Renin Activity as a Key Predictor of Major Adverse Cardiac Events

Takahisa Kondo, MD, PhD; Yoshihisa Nakano, MD, PhD;
Shiro Adachi, MD, PhD; Toyoaki Murohara, MD, PhD

In recent decades there has been substantial improvement in the prognosis of acute myocardial infarction (AMI), mainly because of advances in the rapid restoration of coronary blood flow by percutaneous coronary intervention, as well as in secondary prevention therapies.¹ However, patients with clinical complications such as cardiogenic shock, heart failure, and chronic kidney disease at the onset of AMI still have a poor prognosis.

The renin-angiotensin system (RAS) is a complex system that regulates systemic functions through body salt and blood volume control.² The RAS also exerts proliferative action at the vascular level, leading to angiogenesis and the progression of atherosclerosis^{3,4} thereby contributing to the development of ischemic heart disease.⁵ Furthermore, RAS activation is a key mechanism in cardiac remodeling in patients with AMI and of disease progression in those with ischemic and non-ischemic heart failure;⁵ chronic overactivation of the RAS is associated with cardiovascular adverse events.⁶ The occurrence of these processes in AMI

Article p1324

is further supported by the fact that angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers have beneficial effects in patients with hypertension, myocardial infarction, and heart failure.^{7–9}

In the acute phase of hospital admission for AMI, activation of both the sympathetic nervous system and the RAS system has been observed; these activations subside within the first 72 h in patients without left ventricular dysfunction and overt heart failure.¹⁰ In contrast, persistent RAS activation at the time of hospital discharge is an independent predictor of cardiovascular disease death in postinfarction patients.¹¹ However, the meaning of an elevation in plasma renin activity (PRA) on admission remains unascertained in the setting of AMI.

In this issue of the Journal, Kamon et al¹² report that elevated PRA on admission was independently associated

Figure. Possible mechanisms of elevation in plasma renin activity in patients with acute myocardial infarction. High plasma renin activity on admission was an independent predictor for poor prognosis. ACE, angiotensin-converting enzyme, ARB, angiotensin receptor blocker.

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received April 10, 2019; accepted April 13, 2019; J-STAGE Advance Publication released online April 25, 2019

Department of Advanced Medicine in Cardiopulmonary Disease (T.K., Y.N.), Department of Cardiology (S.A., T.M.), Nagoya University Graduate School of Medicine, Nagoya, Japan

The Guest Editor for this article was Dr. Yoshihiko Saito.

Mailing address: Takahisa Kondo, MD, PhD, Department of Advanced Medicine in Cardiopulmonary Disease, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. E-mail: takahisa@med.nagoya-u.ac.jp

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

with major adverse cardiac events (MACE, defined here as cardiovascular death and hospitalization for heart failure) in 878 AMI patients who underwent emergency coronary angiography. These findings were consistent, regardless of previous medication with RAS inhibitors or β -blockers before the onset of AMI. The results were also consistent when the analysis included patients who were treated with diuretics in the acute phase.

How do we interpret these findings of Kamon et al? Did PRA increase as a result of acute reduction of renal blood flow caused by AMI and the subsequent decrease in cardiac output? Did the high PRA reflect the activation of neuro-hormonal factors and increased sympathetic tone after AMI? Did the high PRA merely reflect decreased fluid volume because of fasting? Or did the high PRA reflect the presence of comorbidity such as heart failure or kidney dysfunction in AMI patients? (**Figure**) As PRA is reportedly not correlated with plasma norepinephrine level or with atrial natriuretic peptide or B-type natriuretic peptide (BNP) level in patients with AMI and heart failure,^{13,14} PRA is unlikely to be a mere reflection of blood volume changes or sympathetic activity. With our current level of knowledge, we can say only that PRA is a neurohormonal biomarker for cardiovascular disease, but its role as a biomarker differs from that of BNP or N-terminal proBNP in the acute phase of AMI.

Kamon et al previously demonstrated that high PRA is a strong and independent prognostic indicator in patients with acute decompensated heart failure treated with RAS inhibitors.¹⁵ In the present study, they have extended this statement to include patients in the acute phase of AMI. In accordance with their findings, measuring PRA could constitute a new application of a classical method of risk stratification in the acute phase of AMI. The report by Kamon et al is of interest for the following reasons. First, high PRA at admission after AMI was associated with a poor prognosis independent of BNP level or ejection fraction. Therefore, measuring PRA on admission should facilitate improved selection of high-risk patients in combination with measurement of BNP or ejection fraction in AMI patients. Second, the findings will be useful from a clinical perspective, because PRA is a consistent prognostic indicator regardless of treatment with RAS inhibitors, β -blockers, or diuretics – a common scenario in patients with hypertension.

When interpreting the results, we need to keep several limitations in mind. Most importantly, this was a retrospective, single-center study, so generalization to other populations needs to be validated. Second, whether high PRA in AMI really reflects activation of the RAS remains unknown. Measuring angiotensin II and aldosterone together with PRA would provide deeper insights. Third, whether high PRA on admission is associated with chronic RAS activation must still be determined.

In summary, the study by Kamon and colleagues leads us to rediscover the importance of measuring PRA in the acute phase of AMI. High PRA on admission may help us

to select a subset of patients at increased risk of cardiovascular death or hospitalization for heart failure in the future.

Conflict of Interest Statement

T. Kondo and Y. Nakano belong to a department endowed by Actelion Pharmaceuticals Japan, Ltd.

References

1. Kihara Y. After the triumph of cardiovascular medicine over acute myocardial infarction at the end of the 20th century: Can we predict the onset of acute coronary syndrome? (Con). *Circ J* 2011; **75**: 2019–2026.
2. Krop M, Lu X, Danser AH, Meima ME. The (pro)renin receptor: A decade of research: What have we learned? *Pflugers Arch* 2013; **465**: 87–97.
3. Li P, Kondo T, Numaguchi Y, Kobayashi K, Aoki M, Inoue N, et al. Role of bradykinin, nitric oxide, and angiotensin II type 2 receptor in imidapril-induced angiogenesis. *Hypertension* 2008; **51**: 252–258.
4. Sata M, Fukuda D. Crucial role of renin-angiotensin system in the pathogenesis of atherosclerosis. *J Med Invest* 2010; **57**: 12–25.
5. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, et al. The cardiovascular disease continuum validated: Clinical evidence of improved patient outcomes. Part II: Clinical trial evidence (acute coronary syndromes through renal disease) and future directions. *Circulation* 2006; **114**: 2871–2891.
6. Masson S, Solomon S, Angelici L, Latini R, Anand IS, Prescott M, et al. Elevated plasma renin activity predicts adverse outcome in chronic heart failure, independently of pharmacologic therapy: Data from the Valsartan Heart Failure Trial (Val-HeFT). *J Card Fail* 2010; **16**: 964–970.
7. Verma S, Gupta M, Holmes DT, Xu L, Teoh H, Gupta S, et al. Plasma renin activity predicts cardiovascular mortality in the Heart Outcomes Prevention Evaluation (HOPE) study. *Eur Heart J* 2011; **32**: 2135–2142.
8. Ichiki T, Burnett JC Jr, Scott CG, Heublein DM, Miyata M, Kinugawa K, et al. Neurohumoral modulation during waon therapy in chronic heart failure: Subanalysis of Waon-CHF Study. *Circ J* 2017; **81**: 709–716.
9. Gwag HB, Lee GY, Choi JO, Lee HY, Kim JJ, Hwang KK, et al. Fate of acute heart failure patients with mid-range ejection fraction. *Circ J* 2018; **82**: 2071–2078.
10. Rouleau JL, Moya LA, de Champlain J, Klein M, Bichet D, Packer M, et al. Activation of neurohumoral systems following acute myocardial infarction. *Am J Cardiol* 1991; **68**: 80D–86D.
11. Rouleau JL, Packer M, Moya L, de Champlain J, Bichet D, Klein M, et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: Effect of captopril. *J Am Coll Cardiol* 1994; **24**: 583–591.
12. Kamon D, Okura H, Okumura A, Nakada Y, Hashimoto Y, Sugawara Y, et al. Plasma renin activity is an independent prognosticator in patients with myocardial infarction. *Circ J* 2019; **83**: 1324–1329.
13. Rouleau JL, de Champlain J, Klein M, Bichet D, Moya L, Packer M, et al. Activation of neurohumoral systems in postinfarction left ventricular dysfunction. *J Am Coll Cardiol* 1993; **22**: 390–398.
14. Emdin M, Fatini C, Mirizzi G, Poletti R, Borrelli C, Prontera C, et al. Biomarkers of activation of renin-angiotensin-aldosterone system in heart failure: How useful, how feasible? *Clin Chim Acta* 2015; **443**: 85–93.
15. Ueda T, Kawakami R, Nishida T, Onoue K, Soeda T, Okayama S, et al. Plasma renin activity is a strong and independent prognostic indicator in patients with acute decompensated heart failure treated with renin-angiotensin system inhibitors. *Circ J* 2015; **79**: 1307–1314.