ESC European Society of Cardiology

European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1649

EDITORIAL COMMENT

Dipeptidyl peptidase 3, a biomarker in cardiogenic shock and hopefully much more

Aurora Magliocca[1], Torbjørn Omland[2,3], and Roberto Latini[1]*

[1]Department of Cardiovascular Medicine, Istituto di Ricerche Farmacologiche Mario Negri – IRCCS, Milano, Italy; [2]Department of Cardiology, Akershus University Hospital, Oslo, Norway; and [3]Center for Heart Failure Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

This article refers to 'Circulating dipeptidyl peptidase 3 is a myocardial depressant factor: dipeptidyl peptidase 3 inhibition rapidly and sustainably improves haemodynamics' by B. Deniau *et al.*, published in this issue on pages xxx.

Cardiogenic shock is a low-cardiac output condition due to primary cardiac dysfunction, resulting in inadequate peripheral tissue oxygen delivery.[1] Despite efforts to improve cardiogenic shock interventions, including mechanical circulatory support and reperfusion therapy for myocardial infarction, outcomes still remain poor.[2] The haemodynamic profile of cardiogenic shock is characterized by low cardiac output, low blood pressure, high filling pressures (central venous pressure and pulmonary capillary wedge pressure) and elevated systemic vascular resistance.[3] The oxygen demand–delivery imbalance of cardiogenic shock results in reduced mixed venous oxygen saturation and increased lactate levels, together with worsening of renal and liver function, and altered mental status. Cardiogenic shock triggers a plethora of endogenous responses, including activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS) in the attempt to increase cardiac output by increasing heart rate and cardiac contractility. At the same time, counter-regulatory systems, such as the natriuretic peptide system, are activated to reduce high filling pressures and ventricular loading and to counteract peripheral vasoconstriction to increase forward blood. Accordingly, circulating levels of most cardiovascular biomarkers are markedly increased in cardiogenic shock,[4] but most are considered epiphenomena and not causal factors in the pathophysiology of cardiogenic shock. The observation made by Deniau *et al.*[5] in this issue of the Journal that the cytosolic enzyme dipeptidyl peptidase 3 (DPP3) not only represents a novel prognostic biomarker but also may be a potential candidate as a bio-target in cardiogenic shock is therefore intriguing.

DPP3, like other members of the dipeptidyl peptidase family, is devoted to the cleavage of vasoactive peptides including angiotensin II and enkephalins (*Table 1*). The limited experimental data that have been published so far suggest that DPP3, through the inactivation of bioactive peptides, is involved in blood pressure regulation, inflammation and pain modulation. In their small, proof-of-concept study, Deniau and colleagues observed that: (i) higher DPP3 levels are associated with mortality in patients with cardiogenic shock; (ii) intravenous administration of DPP3 results in a fast and profound negative inotropic action in healthy mice; (iii) in a mouse model of isoproterenol-induced heart failure (HF), both cardiac and renal function are impaired and DPP3 levels increase, and (iv) an ad hoc inhibitory antibody against DPP3, procizumab (PCZ), reverses cardiac and renal dysfunction in the same murine model. Consequently, DPP3 appears to be a candidate biomarker of outcome severity in cardiogenic shock but, more importantly, it may act as a potential pharmacologic target to improve outcomes in cardiogenic shock through its selective blockade.

It is noteworthy that the time line for the development of a new specific assay of circulating DPP3, to that of a blocking antibody for the same molecule is short, and all has been performed by the same company, to which two of the Authors belong (AB and OH). The same team has developed a humanized non-neutralizing antibody against adrenomedullin (bio-ADM), adrecizumab,[6] on which they are now running a Phase 2 clinical trial in septic shock (http://clinicaltrials.gov identifier: NCT03085758).

The pharmacologic properties of PCZ should also be considered in the evaluation of its therapeutic potential. One of the key findings of the present study is the observation of the rapid myocardial depressant and hypotensive actions of DPP3. The authors demonstrate that the administration of DPP3 in healthy mice rapidly decreases left ventricular shortening fraction and impairs renal haemodynamics with complete recovery 120 min after DDP3 injection. The rapid onset of the negative inotropic action induced by DPP3 is striking, given the putative mechanism of degradation of bioactive peptides such as angiotensin II. Indeed, as shown in the *in vitro* findings of this study, DPP3 caused a decrease of the plasma levels of angiotensin II and other angiotensin peptides in humans and mice. However, data on the *in vivo* kinetics of the

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.1601

*Corresponding author. Department of Cardiovascular Medicine, Istituto di Ricerche Farmacologiche Mario Negri, IRCCS, Via G. La Masa 19, 20156 Milan, Italy. Email: roberto.latini@marionegri.it

Table 1 Dipeptidyl peptidase family

Name	Peptidase activity	Physiological function
Dipeptidyl peptidase 1 – DPP I	Cysteine hydrolase	Immune response in bacterial infection and sepsis
Dipeptidyl peptidase 2 – DPP II	Serine peptidase	Oligopeptide hydrolysis
Dipeptidyl peptidase 3 – DPP III	Metalloaminopeptidase	Angiotensin II, enkephalins, endorphin inactivation
Dipeptidyl peptidase 4 – DPP IV	Serine peptidase	Glucose homeostasis
Dipeptidyl peptidase 6 – DPP VI	Serine peptidase	Modulation of expression and activation of KCND2
Dipeptidyl peptidase 8 – DPP VIII	Serine peptidase	Immune response
Dipeptidyl peptidase 9 – DPP IX	Serine peptidase	Dipeptide hydrolysis
Dipeptidyl peptidase 10 – DPP X	Serine peptidase	Not defined

KCND2, potassium voltage-gated channel subfamily D member 2.

hydrolytic activity of DPP3 are needed to link the *in vitro* catalytic efficiency of the peptidase with its physiological effects *in vivo*.

The investigators also tested the effects of a DPP3-specific inhibitory antibody, PCZ, in a mouse model of isoproterenol-induced HF. They observed the beneficial effect of PCZ on cardiac function and renal haemodynamics. A rapid and sustained normalization of left ventricular shortening fraction and renal resistive index after a single injection of PCZ has been demonstrated in HF mice. As acknowledged by the authors, this model has been chosen to mimic the pathophysiology of acute HF. However, a more comprehensive assessment of the haemodynamic effect of DPP3 inhibition in this model would have been useful to better characterize the cardiovascular physiologic response to PCZ and to explore the potential clinical application of its effect in acute HF patients. Indeed, in a previous study, DPP3 did not affect haemodynamics in healthy mice or in noradrenaline-induced hypertensive mice.[7] The hypotensive effect of DPP3 was observed only in angiotensin II-infused hypertensive mice, underscoring the key role of RAAS activation for DPP3 effects.

Interestingly, the authors observed an increase in myocardial oxidative stress after DPP3 administration and, conversely, a significant reduction of reactive oxygen species (ROS) in HF mice treated with PCZ. These findings are not in line with the recent evidence of increased ROS production in mice with genetic deletion of DPP3 compared to wild-type animals.[8] In that study, the authors generated a DPP3 knockout mouse in which they observed that sustained oxidative stress in the bone tissue resulted in an alteration of the bone tissue and metabolism leading to a bone loss phenotype.

Despite the remarkable findings of this study, the underlying mechanisms for the myocardial and renal protection induced by DPP3 inhibition remain to be elucidated. Future aspects to be clarified concerning the pathophysiology of DPP3-induced myocardial impairment and the beneficial effect of its inhibition include reproducibility, efficacy, and safety in different experimental models of HF.

Although the data are preliminary, based on small numbers and should be considered hypothesis-generating, the story is fascinating and in the absence of effective therapies of cardiogenic shock, should pave the way for other studies to better define the pathophysiological role(s) of DPP3 and its therapeutic potential. To what extent the findings in the cardiogenic shock setting can be generalized to the much broader population of patients presenting with acute HF remains unknown. Although the exact mechanism responsible for the association between DPP3 and outcome in cardiogenic shock remains to be elucidated, the concept of DPP3 inactivation by PCZ as a therapeutic strategy in cardiogenic shock is interesting. Whether PCZ may be of potential clinical use in settings other than cardiogenic shock, e.g. in septic shock, also merits further investigation.

It is quite impressive how times for the development of new biomarkers, assays and targeted therapies are much shorter now than in the past. For comparison, consider the timeline of natriuretic peptides: from the discovery of atrial natriuretic factor by de Bold in 1981,[9] purified and proposed as biomarkers for HF during the next decade and tested as therapy in HF, without great success, during the last 20 years. In that perspective, it is remarkable that even the first chapter in the story of DPP3 authored by Deniau *et al.* contain exciting new data on both its role as a biomarker and as a potential new therapeutic target in acute HF.

Conflict of interest: none declared.

References

1. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation* 2017;**136**:e232–e268.
2. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Rich-Ardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Böhm M, Ebelt H, Schneider S, Schuler G, Werdan K; IABP- SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**:1287–1296.
3. Freis ED, Schnaper HW, Johnson RL, Schreiner GE. Hemodynamic alterations in acute myocardial infarction, I: cardiac output, mean arterial pressure, total peripheral resistance, central and total blood volumes, venous pressure and average circulation time. *J Clin Invest* 1952;**31**:131–140.
4. Fuernau G. Lactate and other biomarkers as treatment target in cardiogenic shock. *Curr Opin Crit Care* 2019;**25**:403–409.
5. Deniau B, Rehfeld L, Santos K, Dienelt A, Azibani F, Sadoune M, Kounde PR, Samuel JL, Tolpannen H, Lassus J, Harjola VP, Vodovar N, Bergmann A, Hartmann O, Mebazaa A, Blet A. Circulating dipeptidyl peptidase 3 is a myocardial depressant factor: dipeptidyl peptidase 3 inhibition rapidly and sustainably improves haemodynamics. *Eur J Heart Fail* 2019 Aug 31. https://doi.org/10.1002/ejhf.1601 [Epub ahead of print].
6. Voors AA, Kremer D, Geven C, Ter Maaten JM, Struck J, Bergmann A, Pickkers P, Metra M, Mebazaa A, Dungen HD, Butler J. Adrenomedullin in heart failure: pathophysiology and therapeutic application. *Eur J Heart Fail* 2019; **21**: 163–171.

7. Pang X, Shimizu A, Kurita S, Zankov DP, Takeuchi K, Yasuda-Yamahara M, Kume S, Ishida T, Ogita H. Novel therapeutic role for dipeptidyl peptidase III in the treatment of hypertension. *Hypertension* 2016;**68**:630–641.
8. Menale C, Robinson LJ, Palagano E, Rigoni R, Erreni M, Almarza AJ, Strina D, Mantero S, Lizier M, Forlino A, Besio R, Monari M, Vezzoni P, Cassani B, Blair HC, Villa A, Sobacchi C. Absence of dipeptidyl peptidase 3 increases oxidative stress and causes bone loss. *J Bone Miner Res* 2019;**34**:2133–2148.
9. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 1981;**28**:89–94.