Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.333326.3675 Volume 31, Issue ٢, FEB. 2025, Supplement Issue
Manuscript ID ZUMJ-2411-3675
DOI 10.21608/zumj.2024.333326.3675
REVIEW ARTICLE

The Role of Copeptin in Heart Failure of Children

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Submit Date 03-11-2024
Revise Date 11-11-2024
Accept Date 11-11-2024

ABSTRACT:

Background: In the contemporary Western world, heart failure (HF) is one of the leading causes of hospitalization and death, and its prevalence is expected to rise in the coming years. Despite the fact that HF therapy has improved prognosis and quality of life, death is still relatively high. Neurohormonal inhibition of an overactive neurohormonal axis is the medical therapy approach. In terms of hospitalization, mortality, and the course of the disease, no one sign has been able to predict or track HF. It is necessary to develop new techniques for prognosis, therapeutic monitoring, and diagnosis. A novel biomarker in HF with encouraging promise is copeptin, a precursor of pre-provasopressin. Copeptin is linked to prognosis and has been reported to be increased in both acute and chronic heart failure. **Conclusions**: Copeptin may be a helpful biomarker for tracking the severity of the disease and for predicting survival and prognosis in HF when combined with other biomarkers.
Keywords: Copeptin; Heart Failure; Children.

INTRODUCTION:

It is increasingly recognized that the biggest threat to the health of the world's population is cardiovascular disease (CVD). 17.8 million deaths (95% CI 17.5–18.0 million) are anticipated, CVDs are responsible for the greatest number of non-communicable disease-related deaths.

Heart failure is defined as failure of heart to pump enough blood to meet the body demands. This led to signs and symptoms as growth failure, respiratory distress and edema associated with circulatory changes **[1].** The cause of heart failure in children may be pressure overload or volume overload or both. The most common cause of heart failure in infancy is CHD. Other causes of HF are metabolic, pulmonary diseases, anemia, collagen vascular diseases and drugs **[1], [2].**

The probability of heart failure in CHD lesions such as tetralogy of Fallot (TOF), and transposition of the great arteries (TGA) can be as high as 80% at 50 years of age, while it is around 20–30% for isolated valvular disease or defects that result in left-to-right shunt. Additional myocardial insults can complicate surgery, including injury to the myocardium, coronary arteries, and conduction system. Post-surgical conduction disease may require permanent ventricular pacing, which can lead to progressive contractile dysfunction. Since these insults often occur in the first years of life, the effects of altered hemodynamics or tissue injury accumulate over years, resulting in early development of HF **[3].**

Arginine vasopressin (AVP) is a key hormone that regulates vasoconstriction, fluid homeostasis, and the endocrine stress response. Copeptin, the C-terminal part of the pro-AVP precursor, is generated in an equimolar amount with AVP in response to osmotic, hemodynamic, and stress stimuli. Copeptin's diagnostic value in clinical practice has been well evaluated has demonstrated potential as a biomarker, and offers extra benefits over AVP. Acute illnesses such acute myocardial infarction, stroke, and sepsis (AMI) have also been linked to elevated copeptin levels **[4].**

The introduction of copeptin measurement could be most beneficial for the diagnosis and treatment of cardiovascular illnesses (CVDs). When combined with other traditional cardiac biomarkers, Copeptin can aid in the prompt exclusion of AMI and the

prediction of HF outcomes. Copeptin is involved in the prognostic prediction, risk assessment, and differential diagnosis of individuals with cardiovascular disease. Even if doctors are paying more and more attention to copeptin, more research and data are needed to improve the diagnosis and distinction of some illnesses before in the future, it can be applied as a routine clinical evaluation. Here, we go over the clinical effectiveness of copeptin in HF with children have CHD some of its drawbacks and potential as a routine biomarker in the future **[5]**.

Biology of Copeptin and Vasopressin:

Copeptin is formed of 39 amino acid long peptide. It is stable and has longer half-life than AVP. In adults, Copeptin is superior biomarker to the already established biomarkers BNP and N.Terminal –Pro BNP in HF patients **[6].**

It is stronger predictor of mortality than BNP or NT-proBNP [7]. It is also increase in acute and chronic ventricular dysfunction. AVP and copeptin secretions are regulated by neuroendocrine mechanisms. The parvocellular neurons of the PVN can produce the precursor, which is transported along the portal vessel to the anterior pituitary. In this pathway, AVP can interact with corticotrophin-releasing hormone (CRH) to stimulate the release of adrenocorticotropic hormone (ACTH) from endocrine cells in the anterior pituitary, reflecting somatic stress levels **[8].**

Copeptin in Heart Failure:

Based on systolic function, heart failure can be categorized as either heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF). HFpEF is the term used when the left ventricular ejection fraction (LVEF) exceeds 50%. when LVEF is less than 40%, it is called HFrEF. Patients with an LVEF between 40 and 49% are considered to be in a "gray area," also known as HF with mid-range EF (HFmrEF). . A diastolic dysfunction without a significant ejection fraction alteration is the hallmark of this form of heart failure **[9].**

The theory proposed by Paulus and Schope **[10]** is that endothelial function may serve as a common trigger for all HFpEF etiologies. More precisely, the pathway of nitric oxide (NO) was identified **.**

Age is the sole determinant of the clinical presentation of pediatric heart failure. Infants and early children with HF typically appear with cyanosis, tachypnea, sinus tachycardia, diaphoresis, and difficulties feeding (from prolonged feeding time intake to frank intolerance) **[11].** Adolescence and older kids could suffer. The main symptoms include tachypnea, fatigue, shortness of breath, and exercise intolerance. There may also be leg pitting edema, oliguria, and abdominal pain**.**

Notably, HFpEF is more difficult to diagnose than HFrEF since it typically does not have a dilated left ventricle, necessitating further testing and serum biomarker analysis **[12].**

The performance of copeptin as a surrogate marker of AVP in risk stratification of patients with HF has been proposed and widely evaluated. Xu et al. found that copeptin and NT-proBNP levels increased as NYHA grade increased in patients with HFrEF, but not in patients with HFpEF. In addition, increased copeptin levels in patients with advanced HF have also been reported to be associated with a reduced cardiac index. These results, together with other evaluations, suggest the clinical value of risk stratification and disease severity of copeptin in patients with HF. **[13].**

Vasopressin System in HF:

The renin-angiotensin-aldosterone pathway and adrenergic receptors are the main targets of modern heart failure treatment due to a well-established understanding of the neurohormonal systems in particular. These include beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor antagonists. It has not been widely recognized that HF patients have an overactive vasopressin system **[14].**

The improper activation of the vasopressin system is thought to be the cause of the severe water retention and volume overload experienced by patients with HF. Furthermore, it is thought that a non-osmotic mechanism controls the release of AVP through angiotensin II, pain, intracardiac pressures, intraarterial pressures, and adrenergic central nerve stimuli. It has been discovered that patients with LV dysfunction and HF (acute HF with hyponatremia and chronic HF with or without hyponatremia) had noticeably higher AVP levels. Pharmacologically, vasopressin receptor antagonists can either reduce vasoconstriction and cardiac remodeling by blocking the V1aR in smooth blood arteries, Alternatively, they can promote aquaresis by blocking the V2R in renal tubules **[15]**. Tolvaptan, a highly selective vasopressin V2 receptor antagonist, may be used to treat patients with volume overload and resistant hyponatremia, despite the fact that it was found to have no effect on long-term mortality or HF-related morbidity in patients hospitalized with HF **[16]**.

Additionally, It is still unknown if copeptin can be used to monitor and direct the medical care of HF patients or if there is a single copeptin cut-off level at which doctors can determine how best to allocate healthcare for HF patients. More well-planned research with longer follow-up times is required to elucidate how copeptin guides beta-blocker BB treatment. Research has looked into if levels of copeptin and NT-proBNP can help patients with HF get the most out of their beta-blocker (BB) up-titration, but the results have been mixed **[17].**

Table (1): Articles about the prognostic value of copeptin (alone or with BNP/NT-proBNP) in predicting the outcome of HF.

REFERENCES	SAMPLE SIZE	MEAN/MEDIAN FOLLOW-UP DURATION	SELECTED CUTOFF VALUE AND CORRESPONDING PROGNOSTIC PERFORMANCE	MAIN CONCLUSION
STOISER ET AL. [35]	268 with advanced HF	15·8 months	Copeptin 18.3 pmol/L AUC 0.672 BNP 448 pg/mL AUC 0.662	Copeptin is an excellent predictor of outcome in advanced HF patients. Its value is superior to that of BNP in predicting death and a combined endpoint.
GEGENHUBER ET AL. [36]	137 with acute destabilized HF	365 days	Copeptin [AUC 0.688 (0.603–0.764)]−15 pmol/L: sensitivity 85% (71–94), specificity 42% (32–52), PPV 38%, NPV 87%;−45 pmol/L: sensitivity 56% (40–72), specificity 76% (66–84), PPV 50%, NPV 80% BNP [AUC 0.716 (0.633–0.790)]−495 ng/L: sensitivity 83% (68–93), specificity 41% (31–51), PPV 37%, NPV 85%;−1,250 ng/L: sensitivity 56% (40–72), specificity 76% (66–84), PPV 50%, NPV 80%	MR-proANP, MR-proADM, and Copeptin measurements might have similar predictive properties compared with BNP determinations for one-year all-cause mortality in acute destabilized HF.
NEUHOLD ET AL. [37]	786 HF	15.8 months	Copeptin (AUC 0.711) BNP (AUC 0.711) copeptin + BNP (AUC 0.744)	Increased levels of copeptin are linked to excess mortality, and this link is maintained irrespective of the clinical signs of severity of the disease. Copeptin was superior to BNP or NT-proBNP in this study, but the markers seem to be closely related.

REFERENCES	SAMPLE SIZE	MEAN/MEDIAN FOLLOW-UP DURATION	SELECTED CUTOFF VALUE AND CORRESPONDING PROGNOSTIC PERFORMANCE	MAIN CONCLUSION
VOORS ET AL. [38]	224 with HF	33 months	Copeptin (AUC 0.81) 25.9 pmol/L: sensitivity 67.7%, specificity 82.5%, PPV 39.6%, NPV 93.8%; BNP (AUC 0.66) 181 pmol/L: sensitivity 50.0%, specificity 79.2%, PPV 28.6%, NPV 90.5%; NT-proBNP (AUC 0.67) 1,980 pmol/L: sensitivity 53.1%, specificity 79.9%, PPV 30.4%, NPV 91.1%.	Copeptin is a strong and novel marker for mortality and morbidity in patients with HF after AMI. In this population, the predictive value of copeptin was even stronger than BNP and NT-proBNP.
SMITH ET AL. [39]	Total 5,187 (112 with HF)	14 years	NA	Natriuretic peptides, but not other biomarkers, improve discrimination modestly for both diseases above and beyond conventional risk factors and substantially improve classification for HF.
POTOCKI ET AL. [29]	287 with acute dyspnea	30 days	Copeptin [AUC 0.83 (0.76–0.90)] 53 pmol/L NT-proBNP [AUC 0.76 (0.67–0.84)] BNP [AUC 0.63 (0.53–0.74)]	Copeptin is a new promising prognostic marker for short-term mortality independently and additive to natriuretic peptide levels in patients with acute dyspnea.

CONCLUSIONS:

Copeptin may be a helpful biomarker for tracking the severity of the disease and for predicting survival and prognosis in HF when combined with other biomarkers.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

FINANCIAL DISCLOSURES:

This review article was not supported by any source of finding.

SOURCES OF FUNDING:

No specific grant was obtained for this research from governmental, private, or nonprofit funding organizations.

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Citation

Shedeed, S., Khalifa, N., Hamza Badawy, E., Rashad, M. The Role of Copeptin in Heart Failure of Children. *Zagazig University Medical Journal*, 2025; (724-728): -. doi: 10.21608/zumj.2024.333326.3675