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Perspective

DPP3 in Cardiogenic Shock

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Introduction

In the 1960s, Brand and Lefer identified what they believed to be a low molecular weight peptide released in response to splanchnic vasoconstriction in a model of hemorrhagic shock and called it myocardial depressant factor (1). They thought it had an abdominal origin and they observed its effects in reducing cardiac performance in a variety of models of shock. This concept—that there is a circulating inhibitor of myocardial function—has survived over the years and there are a variety of clinical situations in which it has been hypothesized to be important, including potentially in patients with stunned myocardium and in a variety of shock states including cardiogenic shock. Recently, evaluation of a novel intracellular zinc-dependent metallopeptidase called dipeptidyl peptidase 3 (DPP3) that is involved in the metabolism of other peptides has identified it as having similar characteristics. Its biochemistry and physiology have recently been reviewed (2). It is widely distributed throughout the body although perhaps enriched in blood, spleen, and cardiovascular tissue. Thus, for entities such as cardiogenic shock, cardiac, vascular, and critical organ sources are likely contributory. It is thought to be released into circulation from dying cells and it has been suggested that it interacts with inflammatory pathways, blood pressure regulation, and pain modulation by inhibiting the effects of a variety of peptides including angiotensin II, enkephalins, and endorphins.

Because of the association of these influences, DPP3 has been evaluated in a variety of experimental models and has been found to rapidly reduce myocardial contractility when injected into mice (3). More importantly, in those same animal models, myocardial contractility is rescued when DPP3 is subsequently inhibited by antibodies raised to antagonize the peptide.

It is clear that these effects on cardiac function are complex and likely multifactorial. In patients with cardiogenic shock, increased levels were associated with severe organ dysfunction and short-term mortality (3–5). In these patients, DPP3 is often increased at admission but increases if hemodynamic compromise ensues. If hemodynamics remain stable or improve, DPP3 levels tend to decrease (4, 5). The demonstration of these phenomena has led to excitement in regard to the possibility that DPP3 may play an integral role in the pathogenesis of reduced cardiac contractility seen in a variety of acute ischemic syndromes, including cardiogenic shock. Thus, there is now interest in inhibition or antagonism of DPP3 as a potential therapeutic strategy to alleviate those cardio-depressive outcomes. In this context, assays to measure DPP3 have recently been developed that have the potential to serve both as a diagnostic tool and as a way of monitoring any therapeutic interventions that might be developed.

Analytical Methods

The analytical methods for measuring DPP3 in blood utilize specific monoclonal antibodies to separate DPP3 from other related aminopeptidases. These measurements detect either DPP3 enzymatic activity or DPP3 protein concentration. Little is known whether measuring DPP3 enzymatic activity will be clinically useful. However, the enzyme function is inhibited by chelation so studies cannot be performed in EDTA plasma. Most recent studies have utilized an immunoluminometric assay with 2 monoclonal antibodies toward 2 unique epitopes in the 83 kDa protein to measure DPP3 protein concentration (6), specifically without interference from other members of the M49 zinc-dependent metallopeptidase family. This assay can measure concentrations between 2.5 and 200 ng/mL with the 97.5th percentile of a healthy reference population being 22 ng/mL (90% CI 18–34 ng/mL) (5). While no clinical utility has been described of abnormally low DPP3 concentration, the ubiquitously expressed DPP3 is known to be released on cellular death resulting in increased circulating concentrations in critically ill patients with conditions such as cardiogenic, hemorrhagic, and septic shock. From that perspective, increases have been shown to manifest potent adverse prognostic significance. This assay is currently labeled as research use only and is not presently available for routine clinical use in the United States.

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Clinical Studies

The ability to specifically measure circulating concentrations of DPP3 accurately has led to a variety of clinical investigations in patients with cardiogenic shock (3–5). It has been observed that higher levels of DPP3 are associated with worse contractile performance and an adverse prognosis in patients who present with an acute coronary syndrome over the entire span of subsets that exist in that space, such as ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction. In addition, it appears that higher blood concentrations identify patients who are apt to subsequently develop cardiogenic shock. There are data to suggest that part of this effect is related to the fact that higher concentrations are associated with larger sized infarctions as measured by MRI (4). This may well be an important factor, particularly in patients with cardiogenic shock where ongoing ischemia due to the combination of coronary hypoperfusion along with marked increases in myocardial oxygen consumption can cause ongoing necrosis and, therefore, an increase in the extent of infarction in a given patient. The inability to antagonize this process of ongoing myocardial injury could be a reason why patients with cardiogenic shock are refractory to so many therapies.

With this in mind, a new therapeutic modality that targets DPP3 and lowers its circulating concentration is under investigation. A specific monoclonal antibody called Procizumab has been developed that targets DPP3 for inactivity and degradation (3). It is being tested in Europe to explore whether or not it is safe in humans. If safe, then a trial attempting to interdict the hemodynamic perturbations in patients and the increased myocardial necrosis associated with cardiogenic shock may well be undertaken. Nonetheless, there is much to learn.

Future Directions

Analytically, studies are needed to more precisely define the in vivo and in vitro kinetics of DPP3. It would also be helpful to be able to determine the etiology of DPP3 increases, which may vary depending on what type of shock is present. Finally, it is unclear whether the extent of likely therapeutic benefit can be determined from measuring peak DPP3 concentrations or monitoring serial values.

Clinically, there a therapeutic potential through targeting DPP3 in vivo with the goal of restoring cardiac function in situations such as cardiogenic shock where there are currently few beneficial therapeutic options. In addition, elucidation of the mechanisms by which DPP3 contributes to cardiac dysregulation may be key to refining how to use it DPP3 inhibition optimally. It is also clear that there are other shock states where reduced myocardial suppression as a result of some sort of myocardial depressant factor may play a role. For example, patients with septic shock are known to have myocardial injury (release of cardiac troponin and cardiac specific cell free DNA) and depressed myocardial function. If one could antagonize these effects, it might be of benefit clinically. However, for the present the focus of the therapeutic initiatives targeting DPP3 has been in cardiogenic shock. This approach is unproven but worthy of consideration: it could be the start of an entirely new therapeutic paradigm.

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References

1. Lefer AM, Cowgill R, Marshall FF, Brand ED. Characterization of a myocardial depressant factor present in hemorrhagic shock. Am J Physiol 1967;213:492–8.
2. Ye P, Duan W, Leng Y-Q, Wang Y-K, Tan X, Wang W-Z. DPP3: from biomarker to therapeutic target of cardiovascular diseases. Front Cardiovasc Med 2022;9:974035.
3. Deniau B, Rehfeld L, Santos K, Dienelt A, Azibani F, Sadoune M, et al. Circulating dipeptidyl peptidase 3 is a myocardial depressant factor: dipeptidyl peptidase 3 inhibition rapidly and sustainably improves hemodynamics. Eur J Heart Fail 2020;22:290–9.
4. Wenzl FA, Bruno F, Kraler S, Klingenberg R, Akhmedov A, Ministrini S, et al. Dipeptidyl peptidase 3 plasma levels predict cardiogenic shock and mortality in acute coronary syndromes. Eur Heart J 2023;44:3859–71.
5. Innelli P, Lopizzo T, Paternò G, Bruno N, Radice RP, Bertini RP, et al. Dipeptidyl amino-peptidase3 (DPP3) as an early marker of severity in a patient population with cardiogenic shock. Diagnostics 2023;13:1350–60.
6. Rehfeld R, Funk E, Jha S, Macheroux P, Melander O, Bergmann A. Novel methods for the quantification of dipeptidyl peptidase 3 (DPP3) concentration and activity in human blood samples. J Appl Lab Med 2019;3:943–53.