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学 位 論 文 名	心血管疾患入院患者における腎血管抵抗で層別化した収縮期血圧と心血管イベントリスクの関係: J-VAS 研究
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## 論文内容の要旨

### 1 研究目的

The threshold of blood pressure (BP) reduction in cardiovascular patients is debatable due to the J-shaped curve phenomenon, which is particularly observed in patients with increased arterial stiffness. The renal resistive index (RRI) correlates well with systemic arterial stiffness; therefore, we aimed to demonstrate the role of RRI in guiding the choice of optimal BP.

### 2 研究方法

A retrospective analysis of prospectively collected data of the hospitalized cardiovascular patients at Jichi Medical University Hospital. All patients had the RRI measurement performed and were assigned to a higher ( $RRI \geq 0.8$ ) or lower RRI group. Each group was subdivided by quartiles of the BP at discharge. The primary endpoints were fatal and nonfatal cardiovascular events, including heart failure (HF), acute coronary syndrome (ACS), acute aortic disease (AAD), acute arterial occlusion, and stroke.

### 3 研究成果

The mean follow-up period was 1.9 years (3,365 person-years),  $n = 1,777$  (mean age 64.7 years). There were 252 cardiovascular events occurred, 24.0% and 12.2% in the higher and lower RRI populations,  $P < 0.001$ . In the higher RRI group, the lowest systolic BP (SBP) quartile ( $<105$  mm Hg) was a risk factor for cardiovascular events when compared with the highest SBP quartile ( $\geq 130$  mm Hg; adjusted hazard ratio, 2.42; 95% confidence interval, 1.17–5.03;  $P = 0.017$ ). A 1 SD decrease of SBP (17.5 mm Hg) was associated with a 25% increase in the risk of cardiovascular events. In the lower RRI group, these associations were not observed.

#### 4 考察

There was an inverse linear association between SBP and the risk of future cardiovascular event. The lowest SBP quartile had a significant impact on future cardiovascular event in the subgroup with  $\text{RRI} \geq 0.8$  but not in the subgroup with  $\text{RRI} < 0.8$ . The possible explanation of this findings was the associated progressive of arterial stiffness in the group with higher RRI, according to the previous literatures, a J-shape curve phenomenon was found in this selected group of patients, whose arterial stiffness was represented by wide pulse pressure or high pulse wave velocity. Furthermore, a very low blood pressure was reported to be associated with brain damage, cognitive impairment, and complications such as syncope and falling that also lead to poorer outcomes. The present study also found that patients with higher RRI had significantly lower estimated glomerular filtration rate (eGFR) and may also have had worsen the long-term outcome, especially when the BP was kept too low.

#### 5 結論

Lower SBP at discharge was associated with a risk of cardiovascular events in the hospitalized atherosclerotic cardiovascular patients with  $\text{RRI} \geq 0.8$ .

### 論文審査の結果の要旨

Dr. Praew Kotruchin found that lower systolic blood pressure at discharge was associated with a risk of cardiovascular events in hospitalized cardiovascular patients with high renal resistive index (RRI) ( $\geq 0.8$ ) as measured using ultrasonography in a retrospective analysis of prospectively collected data from hospitalized cardiovascular patients.

This study has a large sample size ( $n = 1,777$ ), which increased the robustness of the results. Hospitalized cardiovascular patients were classified according to RRI value and subsequently followed up to the time of first cardiovascular event after discharge. This approach can be considered both novel and relevant, and the study results support the use of RRI for the stratification of atherosclerotic cardiovascular patients and its potential use as a tool for guiding the choice of optimal blood pressure threshold in hospitalized cardiovascular patients. Overall, these results represent important findings regarding appropriate blood pressure control in cardiovascular patients with variable arterial stiffness.

Based on these considerations, this manuscript is determined to be appropriate as a thesis. Additionally, the partial update to the manuscript described in “Results of Defense” is adequately described.

## 試問の結果の要旨

Dr. Praew Kotruchin has shown that lower systolic blood pressure at discharge is associated with increased risk of cardiovascular events in hospitalized cardiovascular patients with high renal resistive index (RRI) ( $\geq 0.8$ ), measured using ultrasonography in a large retrospective analysis of prospectively collected data from Jichi Medical University Hospital. The study has already been published in high-quality English-language journals. The presentation given by Dr. Kotruchin was clear and straightforward, and all questions and comments from the members of the judging committee were responded to appropriately. The following are the questions from the members of the judging committee and Dr. Kotruchin's responses.

Comments: Using a large clinical dataset, the applicant revealed the relationship of RRI to blood pressure and cardiovascular events. Although the results have been published previously, the reviewer has some questions about the analytical methods. Because both RRI and blood pressure are numerical data, the applicant should first use them directly in the proportional hazard models to observe the physiological existence of these relationships. By transferring the numerical data into categorical data using a cut-off point or division into quartiles, the amount of data is decreased. Of course, analyses such as that described in this theses are important, but should perhaps be supplemental information. The cut-off point might be arbitrary. This is a retrospective follow-up study using clinical data. Therefore, standardization of the evaluation of RRI and endpoints was limited. If the applicant plans to undertake further research on this subject, the reviewer recommends the use of a prospective follow-up study with optimal standardization.

Response: In response to the reviewer's comment, Dr. Kotruchin has performed Cox regression models adjusted for age, sex, diabetes mellitus, hypertension, smoking, body mass index, serum creatinine level, low-density lipoprotein, and high density-lipoprotein in the total population and found that, as continuous variables, RRI (per 1-SD) and systolic blood pressure at discharge (per 1-SD) were both associated with the primary composite endpoint (HR, 1.15; 95% CI 1.01–1.33;  $P = 0.045$ , and HR, 0.84; 95%CI 0.73-0.97;  $P = 0.014$ , respectively).

Comment: Renal vascular resistance is equivalent to pulse wave velocity (PWV). Isn't PWV sufficient? What is the advantage of using renal vascular resistance?

Response: Although PWV and RRI correlate well with each other, PWV represents large-artery pathology while RRI represents small-artery pathology. Furthermore, from the available evidence, RRI has been shown to be associated with both cardiovascular and renal

morbidity and mortality when combined with estimated glomerular filtration ratio (eGFR), which is its advantage.

Comment: I think renal vascular resistance is a good indicator, but there may be a significant inter-operator difference between the technicians performing the tests. What were variations between laboratory technicians?

Response: We were also concerned about potential variations between laboratory technicians; therefore, the same sonographer performed all RRI measurements in the present study. However, if we carry out a multicenter study in the future, all sonographers who will perform RRI measurements will be trained on the same protocol prior to participation in the study.

Comment: In Figure 4, the difference between Q1 group and Q4 group decreased from that reported 3 years ago. What is the reason for this decrease?

Response: This decrease can be explained by a reduction in population size over time.

Comment: Do drugs that reduce renal vascular resistance improve the prognosis of patients with low systolic blood pressure?

Response: Renal vascular resistance is a gradual process, meaning that drugs that can modify the RRI, such as renin–angiotensin system blockers, may have long-term benefits. However, few prospective trials examining this hypothesis have been reported. In the present study, patients with low blood pressure were found to have a poorer prognosis, and renin–angiotensin system blockers were administered to these patients in the acute phase, they may be more harmful than beneficial. Therefore, it is recommended to initiate these drugs in an outpatient titration setting in patients in a stable condition.

Comment: As a single-center study, this research is successful. Do you plan to verify the results of this research at multiple centers in the future?

Response: I plan to initiate a multi-center and/or multi-ethnic trial in the future.

Comment: How do you wish to extend this research in the future?

Response: I plan to examine RRI and cardiovascular prognosis in acute cardiovascular patients in the emergency room of my institution (Khon Kaen University), given the limited data available in Southeast Asian populations.

Comment: What is the mechanism of your finding that lower systolic blood pressure at discharge was associated with an increased risk of cardiovascular events in hospitalized cardiovascular patients with renal resistive index (RRI) > 0.8 as evaluated using ultrasonography?

Response: The progression of arterial stiffness is believed to result from a greater risk of decreased SBP, the so-called J-curve phenomenon. RRI was also found to correlate well with systemic hemodynamic parameters such as pulse pressure and pulse wave velocity, which represent arterial stiffness. Our study confirms these observations, since the impact of low SBP was observed only in the group with higher RRI, which represented progressive arterial stiffness, while in the group with lower RRI, no impact of SBP on future cardiovascular events was observed. These results support the role of RRI as a parameter for the stratification of atherosclerotic cardiovascular patients and indicate its potential use as a tool for guiding the choice of optimal BP threshold.

Comment: There appears to be a typo in the number of patients in Table 6.

Response: I will correct this. (Dr. Kotruchin correctly revised this error.)

Based on the above presentation and the question and answer session, all members of the judging committee were in agreement that Dr. Praew Kotruchin should pass this Defense.