Editorial

Potential value of circulating corin levels in acute and chronic myocardial infarction

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Comment on: Zhou X, Chen J, Zhang Q, *et al.* Prognostic Value of Plasma Soluble Corin in Patients With Acute Myocardial Infarction. J Am Coll Cardiol 2016;67:2008-14.

Received: 12 May 2017; Accepted: 30 May 2017; Published: 09 June 2017.

doi: 10.21037/jlpm.2017.05.10

View this article at: http://dx.doi.org/10.21037/jlpm.2017.05.10

In the heart, corin is a membrane-anchored, serine protease that cleaves and activates pro-ANP and pro-BNP, thereby modulating salt-water balance, vasodilatation and cardiac function (1). Cardiac corin can also be released from cardiomyocyte membranes and enter the circulation as a soluble form, where it can readily be measured in the blood. Recent studies have shown a linkage between circulating or soluble corin and a broad spectrum of cardiovascular diseases, such as heart failure (HF) (2-4), stroke (5), diabetes (6) and hypertension (7,8). The diagnostic and prognostic significance of circulating corin in acute myocardial infarction (MI) have also been explored (4,9-12). The interesting recent report by Zhou *et al.* (11) of 1,382 of MI patients, including patients with ST-segment elevation (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), is the largest study to examine the clinical significance of circulating corin in acute MI. They found that plasma corin was a useful predictor of major adverse cardiac events (MACE), including all-cause mortality, HF hospitalization, or recurrent AMI and all-cause mortality. They also found that plasma corin has an important prognostic value, particularly, in STEMI patients (11). Other studies have also examined the value of circulating corin in predicting the prognosis of MI patients (*Table 1*) (9,10,12), but the findings are not consistent among these reports.

The pattern of change in circulating corin levels in patients with acute MI varies among these studies (*Table 1*). In the Zhou *et al.* study, controls were not included (11), however, in other studies, levels of circulating corin post MI were increased (12), decreased (9,10) or even unchanged (4), when compared to controls. There are potential reasons for the differences between these studies. First, the temporal pattern of corin levels following acute MI is unknown. Acute MI is likely to enhance the release of corin into the blood from necrotic and perhaps ischemic myocytes. Consistent with this notion, patients with acute STEMI undergoing acute reperfusion by percutaneous intervention were found to have increases in corin levels that were correlated with the size of their MI (12). Acute STEMI is typically associated with greater release of troponin and other cardiac biomarkers, reflecting greater ischemic injury, than non-STEMI (13). Second, ischemic cardiomyocytes and activated inflammatory cells secrete proteolytic enzymes, such as cathepsins, calcium-activated neutral proteases and matrix metalloproteinases (14-16), which may degrade corin in the blood. Unfortunately, in many of these studies, blood samples were not treated with protease inhibitors (9-11) and the time period of storage before testing is unclear. It is also unclear whether serum or plasma measurements affect corin levels. Third, there are significant variations among these studies in the timing of blood sampling in relation to the onset of ischemia. *Table 1* shows that blood samples were collected from patients either on admission (11) or within 24 hours of admission (9,10). However the time of blood sampling in relation to the onset and duration of ischemic symptoms is unknown. Finally, there are differences among these studies in the patients studied; some studies only included STEMI patients (12), others represent a mixture of STEMI and NSTEMI (10,11), or acute coronary

Table 1 Summary of clinical studies related to circulating corin in acute MI

Reference	Patient enrolled in study	Blood samples used for corin assay	Period of observation	Relation between corin levels and outcomes
Zhou *et al.* (11)	1,382 patients with AMI (STEMI + NSTEMI)	Plasma prepared from blood drawn on admission	Median follow-up 634 d	Low levels linked to higher MACE and all-cause mortality
Zhang *et al.* (10)	856 patients with AMI (STEMI + NSTEMI)	Serum prepared from venous blood within 24 h of admission	Case-control study, no follow-up	Low levels associated with higher incidence of STEMI and NSTEMI
Feistritzer *et al.* (12)	50 STEMI patients with PCI	Plasma from EDTA blood samples drawn at a median of 1.9 days (IQR, 1.1–3.3 days) after symptom onset	Median follow-up 123 d	High corin levels associated with larger infarcts
Dong *et al.* (4)	73 AMI patients with AMI 198 healthy control subjects	Plasma prepared from blood collected within 12 h of the ischemic onset	Not available	Plasma corin levels in AMI patients similar to healthy controls
Peleg *et al.* (9)	152 ACS patients +103 healthy control subjects	Serum prepared from blood within 24 h of admission	Up to 3 years following discharge	Low plasma corin levels are associated with post-ACS MACE

MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI; MACE, major adverse cardiac event; ACS, acute coronary syndrome.

syndrome patients (9). Given the difference in severity of coronary artery occlusion and infarct size among these groups (17), we would predict significant differences in circulating corin levels, particularly if corin is released as result of cardiomyocyte injury or necrotic death, after MI.

How can we reconcile the observations of high soluble corin levels in acute MI, with the finding that low soluble corin levels are associated with poor longer term outcomes? In HF patients, circulating blood levels of corin are significantly lower than healthy controls (2,4,18). Experimental studies and analyses of explanted hearts show that corin transcript and protein levels are significantly reduced in HF (19-21). Indeed, there is a strong positive correlation between corin expression and left ventricular systolic function, with higher cardiac corin levels linked to higher ejection fractions (21). If corin blood levels reflect endogenous cardiac corin expression, it is logical that soluble corin levels will be suppressed in patients with underlying chronic ischemic cardiomyopathies. Nevertheless, during acute MI, there should be transient release of corin from ischemic and/or necrotic cardiomyocytes. The magnitude of rise in blood corin levels over time should reflect the amount of acute myocardial injury. However, in the chronic phase after acute MI, corin levels would be predicted to be lower, reflecting the severity of ischemic cardiomyopathy. In this way, corin may prove to have unique value as a biomarker, reflecting acute MI with rises in soluble levels and, in the chronic post-MI phase, as an indicator of the severity of ischemic cardiomyopathy. This study by Zhou *et al.*, together with other recent studies, have suggested that soluble corin may have unique prognostic value, but clinical studies will be necessary to compare corin to other established biomarkers. In addition, experimental studies are needed to better understand the mechanisms and pathophysiologic significance of changes in soluble corin levels in acute and chronic ischemic heart disease.

Acknowledgments

Funding: This work was supported by American Heart Association grant (14SDG20510068 to D Wang) and NIH grants (HL092750, NS089707 to GL Reed).

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by Section Editor Junhong Wang (Department of cardiology, the First Affiliated Hospital with Nanjing Medical University, Nanjing, China).

Conflicts of Interest: Dr. Reed is a founder of Translational Sciences.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jlpm.2017.05.10
Cite this article as: Wang D, Reed GL. Potential value of circulating corin levels in acute and chronic myocardial infarction. J Lab Precis Med 2017;2:26.