Editorial

What Cardiologists Should Know About Copeptin

¿Qué deben saber los cardiólogos sobre la copeptina?

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INTRODUCTION

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide.1–3 The risk of death and the benefit from early revascularization are highest within the first hours, and therefore early diagnosis is critical. Biomarkers play a critical role in the early diagnosis of AMI. In fact, an elevation in cardiac troponin (cTn) of at least one measurement above the 99th percentile of a healthy reference population has become a condition sine qua non for the diagnosis of AMI.1–3

WHAT IS THE UNMET CLINICAL NEED?

Biomarkers, to be more precise cTn, complement clinical assessment and the 12-lead electrocardiogram in the diagnosis and management of patients with suspected AMI. In AMI, cTn and cTnT are released from necrotic myocardium. A major limitation of conventional cTn assays is their low sensitivity at the time of patient arrival to the emergency department (ED), owing to a delayed increase of circulating levels in peripheral blood that requires serial sampling and prolonged monitoring for 6 to 12 h in a significant number of patients.1–3 This sensitivity deficit contributes substantially to diagnostic uncertainty, delays in the initiation of the appropriate therapy, and increases in resource use and treatment costs.1–3

WHAT IS COPEPTIN?

Copeptin is a novel blood biomarker that has entered the clinical arena thanks to the development of an analytically sound method to measure a signal that is released stoichiometrically with biologically active vasopressin. Although our insights into the exact pathophysiology of vasopressin and copeptin are still incomplete, currently available data can best be summarized as suggesting that copeptin levels reflect and quantify endogenous stress. As a signal, copeptin is therefore distinct from B-type natriuretic peptides, which reflect hemodynamic cardiac stress (end-diastolic wall stress). Copeptin, the c-terminal part of the vasopressin prohormone, is secreted stoichiometrically with arginin-vasopressin from the neurohypophysis. Copeptin levels seem to closely reflect the individual endogenous stress level as well as the risk of death in multiple medical conditions, including AMI4–14 (Figure 1). As endogenous stress is present already at the onset of AMI, copeptin appears to be able to identify AMI very early after symptom onset, even when cTn is still negative (Figure 2A).4–15 As endogenous stress is a very unspecific signal, it can only be used in this indication in combination with cTn. When used in conjunction with conventional 4th generation cTnT (a well characterized conventional cTn assay), the added value of copeptin regarding diagnostic accuracy upon ED arrival was substantial.4–6 As the time course of endogenous stress and detectable cardiomyocyte damage is reciprocal, copeptin seems to be the ideal marker to compensate for the sensitivity deficit of conventional cTn assays in early presenters.

DOES COPEPTIN ALSO PROVIDE ADDED VALUE WHEN USING HIGH-SENSITIVITY CARDIAC TROPONIN?

Initial pilot studies investigating the combination of copeptin with high-sensitivity cTnT (hs-cTnT) suggested that copeptin may still provide some incremental value regarding diagnostic accuracy upon ED arrival (Figure 2B), but of much smaller magnitude than that observed with the conventional 4th generation cTnT.4–14 Copeptin also provides substantial added prognostic information regarding the risk of short-term and long-term mortality in addition to either cTn or hs-cTnT. The concept in which copeptin

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seems to have the greatest appeal to clinicians is its use within a dual-marker strategy for very early rule-out of AMI: patients with acute chest pain presenting to the ED with initial negative values (< 99th percentile) of hs-cTn and also low levels of copeptin (e.g., < 10 pmol/L) do have a very high negative predictive value (around 99%) for AMI and seem to be ideal candidates for very early rule-out of AMI and rapid discharge from the ED without the need for serial cTn testing. Obviously, the potential for economic savings with this approach is enormous. In fact, data from a large, multicenter, randomized, controlled study evaluating the safety and efficacy of this approach as compared to standard of care (2nd cTn measurement after 3–6 h) have confirmed the safety and efficacy of this strategy.11

Currently there is no consensus among experts whether the incremental value provided by copeptin is sufficient to merit its introduction into routine clinical care of patients with acute chest pain in the ED. In institutions currently using conventional cTn assays such as the fourth generation cTnT or all currently available point-of-care cTn assays (which achieve sensitivities similar to the 4th generation cTnT), the incremental value is very large and in our opinion strongly argues in favor of routine addition of copeptin testing at the first blood draw. In institutions using hs-cTn assays and the 99th percentile as the decision point for AMI as recommended in the universal definition of AMI,1–3 future studies as well as clinical acceptance issues will define whether the additional use of copeptin will become a clinically accepted early rule-out strategy.

APPLICATION OFCOPEPTIN BEYOND ITS USE FOR RAPID RULE-OUT OF ACUTE MYOCARDIAL INFARCTION

Copeptin may provide substantial additive information also in patients with mild hs-cTn elevation. As mild elevations in hs-cTn may also be caused by multiple chronic conditions, including heart failure, hypertensive heart disease, or valvular heart disease, copeptin may help to separate these stable chronic conditions, which are expected to be associated with rather low copeptin levels, from patients with AMI or myocarditis, both of which associated with very high copeptin levels.

CONCLUSION

In conclusion, the dual-marker strategy combining the quantitative signals of cardiomyocyte damage (cTn) and endogenous stress (copeptin) provides high accuracy for the early diagnosis of AMI and may well become one of the preferred clinical strategies in the near future.

CONFLICTS OF INTEREST

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REFERENCES

Comparison
Diagnostic
Incremental
improves
Ray
Potocki
Keller
troponin
early
Clin
patients
long-term
Med.
assays,
acute
Charpentier
and
Tzikas
T,
with
Combined
C,
prognosis
in
Reichlin
troponin
2011;57:1452–5.
and
pre-existing
infarction.
Men,
copeptin
rule-out
of
am
M.
and
Borna
Thelin
Department.
Ann
freidank
Morgenthaler
NG,
et
al.
Incremental
value
of
copeptin
for
rapid
rule-out
of
acute
myocardial
infarction.
J
Am
Coll
Cardiol.

5. Keller
T,
Tzikas
S,
Zeller
T,
Czyz
E,
Lillipop
L,
Ojeda
FM,
et
al.
Copeptin
improves
diagnosis
of
acute
myocardial
infarction.
J
Am
Coll
Cardiol.
2010;55:
2096–106.

6. Giannitsis
E,
Kehayova
T,
Vafaie
M,
Katus
HA.
Combined
testing
of
high-
sensitivity
troponin
I
and
copeptin
on
presentation
at
prespecified
cutoffs
improves
rapid
rule-out
of
non-ST-segment
elevation
myocardial
infarction.
Clin
Chem.
2011;57:1452–5.

7. Potocki
M,
Reichlin
T,
Thalmann
S,
Zellweger
C,
Twerenbold
R,
Reiter
M,
et
al.
Diagnostic
and
prognostic
impact
of
copeptin
and
high-sensitivity
cardiac
troponin
I
in
patients
with
pre-existing
coronary
disease
and
suspected
acute
myocardial
infarction.
Heart.

8. Ray
P,
Charpentier
S,
Chenevier-Gobeaux
C,
Reichlin
T,
Twerenbold
R,
Claessens
YE,
et
al.
Combined
copeptin
and
troponin
to
rule
out
myocardial
infarction
in
patients
with
chest
pain
and
a
history
of
coronary
artery
disease.
Am
J
Emerg
Med.

9. Balnelli
C,
Meune
C,
Twerenbold
R,
Reichlin
T,
Rieder
S,
Drexler
B,
et
al.
Comparison
of
the
performances
of
cardiac
troponins,
including
sensitive
assays,
and
copeptin
in
the
diagnosis
of
acute
myocardial
infarction
and
long-term
prognosis
between
women
and
men.
Am
Heart
J.

10. Maisel
A,
Mueller
C,
Neath
SX,
Christenson
RH,
Morgenthaler
NG,
Nowak
RM,
et
al.
Copeptin
helps
in
the
early
detection
of
patients
with
acute
myocardial
infarction:
the
primary
results
of
the
CHOPIN
Trial.
J
Am
Coll
Cardiol.

11. Moesczel
M.
Instant
early
rule-out
using
cardiac
troponin
and
copeptin
in
low-
to
intermediate-risk
patients
with
suspected
ACS:
A
prospective,
randomized
multicenter
study
[accessed
2013
Nov
8]).
Hot
Line.
Clinical
Trial
Update
and
Registry
Sessions.
ESC
Congress
2013.
Amsterdam,
The
Netherlands
31
August
4
September
2013.
Available
at:
http://www.escardio.org/congresses/esc-
2013/congress-reports/Pages/709-BIC-8.aspx#.Unuy6-IwJ_w

12. Sebbane
M,
Lefebvre
S,
Kuster
N,
Jreige
E,
Jacques
E,
Badiou
S,
et
al.
Early
rule
out
of
acute
myocardial
infarction
in
ED
patients:
value
of
combined
high-
sensitivity
cardiac
troponin
I
and
ultrasensitive
copeptin
assays
at
admission.
Am
J
Emerg
Med.

13. Llorens
P,
Sánchez
M,
Herrero
P,
Martín-Sánchez
FJ,
Piñera
P,
Miró
O;
on
behalf
of
COPED
study
investigators.
The
utility
of
copeptin
in
the
emergency
department
for
non-ST-elevation
myocardial
infarction
rapid
rule
out:
COPED-MIRRO
study.
Eur
J
Emerg
Med.

14. Thelin
J,
Borna
C,
Erlinge
D,
Ohlin
B.
The
combination
of
high
sensitivity
troponin
I
and
copeptin
facilitates
early
rule-out
of
ACS:
a
prospective
observational
study.
BMC
Cardiovasc
Disord.
2013;13:42.

15. Charpentier
S,
Lepage
B,
Maupas-Schwalm
F,
Cinq-Frais
C,
Richard-Bréaud
M,
Botella
JM,
et
al.
Copeptin
improves
the
diagnostic
performance
of
sensitive
troponin
I-Ultra
but
cannot
rapidly
rule
out
non-ST-elevation
myocardial
infarction
at
presentation
to
an
department.
Ann
Emerg
Med.