Copeptin for All: A Biomarker From Infant Pathology to Adult Cardiovascular Disease

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Unic-Stojanovic et al, in this issue of Angiology, evaluated whether or not copeptin levels are associated with carotid cross-clamping in patients undergoing carotid endarterectomy (CEA).¹ Although copeptin levels increased from baseline to postoperatively in all patients, no association was found between serum copeptin levels and the duration of carotid artery cross-clamping.¹

Copeptin (C-terminal fragment of proarginine vasopressin) is a novel surrogate marker released in equimolar amounts to arginine vasopressin in response to several stressful situations/conditions, such as trauma, sepsis, lower respiratory tract infections, hemorrhagic, and septic shock.²⁻⁴ Copeptin levels also increase in cardiovascular diseases (such as ischemic stroke, acute myocardial infarction, heart failure, and intracerebral hemorrhage) and traumatic brain injury.⁵⁻⁸ In patients with ischemic stroke, copeptin levels predict functional outcome and mortality at 12 months.⁹,¹⁰ Furthermore, copeptin levels predict recurrent cerebrovascular events after a transient ischemic attack.¹¹,¹² Finally, preoperative copeptin levels predict perioperative and postoperative outcomes in patients undergoing vascular surgery.¹³

Any stimulus/stress that triggers the activation of the hypothalamic–pituitary axis induces the release of adrenocorticotropic hormone, glucocorticoids/cortisol, and arginine vasopressin into the systemic circulation.¹⁴,¹⁵ Measurements of circulating arginine vasopressin levels are cumbersome because of the molecule’s instability and short half-life.¹⁶ Copeptin is a stable by-product of vasopressin synthesis and can be quantitatively determined in plasma, thus reliably reflecting vasopressin release.¹⁶

An acute ischemic thromboembolic stroke is coupled with acute brain injury, increased oxidative stress, and a complex cascade of metabolic events leading to neuronal cell death.¹⁴ Acute brain ischemia also initiates a complex sequence of events in the central nervous system and the hypothalamic–pituitary–adrenal axis including increase in vasopressin/copeptin levels through induction of vasopressin messenger RNA and protein expression.¹⁵ An earlier study by the authors demonstrated that copeptin levels are increased in patients undergoing CEA but more so in patients with a perioperative stroke.¹⁷ Several inflammatory mediators released during surgery (such as tumor necrosis factor α, interleukin 1, and interleukin-6) have a substantial role in activating the hypothalamic–pituitary–adrenal axis.¹⁷ These results suggest that copeptin levels may be helpful in individual risk assessment in patients with a perioperative stroke during CEA.¹⁷

Besides adults, copeptin levels are useful for evaluation of outcomes in infants/neonates. Copeptin levels increase in conditions associated with perinatal stress, such as birth acidosis, asphyxia, chorioamnionitis, and sepsis.¹⁸,¹⁹ Furthermore, copeptin/vasopressin levels play an important role in impaired glucose homeostasis and insulin resistance-associated disorders.²⁰⁻²² Copeptin levels positively correlate with birth weight in large-for-gestational age infants²³ and are also increased in intrauterine growth restricted infants.²⁴ Consequently, copeptin levels accurately reflect pathological conditions in the perinatal period associated with increased stress. These changes in copeptin levels support the “fetal programming” (or “fetal origins of adult disease”) hypothesis, which implies that alterations in fetal nutrition may result in developmental adaptations that permanently change the physiology and metabolism of the offspring, thereby predisposing individuals to metabolic, endocrine, and cardiovascular disorders later in life.²⁵,²⁶

Copeptin is a highly sensitive marker of perinatal stress.²⁷ Copeptin levels correlate with abnormal conditions such as compromised placental perfusion, estimated fetal weight below the fifth percentile, alterations in umbilical artery pH, and intraventricular hemorrhage.²⁷ Additionally, copeptin levels could potentially be used as a marker of the effect of various therapeutic measures. Future studies should assess the effect of various treatment strategies indirectly by evaluating copeptin levels.

In the study by Unic-Stojanovic et al, copeptin levels were not affected by the duration of the carotid cross-clamping.¹ During carotid cross-clamping, cerebral blood flow is mainly maintained via the contralateral carotid and the vertebral arteries, thus preserving adequate blood supply to the brain.

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The lack of brain ischemia during carotid cross-clamping is verified by the lack of any difference in postoperative copeptin levels between patients with carotid cross-clamping time ≤13 versus >13 minutes. Copeptin levels increased postoperatively in all patients undergoing CEA, probably as a result of surgical stress. Postoperative copeptin levels increased even more in patients with an ischemic stroke during CEA.\(^{17}\)

The results from studies on adults\(^{2-17}\) and neonates\(^{18-23}\) suggest that copeptin is involved in several pathological conditions and may be used as a marker/predictor of various stress disorders both in adults (eg, central nervous system diseases, diabetes mellitus, metabolic syndrome, sepsis, stroke, infections, and kidney diseases)\(^{2-17}\) and in infants/neonates (eg, asphyxia, chorioamnionitis, sepsis, and birth acidosis)\(^{18-23}\). These results suggest a role for copeptin as a diagnostic and prognostic tool in adults with stroke\(^{5,9,10,12,17}\) and myocardial infarction\(^{4,7}\) as well as in newborns with intrauterine pathology.\(^{21-24,27}\) Future studies should evaluate the efficacy of several treatment measures using changes in copeptin levels as a guiding/assessment tool.

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