension, hypercholesterolemia, cigarette smoking, and medications" had been included in the analysis. A detail list of medications should be included in table 1, including ACE-i, ARBs as well as statins prevalence.

(b) Furthermore, statins have been demonstrated increase collateral coronary development (Pourati, Am Heart Jorn, 2003): did authors perform statistical analysis including statins and, if so, which are their results?

Ans:
(a). We already added the list of medications in table 1 including anti-PLT, ACEI, ARB, BB, nitrate, CCB, diuretic, and statin.
(b). In our revised table 1, statin did not have significant difference between good and poor collaterals group. (p = 0.159).  
(added in Table 1, revised manuscript)

Minor Revisiones:

1-Some punctuation slips:
Methods (study design, line 14): please add the point
Ans: We already revised the article.

Discussion, line 10: please add the closing parentheses
Ans: We already revised the article.

Discussion, line 50: please add the point
Ans: We already revised the article.

2-Result Section (line 5): "male and female", please correct.
Ans: We already revised the article.
3-Results Section: prevalence results as compared in the text are slight different from expressed in table 1 (43.5% in the text, 43.8 % in the table)
Ans: We are sorry for the mistakes. Correct data is 43.8%. We already revised the article.

4-Discussion (line 3): prevalence of CKD patients with no collaterals results 42.4% while it results 42.6% in the Result section
Ans: We are sorry for the mistakes. Correct data is 42.6%. We already revised the article.

5-Table 2: Please sort variables used for logistic analysis in the order as they appear in the text.
Ans: We already revised the Table 2.
(in Table 2, revised manuscript)

Sincerely yours,

Po-Chao Hsu Suh-Hang H Juo
Ho-Ming Su Szu-Chia Chen
Wei-Chung Tsai Wen-Ter Lai
Sheng-Hsiung Sheu Tsung-Hsien Lin

Corresponding author: Dr. Tsung-Hsien Lin

Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Tzyou 1st Road, Kaohsiung. 80708, Taiwan, ROC

E-mail: lth@kmu.edu.tw, Tel: 88673121101 ext 7738, Fax: 88673234845

2012/07/9