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Immunoanalytical characteristics and value of copeptin in the exclusion of the diagnosis of myocardial infarction

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Abstract :
Copeptin is a glycopeptide synthesized by the hypothalamus and released into the blood circulation following acute vascular stress such as myocardial infarction (MI). Its interest lies in the precocity of its peak and in its kinetics. The combination of troponin (Tn) and copeptin represents a powerful tool for the exclusion of MI diagnosis at time admission to the emergency room. Two methods for the immunological determination of copeptin are currently available, an automated immunometric technique (Brahms CT proAVP LIA®) and a TRACE technique developed on the Kryptor® automated system (Brahms, ThermoFisher). Several studies have shown that copeptin has a very good MI exclusion value. First it was high in case of MI, and secondary the combination of copeptin and Tn had a better negative predictive value (NPV) (≥ 98%) for MI diagnosis compared to when each marker is measured alone.

Key words: *copeptin, myocardial infarction, vasopressin, troponin.*

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I. Introduction :

Copeptin is a glycopeptide synthesized by the hypothalamus. It is a fragment of a molecular precursor of vasopressin (AVP) and is notably a moderator of renal function.

It is released into the blood circulation following acute vascular stress, specifically MDI, and is known by the precocity of its peak in the first minutes after MDI and by its kinetics. The combination of Tn-copeptin represents a powerful tool for the exclusionary of the diagnosis of MI [1,2].

Copeptin is a new potential biomarker, which has currently place in the clinical and biological workup especially of MI. It is also a predictive factor of the lethal risk of progressive heart failure [3].

The objective of our work is to clarify the immunoanalytical characteristics of copeptin and to specify its role in the exclusion of the diagnosis of MI.

Immunoanalytical characteristics of copeptin:

Structure

Copeptin was first isolated in 1972 by Holwerda from porcine posthypophysis. It is a glycosylated peptide of 39 amino acids, rich in leucine and with a molecular weight of 5000 Da. It is synthesized in the hypothalamus and stored in the neurohypophysis after several cleavages. It is derived from the proteolytic cleavage of a precursor protein, the preprovasopressin (proAVP), which consists of 164 amino acids and is encoded by the AVP gene located on chromosome 20 at position 20p13. This precursor protein comprises a signal peptide, AVP, neurophysin II and copeptin [4].

Thus, copeptin constitutes the C-terminal part of provasopressin (CT-proAVP). Therefore, copeptin and AVP are co-secreted by the neurohypophysis and released into the bloodstream, following a signal, in equal stoichiometric proportions [5].

Pre-analytical phase

Water status and plasma osmolarity influence blood copeptin concentrations. It is therefore necessary to avoid a prolonged hydrous diet or a significant intake of water before sampling (except, of course, in the context of the dynamic exploration of a disorder of AVP secretion [6].

Venous blood is collected by puncture at the elbow. The copeptin assay is performed on plasma (EDTA, heparin) or on serum. The instructions provided by the manufacturers of the sampling equipment and the assay kit must be followed. No special pre-analytical precautions are recommended for the determination of copeptin [7].

Centrifugation conditions must follow the instructions of the manufacturer of the sampling equipment. Copeptin is stable in serum or plasma for 7 days at room temperature and 2 weeks at 4◦C. If the assay is to be performed within 24 hours of blood collection, it is recommended that samples be stored at room temperature or between 2-8◦C. Otherwise, it is advisable to aliquot and freeze them at -20◦C. Samples can be frozen and thawed three times in a row. Icteric, hemolytic, lactescent, cloudy, or fibrin trace samples may give inaccurate results. Therefore, results from such samples should be interpreted with caution or a control sample should be requested [7].

II. Methods of determination of copeptin

Two immunoassay methods for copeptin are currently available based on a sandwich technique based on the detection of the antigen/antibody (Ag/Ac) immune complex [7]:

Immunometric technique: on automaton (CT proAVP LIA® Brahms)

This technique involves a two-hour incubation, where the first polyclonal Ac allows Ag capture and is bound to the solid phase (polystyrene tubes). The second polyclonal Ac is the tracer that is labeled with acridinium ester to generate a chemiluminescence reaction [2,7].

Technique TRACE TM (*Time-Resolved Amplified Cryptate Emission*)

This method was developed in 2009 on Kryptor® (Brahms, ThermoFisher) involving a 19 min incubation and a wide measurement range (4.8 to 1200 pmol/L with automatic dilution). It is a one-step reaction in homogeneous phase, based on a non-radiative energy transfer between a donor (cryptate structure containing a europium ion) and an acceptor (modified light-absorbing algal protein: XL665), each of which is bound to an antibody [2,7].

The formation of an Ag/Ac immune complex allows energy transfer, the fluorescence signal obtained is thus proportional to the concentration of copeptin in the sample [7].

The results of the copeptin assay are expressed in pmol/L. Unlike AVP, which is undetectable in subjects with low osmolarity, copeptin is detectable in more than 97% of healthy subjects, regardless of their plasma osmolarity [7].

Interest of copeptin assay in MI:

As mentioned earlier, copeptin is co-secreted with vasopressin in equal proportions by hypothalamic neurons in the posthypophysis. It has a short in vivo half-life of 25 minutes, as does AVP. But it is relatively stable in vitro once the blood sample is taken. It therefore represents a faithful witness of the secretion of AVP and its determination is much easier than that of AVP, which presents a short life span and an instability in vitro. The determination of copeptin is therefore of clinical interest in relation to the multiple cardiovascular and renal functions of AVP.

During MI, copeptin rises very early, whereas Tn remains undetectable (4 hours after the onset of symptoms) [9]. A normal level of copeptin and Tn at the time of admission to the emergency room can thus exclude the diagnosis of MI with a negative predictive value of more than 99%. The copeptin assay can also be coupled with ultrasensitive Tn assay, which increases the diagnostic performance [11].

Numerous studies have demonstrated the value of copeptin testing in MI. Khan SQ et al. were the first to show that copeptin increased in post-MCI with a peak at D1 (18 pmol/L), then a plateau between D3 and D5. Furthermore, the authors showed that high copeptin values were an independent predictor of death or heart failure at 30 days [8].

Other studies have shown that copeptin was significantly increased in MI (median 20.8 pmol/L) but not in unstable angina. They also proved that the combination of Tn/copeptin in the first 4 hours after the onset of symptoms had a major interest in the exclusion of MI with a sensitivity of 98.8%, a specificity of 77.1% and above all an NPV of 99.7% when both parameters were negative [9].

These results were also confirmed by Keller T et al. who showed that the combination of copeptin and Tn assays on admission in patients with chest pain less than two hours old can exclude MI with a 95% NPV when both markers were negative [10].

Similarly, a study performed in Germany in patients with chest pain less than 12 hours old who had copeptin and ultrasensitive Tn assays at H0, H3 and H6 showed that this association had a 99.03% NPV to exclude MI [11].

Thus, these different studies confirm the importance of the Tn/copeptin combination in the exclusion of MI. They also contribute to underline the importance of setting up an efficient emergency biological test, allowing to relieve the emergency room by justifying the decision to discharge a patient when Tn and copeptin are negative. The aim of these studies was also to evaluate a possible risk of cardiac events within 30 days of the negative test, proving the excellent NPV of copeptin [3].

Following an episode of MI, an increase in copeptin is associated with excess mortality and a high risk of heart failure within a short time (2 months). In chronic heart failure, an elevated copeptin level is an indicator of poor medium- and long-term prognosis, particularly in terms of mortality and hospitalization for decompensation, and this predictive power can be increased by concomitant measurement of brain natriuretic peptide (BNP). In addition, copeptin can be combined with natraemia and natriuretic peptides in acute heart failure to predict excess 90-day mortality and a high probability of subsequent hospitalization. At the same time, the association of an elevated copeptin with hyponatremia seems to have a particularly unfavorable prognosis [12].

Currently in France, 14 university hospital centers (CHU) have integrated copeptin in their decision algorithm. We cite Prof. Jean-Paul Cristol at the University Hospital of Montpellier who described the physiology of copeptin and its key function as a surrogate for the AVP assay, and Dr. Pierre Géraud Claret at the University Hospital of Nîmes who presented the state of the art of copeptin based on the literature. Drs. Christine Morin and Vincent Pegoraro described the positive impact already guaranteed by copeptin at Calais University Hospital. Guillaume Lefèvre and Christine Morin at the Tenon University Hospital in Paris have created a multidisciplinary working group, with the objective of studying the use of copeptin and its evaluation beyond cardiology [13].

In Germany, Prof. Martin Moeckel, member of the Acute Cardiovascular Care Association and the Biomarker Core Group of the European Society of Cardiology, described the interventional study "Biomarkers in cardiology 8", which concluded that copeptin was able to exclude MI in 66% versus 12% of patients admitted to the emergency department with chest pain [13].

Other studies in other European countries, such as Switzerland, have shown the place of copeptin in the biological workup for different diagnosis [14].

III. Conclusion :

Copeptin is a reliable surrogate parameter for AVP. In contrast to AVP, it is stable and can be measured easily with an immunoassay in serum or plasma.

Copeptin is a promising new parameter playing a very important role in the exclusion of MI, on one hand it is elevated in MI, on the other hand the combination of copeptin and Tn has a better NPV (≥ 98%) for the excluding of MI than each of the markers when assayed alone.

A multimarker MDI exclusion strategy, could allow for better triage of patients in an emergency department.

Conflicts of interest :
The authors declare no conflict of interest.

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