Copeptin Reflect Left Ventricular Systolic Function at Early Stage of Acute Myocardial Infarction in a Pig Model

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Wenjia Li[1,2*], Wenjian Sun[1,2*], Liang Lyu[1,2], Gang Wang[1,2], Weixin Yang[1,2], Hongfei An[1,2], Liling Chen[3], Jianhui Fan[1,2], Yan Yue[1,2] and Rongshun Zhang[4]

[1]Department of Radiology, The First People's Hospital of Yunnan Province, Xishan District, Kunming, Yunnan, China. [2]The Affiliated Hospital of Kunming University of Science and Technology, Kunming, Yunnan, China. [3]Kunming Medical University, Chenggong District, Kunming, Yunnan, China. [4]The Third People's Hospital of Yunnan Province, Guandu District, Kunming, Yunnan, China.

ABSTRACT

INTRODUCTION: Measurement of biomarkers early after acute myocardial infarction (AMI) might provide a cost-effective and widely available tool to assess infarct severity, myocardial dysfunction, and clinical outcomes. We aimed to induce AMI in miniature pigs, measure the levels of serum biomarkers and global LV function dynamically and explore the release kinetics and optimal sampling time points of copeptin and its correlation with global LV function.

METHODS: We induced AMI in the experimental group using a closed-chest model. Left ventricular (LV) function was detected by dual-source computed tomography (DSCT) and serum copeptin was determined by ELISA.

RESULTS: The serum copeptin levels were increased at 1 hour, peaked at 3 hours, gradually decreased after 6 hours, and returned to baseline 3 days after AMI. At 3 to 6 hours, the copeptin cutoff of 16.97 to 17.44 pmol/l had 100% sensitivity and 100% specificity ($P \leqslant .001$) for AMI. Serum copeptin levels at 3 hours and 3 days were negatively correlated with the 3-hours LVEF ($P \leqslant .001$), respectively.

CONCLUSION: Serum copeptin levels change in time, and measurements at 3 to 6 hours after AMI had the highest predictive value.

KEYWORDS: Copeptin, acute myocardial infarction, left ventricular global function, received operating characteristic analysis, pig model

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CORRESPONDING AUTHOR: Rongshun Zhang, Department of Radiology, The Third People's Hospital of Yunnan Province, 292, Beijing Road, Guandu District, Kunming, Yunnan 650011, China. Email: zrs19820317@163.com

Introduction

Acute myocardial infarction (AMI) is a serious but common type of coronary atherosclerotic heart disease (CHD) and has become a major public health concern worldwide.[1,2] Available data from community studies indicate that the incidence of AMI is 141 to 230 per 100 000 individuals, with a male predominance and 28-day mortality rates of 9% to 18%.[3,4] The risk factors for AMI include tobacco, hypertension, obesity, physical inactivity, dyslipidemia, diabetes, metabolic syndrome, family history, genetics, and chronic kidney disease.[5,6]

In the early stage of AMI, risk stratification is essential for the adequate management of the patients. Besides imaging examinations, biomarkers such as cardiac troponins (cTn), brain natriuretic peptide (BNP), high-sensitivity C-reactive protein (hsCRP), aspartate transaminase (AST), lactate dehydrogenase (LDH), and creatine kinase (CK) are used to assess AMI severity.[7,8] Still, these markers have shortcomings such as a lack of specificity and a high rate of false-positive results.[7,8] Circulating serum levels of high-sensitivity cTn (hs-cTn) can be used to diagnose AMI,[9,10] but there is a "troponin-blind" period during the early stage after AMI symptom onset that limits the applicability of this test.[11] In patients with chronic heart failure, therapy guided by BNP and N-terminal pro-BNP (BT-proBNP) levels showed improved prognosis,[12] but their application in AMI patients needs further study. Nevertheless, measurement of biomarkers early after AMI might provide a cost-effective and widely available tool to assess infarct severity, myocardial dysfunction, and clinical outcomes,[13] but the best biomarkers or models based on multiple biomarkers still need to be determined.

Copeptin (or C-terminal provasopressin) is a glycosylated 39-amino-acid peptide secreted into the circulation during AMI and has emerged as a novel biomarker for AMI.[13,14] Clinical studies suggest that serum copeptin levels can not only be used as an alternative to excluding early AMI in patients who have had negative troponin tests,[15-18] but also be used as an auxiliary index to evaluate left ventricular (LV) function and morbidity and mortality of heart failure following AMI.[19,20] Hence, serum copeptin levels could be an important biomarker for predicting long-term outcomes in AMI patients.[21]

* These authors contributed equally to this work.

Still, previous studies are limited by a relatively late selection of baseline time points, and the time point at which serum copeptin levels are measured in AMI patients is critical, and there is significant between-study heterogeneity regarding the optimal time point for copeptin sampling.[22,23] Studies measuring copeptin levels at different time points during the sub-acute phase after AMI are lacking, and therefore the best time point for assessing copeptin concentration remains unknown.[22] In addition, the release kinetics of copeptin during AMI has not yet been examined, partially because it is not possible to accurately define the onset of AMI in routine clinical practice.[23]

Therefore, our study aimed to induce AMI in miniature pigs, measure the levels of serum biomarkers and global LV function dynamically and explore the release kinetics and optimal sampling time points of copeptin and its correlation with global LV function.

Materials and Methods

Animal preparation

The sample size required for the study was calculated using PASS 15.0, where $\alpha = .05$ was the test level and $1 - \beta = .9$ was the test power. The ratio of the control group to the AMI group was 1:1. According to pre-experiment tests, the mean difference for serum copeptin levels between the control and experimental groups was 8.41 pmol/l. The standard deviation was set from 1 to 3 by an interval of 1. The results showed that 2 to 4 animals per group were required. A total of 14 healthy adult Diannan small-eared (DSE) pigs were provided by Kunming Medical University. Both male and female pigs were included, with an average weight of 39.6 ± 5.6 kg. The animals were randomly assigned to the control (n = 6) or the AMI (n = 8) group.

The experimental protocols in this study were based on the methods published by Li et al All DSE pigs were fasted for 12 hours and drinking water was removed from the cages 4 hours prior to surgery. Anesthesia was induced using 0.1 ml/kg xylazine hydrochloride (Jilin Huamu Animal Health Products, China) and 5 mg/kg ketamine hydrochloride (Fujian Gutian Pharmaceutical, China). Anesthesia was maintained by administering 3.0% sodium pentobarbital (Jilin Huamu Animal Health Products) via a 24-G trocar through the ear vein. No drugs were used to control breathing or heart rate throughout the procedure. AMI was induced using a closed-chest model following baseline examination using third-generation dual-source computed tomography (DSCT; details are provided below). Briefly, a 6-F guidewire (DMS, FMD Co., Ltd., Japan) was placed in the right femoral artery and a 6-F guide catheter (Launcher, Medtronic, USA) was placed in the left main trunk. Anatomic characteristics of the left coronary arteries were visualized using coronary angiography. A detachable balloon (diameter: 2.0-2.5 mm; Sprinter Legend, Medtronic, USA) was used to occlude the third distal region of the left anterior descending artery (distal to the second diagonal artery). The occlusion was confirmed by coronary angiography. The entire procedure was monitored using electrocardiography, during which all animals were administered a constant infusion of normal saline to avoid dehydration.

Blood sample collection and serum copeptin measurement

Five milliliters of venous blood were sampled under aseptic conditions from the front cavity vein of each pig before surgery and at 1, 3, 6, 12, and 24 hours, and 2, 3, 7, and 30 days after AMI induction. Serum samples were obtained by centrifugation at 3000*g* for 15 minutes. Samples were stored at −80°C, and repeated freeze and thaw was avoided. Serum copeptin levels were measured using enzyme-linked immunosorbent assay (Changjin, Co. Ltd., China).

DSCT imaging and postprocessing procedures

Third-generation DSCT (Definition FORCE, Siemens Healthcare, Germany) was used to scan the animals before the procedure and at 1, 3, 6, 12, 24 hours, and 2, 3, 7, and 30 days after AMI induction. A standardized examination protocol was used based on the following parameters: pitch = 0.15 to 0.28, tube rotation time = 0.25, slices collimated for both detectors = 0.6 × 128, scanning time = 3.59 to 7.72 seconds, tube voltages *A* = 90 kV, and tube voltages *B* = Sn150 kV. Iohexol (350 mg I/ml) was administered through a 24-G needle in the ear vein for contrast enhancement with a flow rate of 2 to 2.5 ml/second (per a dual-phase injection protocol), followed by an injection of 20 to 25 ml of contrast medium and normal saline (1:1 ratio) at a flow rate of 2 to 2.5 ml/second. The scan datasets were further analyzed using an off-line workstation (Syngo.via, Siemens Healthcare). The quantitative cardiac indices were obtained using Syngo software (Siemens Healthcare). The LV ejection fraction (LVEF), cardiac output (CO), ejection fraction (EF), stroke volume (SV), LV end-diastolic volume (LEDV), end-diastolic LV mass, and LV end-systolic volume (LESV) were calculated using a modified Simpson's method.[24]

Statistical analysis

All statistical analyzes were done using SPSS 22.0 (IBM, USA). The normality of the data was tested using the Shapiro-Wilk test. Continuous data are presented as means ± standard deviations and compared using the 2-tailed independent samples *t*-test. One-way repeated measures analysis of variance was used to compare parameters measured at 3 or more time points within the same group. The receiver operating characteristic (ROC) curve was plotted to determine the optimal cutoff value of serum copeptin concentrations in AMI diagnosis. The area

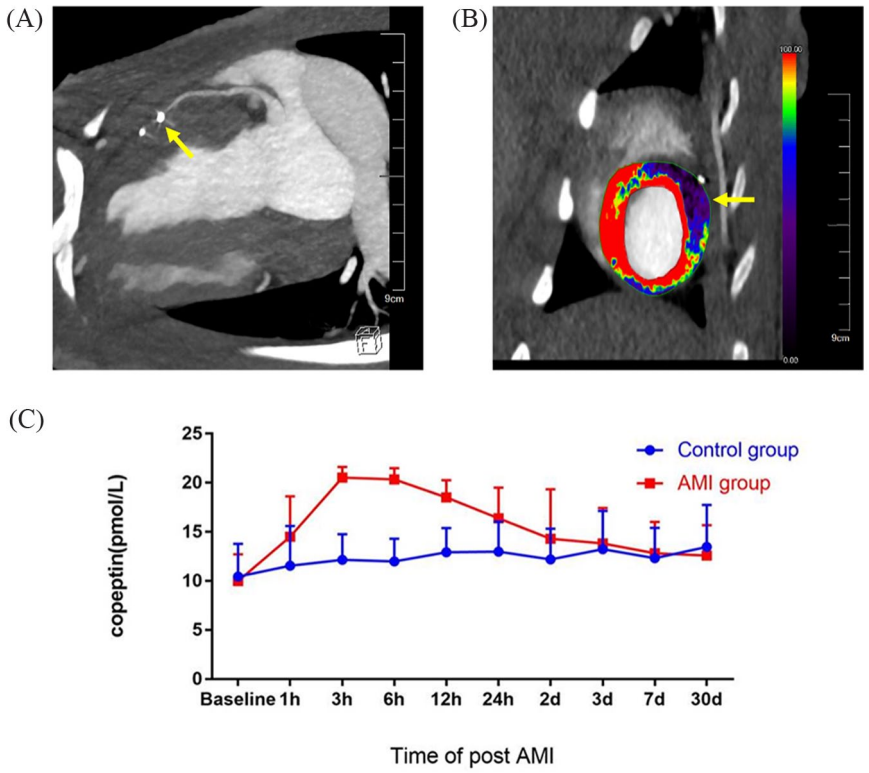

Figure 1. Representative images of the third-generation dual-source computed tomography (DSCT) measurements and copeptin levels. (A) Maximum intensity projection (MIP) showing that the distal end of the left anterior descending artery (LAD) was occluded, and the position of the balloon was clearly visible (yellow arrow). (B) Images of the left ventricular (LV) end-systolic short-axis position showing remarkable perfusion defect in the affected segments. (C) Dynamic changes in serum copeptin levels in pigs in the acute myocardial infarction (AMI) (red) and control (blue) groups. n = 6. Data are expressed as means ± standard deviations. Tests of within-subject effects: $F = 14.13$, $P \leq .001$; tests of between-subject effects: $F = 11.60$, $P = .00$.

under the curve (AUC) was reported with the cutoff variables' sensitivity and specificity. Pearson or Spearman rank correlation analysis was used as appropriate. A P-value ⩽.05 was considered statistically significant.

Results

Generation of a AMI pig model

In the experimental group, 8 animals underwent AMI induction. About 2 pigs died (one of ventricular fibrillation 20 minutes after coronary occlusion, and the other of excessive anesthesia 2 hours after the operation). The remaining 6 pigs survived the procedure. The AMI model was successfully established, as confirmed by DSCT (Figure 1A and B). The success rate of establishing the AMI pig model was 75%. Eventually, 12 pigs (control group, n = 6; AMI group, n = 6) underwent serial third-generation DSCT examinations and copeptin measurements after the operation.

Dynamic changes in serum copeptin levels

The changes in serum copeptin levels from baseline were evaluated at 1, 3, 6, 12, and 24 hours, and 2, 3, 7, and 30 days after AMI (Figure 1C). There were no significant changes in serum copeptin levels in time in the control animals (all $P \geq .05$). In the AMI group, the serum copeptin levels were significantly increased at 1 hour (14.50 pmol/l; IQR, 7.28-18.13 pmol/l), compared with baseline levels (9.99 pmol/l; IQR, 6.62-14.67 pmol/l, $P \leq .05$). Serum copeptin levels peaked at 3 hours after AMI induction (20.54 pmol/l; IQR, 18.85-20.90 pmol/l), gradually decreased after 6 hours, and then returned to baseline values after 2 to 3 days (13.83 pmol/l; IQR, 8.07-17.32 pmol/l, $P \geq .05$).

Optimal cutoff value of serum copeptin levels for predicting AMI

ROC curve analyzes were used to determine the optimal cutoff value of serum copeptin levels at different time points to predict AMI. As shown in Figure 2A, the cutoff value of serum copeptin levels at 1 hour after AMI was 14.07 pmol/l, with a sensitivity of 66.7% and a specificity of 75.0% (AUC = 0.715, 95%CI: 0.503-0.928, $P \leq .001$). At 3 to 6 hours after AMI, the cutoff value of serum copeptin levels was 16.97 to 17.44 pmol/l, with a sensitivity of 100% and a specificity of 100% (AUC = 1.000, 95%CI: 0.000-1.000, $P \leq .001$). At 2 to 3 days after AMI, the cut-off value of serum copeptin levels was 14.07 to 15.17 pmol/l, with a sensitivity of 66.7% and a specificity of 50% to 83.3% (AUC = 0.566-0.747, 95%CI: 0.327-0.529—0.805-0.964, $P \leq .001$).

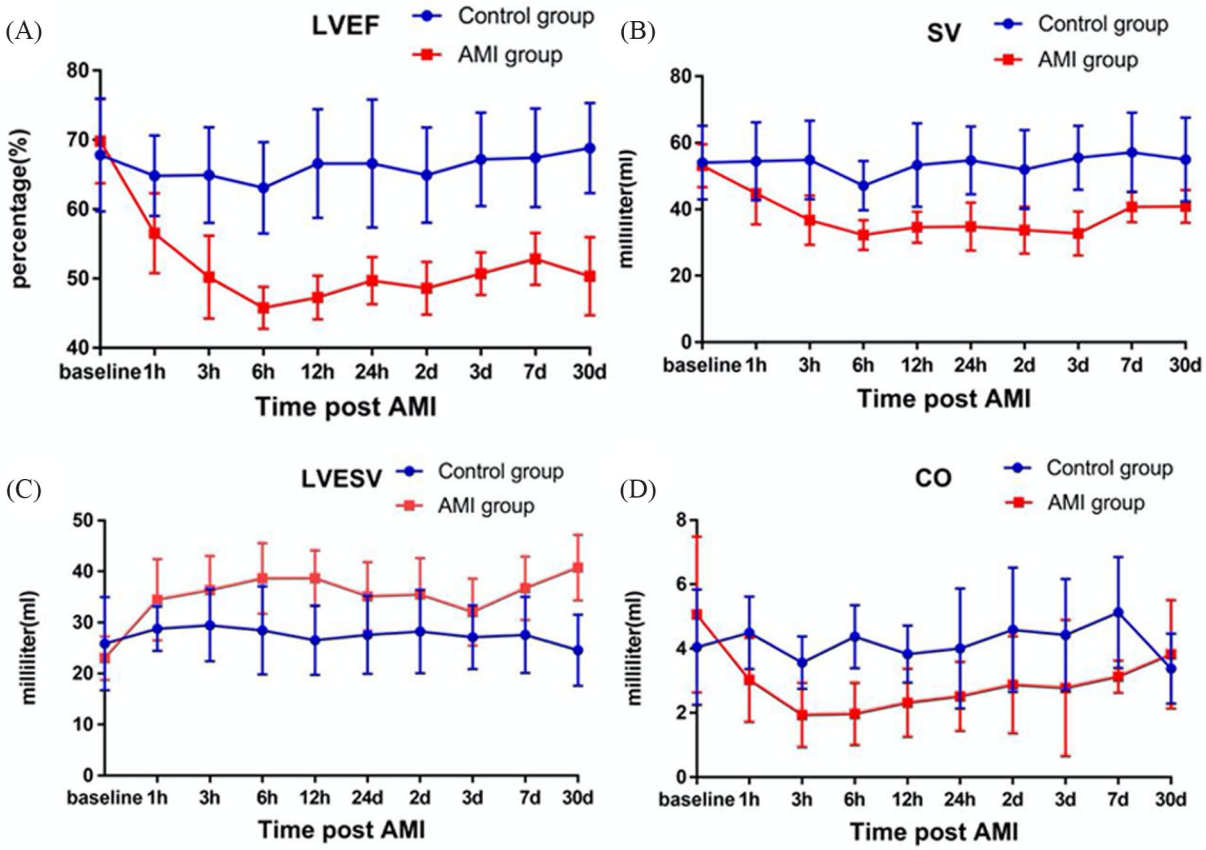

Figure 2. Dynamic changes in LV functional parameters as assessed by serial third-generation DSCT in pigs of the AMI (red) and control (blue) groups. (A) Left ventricular ejection fraction. (B) Stroke volume. (C) Left ventricle end-systolic volume. (D) Cardiac output.

Dynamic changes of global LV function after AMI

As shown in Figure 2,[25] there were significant differences in the 4 parameters of LVEF, LVESV, SV and CO between the control group and the AMI group ($P \leqslant .05$). Specifically, 30 days after AMI, LVEF decreased from the baseline value of 69.83% ± 6.09% to 50.33% ± 5.66%, SV decreased from 53.07 ± 6.51 to 40.85 ± 4.97 ml, and LVESV increased from 22.97 ± 4.55 to 40.71 ± 6.42 ml, CO decreased from 5.06 ± 2.42 to 3.82 ± 1.69 l/minutes. These changes were most pronounced at 1 hour after AMI, reached a low peak at 6 hours after infarction, and then showed a gradual recovery trend.

Correlation between copeptin levels and global LV function

As shown in Figure 3B and C, serum copeptin levels at 3 hours and 3 days were negatively correlated with the 3-hour LVEF ($r = -.61$, $P \leqslant .001$), but not with 3-day LVEF ($r = -.16$, $P = .47$). Respectively, in addition, 3-hour copeptin levels were negatively correlated to CO ($r = -.71$, $P \leqslant .001$), SV ($r = -.52$, $P = .001$), and SV ($r = -.62$, $P \leqslant .001$), but positively correlated with 3-hour LVESV ($r = .45$, $P = .03$) and 30-day LVESV ($r = .81$, $P \leqslant .001$).

Discussion

Early identification of patients at high risk for AMI using biomarkers can guide more individualized treatment strategies. Serum copeptin can be used as a diagnostic biomarker for AMI,[15-18] but previous studies used different measurement timings.[23] Therefore, this study aimed to determine the time course of serum copeptin levels and investigate the correlation between serum copeptin and LV global function in a pig AMI model. The results suggest that serum copeptin levels change in time, and measurements at 3 to 6 hours after AMI had the highest predictive value. Copeptin levels are negatively associated with LV global function in early AMI.

Our study has the following differences. First, the measurement time points of copeptin were a dynamic continuous process that includes acute and subacute phases after myocardial infarction. Second, our study was based on serial measurements of serum copeptin levels to obtain cut-off values for diagnosing AMI. Third, our study correlated serum copeptin release patterns with changes in global left ventricular function, further confirming that the optimal sampling time window for serum copeptin was 1 to 6 hours and the peak time was 3 to 6 hours after AMI.

Poor prognosis following AMI is closely related to the infarct size and severity of LV dysfunction and adverse remodeling.[13] Early identification, early risk assessment, and subsequent medical treatment for high-risk patients after AMI may allow personalized treatment strategies, which might reduce the development of cardiac dysfunction, poor remodeling, and subsequent adverse clinical outcomes. Still, whether serum

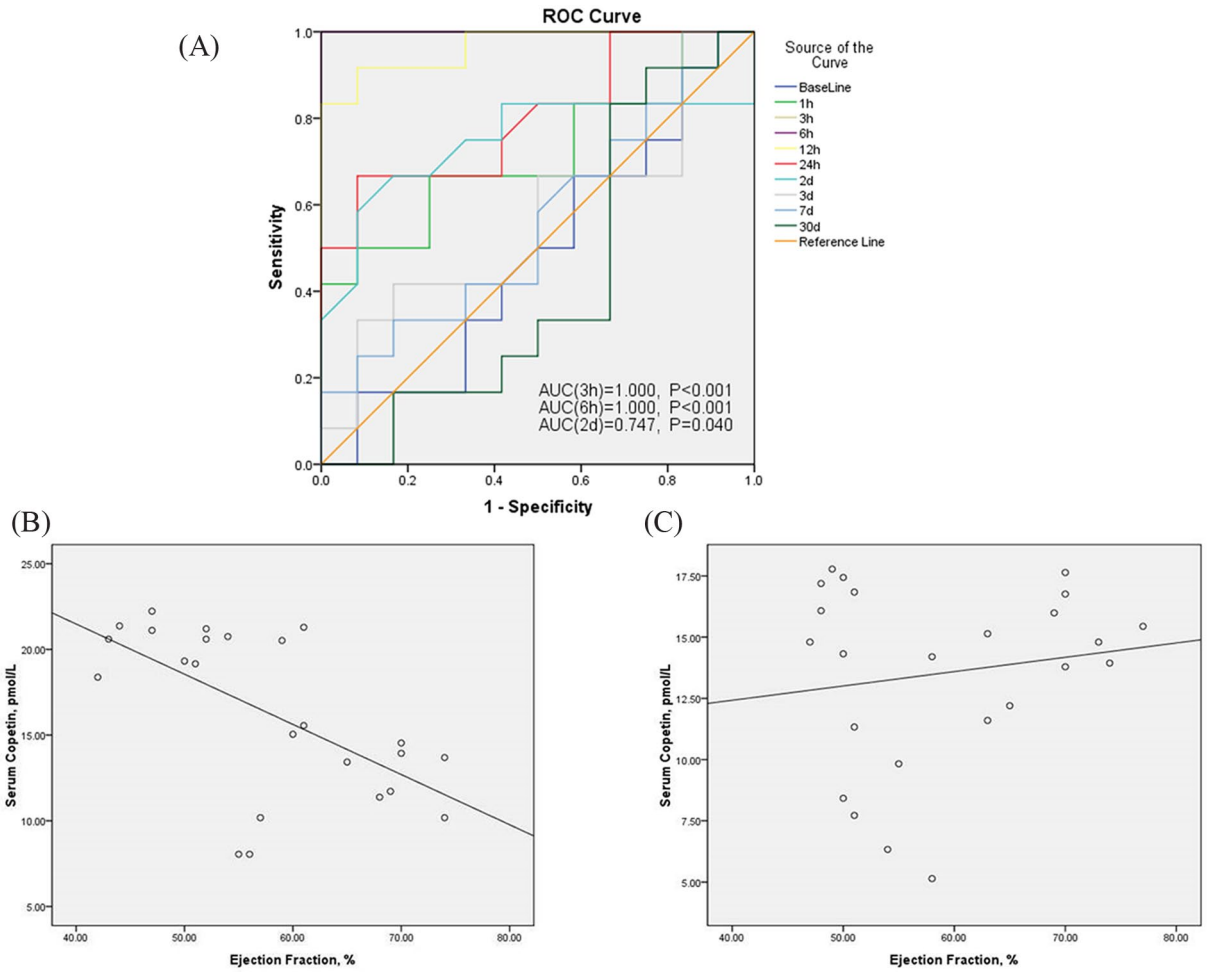

Figure 3. Diagnostic value of copeptin for acute myocardial infarction (AMI). (A) Receiver operating characteristics (ROC) and area under the curve (AUC) analyzes to determine the diagnostic performance of copeptin (pmol/l) at different sampling time points in the AMI pigs. (B, C) Linear correlations between serum copeptin and 3-hour ($r = -.61$, $P \leq .001$) (A) and 3-day ($r = -.16$, $P = .47$) (B) left ventricle ejection fraction (LVEF) in pigs after AMI (n = 6).

copeptin can be used as an independent risk predictor or should be used in combination with other biomarkers, such as troponin, remains a debatable question.[21] With the increased use of imaging and cardiac biomarkers, there is a prospect for combining new biomarkers with imaging modalities to guide clinical practice.[26]

Previous studies showed that copeptin levels can be used for the diagnosis of AMI,[15-18,23,27] but they all used different measurement time points and the best time point still needs to be defined. In addition, because of the variations in methods and patients among studies, no direct comparisons among studies are possible. Hence, understanding the time course of changes in serum copeptin levels and the correlation with LV function, especially in the early stages after symptom onset, is important for the early determination of AMI severity and developing appropriate treatments.[23] Performing such a study in humans might be complicated because the complex setting of the intensive care unit and because the patients can present at different times after the onset of AMI. Therefore, an animal study might provide some answer.

In the present study, AMI was induced in miniature pigs because this model closely simulates human AMI and allows the dynamic evaluation of the pathophysiology and biomarker release in response to AMI initiation and progression. The results showed that copeptin was rapidly released within the first hour after AMI induction, reached a maximum level after 3 hours, decreased gradually after 6 hours, and returned to baseline at 2 to 3 days after AMI. The ROC curve analysis showed that the optimal sampling time points for copeptin were between 1 and 6 hours after AMI. This sampling time window was different from those previously reported. Specifically, both the peak time and return to baseline were delayed compared to the values reported in previous studies.[14,28,29] These discrepancies could be attributed to differences in AMI models, species (pigs vs human), and clinical therapeutic intervention used in AMI patients.

Based on our study, we suggested that, if possible, blood samples from patients to measure serum copeptin levels can be collected on the way to the hospital rather than arriving at the emergency department. This appears to ensure that data on serum copeptin level are obtained during optimal time windows and even peak periods. This may provide more information for clinical diagnosis and treatment. Of course, the feasibility of this method still needs a lot of clinical data to verify.

Under filling of the left ventricle consequent to AMI, results in baroreceptor stimulation, or even the direct damage to the cardiac baroreceptors. These have both been proposed as the most likely causes of copeptin secretion from the posterior pituitary,[30] and could be used to explain the association between increased levels of copeptin after AMI and LV systolic function. Kelly reported that plasma copeptin levels in AMI patients were negatively correlated with LVEF at discharge and during follow-up but were positively correlated with LV volume at follow-up (LVEDV: LVESV). A subsequent CMR study confirmed the association between copeptin levels and LV dysfunction in the subacute (1-3 days) and chronic (4-12 months) stages in STEMI patients who were treated with primary PCI.[31,32] Consistent with the above findings, this study showed that the serum copeptin levels at 3 hours were negatively correlated with 3-hour LVEF, CO, and SV and 30-day LVEF, but were positively correlated with 3-hour LVESV and 30-day LVESV. There are some discrepancies with other studies,[32,33] probably for the same reasons stated above. Still, the optimal sampling time points found in the study (1-6 hours after AMI) are early stage after AMI, which is partially discussed and demonstrated by previous studies.[32,33]

To the best of our knowledge, this study is the first to report the dynamic measurement of copeptin levels in a large AMI animal model. We clearly showed that there is a specific pattern in serum copeptin levels during the course of AMI. We also analyzed the correlation between serum copeptin levels and global LV function at different sampling time points. Future studies should examine whether different treatments (PCI and CABG) could influence the copeptin levels in time.[23,27]

Still, some limitations of this research must be taken into consideration when interpreting the findings. This study did not have a sham group. A quantitative analysis of local LV function at different stages after AMI was not performed. In addition, the observation period was short (only 30 days), which is not sufficient to provide a long-term evaluation of the correlation between serum copeptin levels and LV remodeling. We also ignored other clinical measures such as mean arterial pressure and infarct size.

Conclusions

Serum copeptin levels peaked at 3 hours after AMI induction in the AMI miniature pig model. Serum copeptin levels are correlated with global LV systolic function after AMI. Thus, serum copeptin levels might represent a valuable biomarker for the diagnosis and prognosis of AMI.

Declarations

Ethics Approval and Consent to Participate

All animal protocols in this study were approved by the animal experimental ethical committee of kunming medical university (No. SYXK (Dian) K2015-0002).

Consent for Publication

None.

Author Contributions

Wenjia Li: Conceptualization; Funding acquisition; Writing—original draft. **Wenjian Sun:** Data curation; Methodology; Software; Writing—original draft. **Liang Lyu:** Data curation; Methodology; Supervision; Writing—review and editing. **Gang Wang:** Data curation; Methodology; Writing—review and editing. **Weixin Yang:** Methodology; software; Writing—review and editing. **Hongfei An:** Formal analysis; Investigation; Writing—review and editing. **LIling Chen:** Data curation; Methodology; Writing—review and editing. **Jianhui Fan:** Writing—original draft. **Yan Yue:** Writing—review and editing. **Rongshun Zhang:** Conceptualization; Methodology; Writing—review and editing.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID iDs

Wenjia Li https://orcid.org/0000-0001-6706-9801

Wenjian Sun https://orcid.org/0000-0002-1208-6337

Rongshun Zhang https://orcid.org/0000-0002-2392-1406

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