Serum apelin levels and cardiovascular diseases

Lutfu Askin, Husna Sengul Askin, Okan Tanrıverdi, Ali Gokhan Ozyildiz, Hakan Duman

ABSTRACT

Apelin is a G protein-linked receptor endogenous ligand, synthesized as a 77-amino acid pre-propeptide. Increased expression of apelin is present in many cardiovascular (CV) tissues, including cardiomyocytes. It is a peripheral vasodilator and one of the most potent stimulants of ventricular contraction. Apelin may be a valuable therapeutic for both blood pressure regulation and myocardial performance. More information is needed for the CV pathophysiology of apelin. We will discuss the importance of apelin level in CV diseases in this review.

Keywords: Apelin; cardiomyocytes; inotropy; myocardial performance.

A pelin is originated from white adipose tissue and binds to G protein as a ligand [1, 2]. Apelin appears to be a promising adipocytokine for cardiovascular diseases (CVDs). Since there is no review in the literature about this subject, we aim to focus on the prognostic significance of apelin levels in CVD.

THE ROLE OF SERUM APELIN LEVELS IN ST ELEVATION MYOCARDIAL INFARCTION

Apelin is a potent inotrope besides vasodilation [3]. Low apelin level is one of the causes of heart failure (HF); in a study with rats, it has been shown to protect myocardial damage caused by isoproterenol [4–6].

Apelin is a promising therapeutic target for ischemic heart disease. Liu et al. [7] reported that serum apelin level might be used as an essential predictor of post-PCI prognosis in ST-elevation myocardial infarction (STEMI). Apelin is a component of CV homeostasis [8–10]. In two studies conducted in Poland, plasma apelin levels were lower in STEMI patients and it was insufficient to predict adverse events [11, 12].

Among STEMI, those with low apelin levels have poor clinical profiles. The MACE incidence is also higher in these patients [13]. Apelin decreased in patients with the severe left ventricular (LV) dysfunction, and low apelin levels predict the survival of STEMI patients [4, 14]. The relationship of apelin and morbidity proves that it can be an independent predictor of prognosis [7].

Apelin causes vasodilatation and plays a role in inflammation [14]. Studies showed that apelin prevented the formation of the aortic aneurysm by its direct anti-inflammatory effect [15]. Besides, apelin limits oxidative stress, the main component of myocardial reperfusion injury. Apelin prevents reperfusion damage by reducing reactive oxygen species (ROS) and affecting superoxide dismutase enzyme [16–18]. Furthermore, apelin is an inotropic agent [19].
THE RELATIONSHIP BETWEEN APELIN AND CONTRAST-INDUCED NEPHROPATHY IN PATIENTS WITH CONGESTIVE HF

The effect of the contrast agent to cause nephropathy is through ROS and vasoconstriction [20]. Apelin, a recently discovered cytokine, has several effects on the CV system. In addition to antioxidant and anti-inflammatory activity, apelin plays a role in homeostatic balance by its vasodilator and inotropic effects (Fig. 1) [21–23]. Apelin causes vasodilation by releasing endothelium-derived nitric oxide (NO) [24]. Apelin causes potent heart contraction [25]. In studies with rats, cardiac contraction has been impaired after a decrease in apelin level [26]. Besides, apelin causes ventricular remodeling heart tissue, and its level is increased in HF. Apelin regulates fluid homeostasis by affecting the hypothalamus and pituitary [21]. Short peptide of apelin regulates the CV system, and longer sequence peptides of apelin regulate the immune system [27]. In recently published experiments, apelin has been shown to reduce cytochrome C release and caspase-3 activation in neuron cultures as well as ROS and mitochondrial depolarization. Apelin-13 acts as an endogenous cell-protective cytokine capable of inhibiting excitotoxic death and apoptosis in neurons [28]. In studies of atherosclerosis and diabetes models, apelin increases NO bioavailability by reducing reactive ROS production [29].

APELIN LEVELS IN CORONARY ARTERY DISEASE (CAD)

Increased expression of apelin is present in cardiomyocytes, CV tissues, vascular smooth muscle, and endothelial cells. Apelin has a positive effect on the CV system through a series of reactions, such as vasodilation, contraction, and degradation of inflammation. The anti-atherogenic property of apelin in humans is still unproven [30]. Some researchers suggested that apelin reduction is associated with coronary atherosclerosis. Apelin may be a novel biomarker for determining the severity and development of coronary atherosclerosis, but extensive studies should support this result [26].

ARTERIOVENOUS FISTULA TYPE, NYHA CLASS, AND APELIN LEVELS IN HEMODIALYSIS (HD) PATIENTS

Arteriovenous fistula affects both systolic and diastole in the heart. Fistula may cause HF by increased cardiac output. Apelin was significantly higher in NYHA Class I–II patients than NYHA Class III–IV. The relationship between apelin and LV end-diastolic diameter in hemodialysis patients supports this finding [31]. Apelin is released from the endothelium in the CV system [32]. Malyszko et al. [31] showed that von Willebrand factor is associated with apelin. After myocardial damage, the release of apelin increases from endothelial cells [33]. Malyszko et al. [34] reported that apelin affects cardiac functions in HD patients. As a result, apelin decreases in dialysis patients with CAD, and its level is associated with cardiac functions. Apelin is involved in the pathogenesis of CAD in chronic renal failure (CRF). Due to the inotropic properties of apelin, it may be useful clinically in uremic cardiomyopathy.

Low apelin levels have not yet been disclosed in patients with CRF. Carabolism of cellular proapelin and/or excessive apelin release may cause decreased apelin levels. Hemodynamic factors such as hypervolemia or hyperkinetic circulation may contribute to these findings [27].
APELIN IN HYPERTROPHIC CARDIOMYOPATHY (HCM)

HCM characterized by sarcomeric protein mutation causes sudden death in young. Hypertrophy and fibrosis are the two causes of all adverse events in HCM [35, 36]. Plasma apelin levels correlate with the degree of late gadolinium increase (LGE) in HCM patients. The effect of lower apelin level on fibrosis has not been elucidated yet in HCM. Immunocytochemistry analysis has shown that apelin is exposed in cardiomyocytes, vascular, and endocardial endothelium [37]. The atrium and epicardial adipose tissues are the main resource of apelin. Furthermore, only apelin-13 was shown as the main isoform in human in spectral analysis [38].

Cardiac, renal, and pulmonary artery fibrosis are associated with decreased apelin expression. Cardiac fibrosis often accompanies HF. Apelin rises in the early phase of HF, but progressively reduces during the disease period. In HCM, reduced apelin levels were detected in LGE-positive patients due to atrial fibrosis [39].

SERUM APELIN AND BICUSPID AORTIC VALVE (BAV)

BAV is one of the common congenital diseases. While it has a benign course in childhood, valve dysfunction may develop in advanced ages. BAV cause not only the aortic valve involvement but may also cause enlargement of thoracic aorta [40, 41].

While BAV is frequently accompanied by valvular diseases, concurrent aortic pathologies such as aneurysm and dissection may be present in some patients. The mechanisms that cause these different manifestations are not clear. Unidentified interactions at the molecular level may be responsible for these differences.

After intravenous administration of apelin-13 to rats, decrease in blood pressures (BP) was observed [42]. Tatemoto et al. [24] showed that NO mediated the vasodilatory effects of apelin. Endothelial NO synthase release disruption is the cause of aortic dilatation [43]. Low serum apelin level was observed in the BAV regardless of the aortic diameter. Apelin level reduction may cause aneurysm formation in BAV [43].

THE RELATIONSHIP OF SERUM APELIN LEVELS WITH LV HYPERTROPHY (LVH) IN HYPERTENSION

Increased cardiomyocyte size and fibrosis in the extracellular matrix are pathological changes in LVH [44]. Ye et al. [45] reported that serum apelin level is independently associated with LVH in essential hypertensive patients. Furthermore, apelin may be the therapeutic target to improve blood pressure regulation and cardiac function.

APELIN AND CALCIFIC AORTIC STENOSIS

Aortic valve stenosis (AS) is one of the most common heart diseases, with an annual mortality rate of approximately 14%. Associated structural diseases complicate the treatment of AS. Different factors are related to the onset and progression of AS [46].

Duman et al. [47] showed decreased apelin levels and increased hs-CRP concentrations in patients with severe calcific AS. Their findings may help clarify the pathophysiological role of apelin in CVD.

Conclusion

Recent studies emphasize that apelin is a potent vasodilator and an inotropic agent. Apelin reduces myocardial damage caused by myocardial infarction. Due to its inotropic properties, it may be a new treatment option for patients with HF. Little evidence exists that apelin is an independent predictor for CVD. Extensive studies should support the data to accept that apelin determines the severity and development of coronary atherosclerosis.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – LA, HSA; Design – LA, HSA, OK; Supervision – AGO, HD; Fundings – HD; Materials – LA; Data collection and/or processing – LA, OT; Analysis and/or interpretation – LA, HSA; Literature review – LA; Writing – OT; Critical review – LA.

REFERENCES

1. Hou X, Zeng H, He X, Chen JX. Sirt3 is essential for apelin-induced angiogenesis in post-myocardial infarction of diabetes. J Cell Mol Med 2015;19:53–61.
2. Li L, Zeng H, Hou X, He X, Chen JX. Myocardial injection of apelin-overexpressing bone marrow cells improves cardiac repair via upregulation of Sirt3 after myocardial infarction. PLoS One 2013;8:e71041.
3. Dai T, Ramirez-Correa G, Gao WD. Apelin increases contractility in failing cardiac muscle. Eur J Pharmacol 2006;553:222–8.
4. Chong KS, Gardner RS, Morton JJ, Ashley EA, McDonagh TA. Plasma concentrations of the novel peptide apelin are decreased in patients with chronic heart failure. Eur J Heart Fail 2006;8:355–60.
5. Hou X, Hu Z, Xu H, Xu J, Zhang S, Zhong Y, et al. Advanced glycation endproducts trigger autophagy in cardiomyocyte via RAGE/PI3K/AKT/mTOR pathway. Cardiovasc Diabetol 2014;13:78.

6. Jia YX, Pan CS, Zhang J, Geng B, Zhao J, Gerns H, et al. Apelin protects myocardial injury induced by isoproterenol in rats. Regul Pept 2006;133:147–54.

7. Liu HT, Chen M, Yu J, Li WJ, Tao L, Li Y, et al. Serum apelin level predicts the major adverse cardiac events in patients with ST elevation myocardial infarction receiving percutaneous coronary intervention. Medicine (Baltimore) 2015;94:e449.

8. Magniere JJ, Kleinz MJ, Pitkin SL, Davenport AP. [Pyr1]apelin-13 identified as the predominant apelin isoform in the human heart: vasoactive mechanisms and inotropic action in disease. Hypertension 2009;54:598–604.

9. Yi L, Hou X, Zhou J, Xu L, Ouyang Q, Liang H, et al. HIF-1α genetic variants and protein expression confer the susceptibility and prognosis of gliomas. Neuromolecular Med 2014;16:578–86.

10. Hou X, Hu Z, Huang X, Chen Y, He X, Xu H, et al. Serum osteopontin, but not OPN gene polymorphism, is associated with LVH in essential hypertensive patients. J Mol Med (Berl) 2014;92:487–95.

11. Tycinska AM, Sobkowicz B, Mroczko B, Sawicki R, Musial WJ, Dobrzycki S, et al. The value of apelin-36 and brain natriuretic peptide measurements in patients with first ST-elevation myocardial infarction. Clin Chim Acta 2010;411:2014–8.

12. Kuklinska AM, Sobkowicz, Sawicki R, Musial WJ, Waszkiewicz E, Bolinska S, et al. Apelin: a novel marker for the patients with first ST-elevation myocardial infarction. Heart Vessels 2010;25:363–7.

13. Zhang BH, Guo CX, Wang HX, Lu LQ, Wang YJ, Zhang LK, et al. Cardioprotective effects of adipokine apelin on myocardial infarction. Heart Vessels 2014;29:679–89.

14. Japp AG, Newby DE. The apelin-APJ system in heart failure: pathophysiologic relevance and therapeutic potential. Biochem Pharmacol 2008;75:1882–92.

15. Leeper NJ, Tedesco MM, Kojima Y, Schultz GM, Kundu RK, Ashley EA, et al. Apelin prevents aortic aneurysm formation by inhibiting macrophage inflammation. Am J Physiol Heart Circ Physiol 2009;296:H1329–35.

16. Zeng XJ, Zhang LK, Wang HX, Lu LQ, Ma LQ, Tang CS. Apelin protects heart against ischemia/reperfusion injury in rat. Peptides 2009;30:1144–52.

17. Hou XW, Son J, Wang Y, Yu XY, Lian Q, Majiti W, et al. Granulocyte colony-stimulating factor reduces cardiomyocyte apoptosis and improves cardiac function in adriamycin-induced cardiomyopathy in rats. Cardiovasc Drugs Ther 2006;20:85–91.

18. Hou XW, Wang LF, Wang N, Pang D, Hui B, Zhou YL, et al. The G501C polymorphism of oxidized LDL receptor gene [OLR-1] is associated with susceptibility and serum C-reactive protein concentration in Chinese essential hypertensives. Clin Chim Acta 2008;388:200–3.

19. Xu H, Hou X, Wang N, Hui B, Jin J, Yun S, et al. Gender-specific effect of estrogen receptor-1 gene polymorphisms in coronary artery disease and its angiographic severity in Chinese population. Clin Chim Acta 2008;395:130–3.

20. Sholy H, Zukermann R, Soni A, Nikolsky E. Contrast induced nephropathy: an update on diagnosis, predictors, implications and preventive strategies. Minerva Med 2012;103:465–86.

21. Masri B, van den Berge L, Sorli C, Knibiehler B, Audigier Y. Signalisation apeline et physiopathologie vasculaire [Apelin signalisation and vascular physiopathology]. J Soc Biol 2009;203:171–9.

22. Farkasfalvi K, Stagg MA, Coppen SR, Siedlecka U, Lee J, Soppa GK, et al. Direct effects of apelin on cardiomyocyte contractility and electrophysiology. Biochem Biophys Res Commun 2007;357:889–95.

23. Pisarenko OI, Serebiarkova LI, Pelogekina IuA, Studneva IM, Khkatri DN, Tkitishivili OV, et al. Involvement of NO-dependent mechanisms of apelin action in myocardial protection against ischemia/reperfusion damage. [Article in Russian]. Kardiologiya 2012;52:52–8.

24. Tateme T, Takayama K, Zou MX, Kumaki I, Zhang W, Kurono K, et al. The novel peptide apelin lowers blood pressure via a nitric oxide-dependent mechanism. Regul Pept 2001;99:87–92.

25. Ashley EA, Powers J, Chen M, Kundu R, Finsterbach T, Caffarelli A, et al. The endogenous peptide apelin potently improves cardiac contractility and reduces cardiac loading in vivo. Cardiovasc Res 2005;65:73–82.

26. Chandrasekaran B, Dar O, McDonagh T. The role of apelin in cardiovascular function and heart failure. Eur J Heart Fail 2008;10:725–32.

27. Földes G, Horkay F, Szokodi I, Vuotteenaho O, Ilves M, Lindstedt KA, et al. Circulating and cardiac levels of apelin, the novel ligand of the orphan receptor APJ, in patients with heart failure. Biochem Biophys Res Commun 2003;308:480–5.

28. Zeng XJ, Yu SP, Zhang L, Wei L. Neutrophoretic effect of the endogenous neural peptide apelin in cultured mouse cortical neurons. Exp Cell Res 2010;316:1773–83.

29. Chun HJ, AliZA, Kojima Y, Kundu RK, Sheikh AY, Agrawal R, et al. Apelin signaling antagonizes Ang II effects in mouse models of atherosclerosis. J Clin Invest 2008;118:3343–54.

30. Hashimoto T, Kihara M, Imai N, Yoshida S, Shimoyamada H, Yasuza H, et al. Requirement of apelin-apelin receptor system for oxidative stress-linked atherosclerosis. Am J Pathol 2007;171:1705–12.

31. Malyszko J, Kozminska P, Malyszko J, Mysliwiec M. Type of arteriovenous fistula, NYHA class and apelin in hemodialyzed patients. Int Urol Nephrol 2011;43:185–90.

32. Atluri P, Morine KJ, Liao GP, Panllio CM, Berry MF, Hsu VM, et al. Ischemic heart failure enhances endogenous myocardial apelin and APJ receptor expression. Cell Mol Biol Lett 2007;12:127–38.

33. Sheikh AY, Chun HJ, Glassford AJ, Kundu RK, Kutschka I, Ardigó D, et al. In vivo genetic profiling and cellular localization of apelin reveals a hypoxia-sensitive, endothelial-centered pathway activated in ischemic heart failure. Am J Physiol Heart Circ Physiol 2008;294:F188–98.

34. Malyszko J, Malyszko JS, Kozminska P, Mysliwiec M. Apelin and cardiac function in hemodialyzed patients: possible relations? Am J Nephrol 2006;26:121–6.

35. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet 2013;381:242–55.

36. Mano T, HCM. Int Heart J 2018;59:243–44.

37. Kleinz MJ, Davenport AP. Immunocytochemical localization of the endogenous vasoactive peptide apelin to human vascular and endocardial endothelial cells. Regul Pept 2004;118:119–25.

38. Zhen EY, Higgs RE, Gutierrez JA. Pyrogulatamyl apelin-13 identified as the major apelin isoform in human plasma. Anal Biochem 2013;442:1–9.

39. Huang S, Chen L, Lu L, Li L. The apelin-APJ axis: A novel potential therapeutic target for organ fibrosis. Clin Chim Acta 2016;456:81–8.

40. Basso C, Boschello M, Perrone C, Mecenero A, Cera A, Bicgo D, et al. An echocardiographic survey of primary school children for bicuspid aortic valve. Am J Cardiol 2004;93:661–3.

41. Beroukhim RS, Kruzick TL, Taylor AL, Gao D, Yetman AT. Progression of aortic dilation in children with a functionally normal bicuspid aortic valve. Am J Cardiol 2006;98:828–30.

42. Lee DK, Cheng R, Nguyen T, Fan T, Kariyawasam AP, Liu Y, et al. Characterization of apelin, the ligand for the APJ receptor. J Neuro-
43. Aicher D, Urbich C, Ziemer A, Dimmeler S, Schäfers HJ. Endothelial nitric oxide synthase in bicuspid aortic valve disease. Ann Thorac Surg 2007;83:1290–4.

44. Drazner MH. The progression of hypertensive heart disease. Circulation 2011;123:327–34.

45. Ye L, Ding F, Zhang L, Shen A, Yao H, Deng L, et al. Serum apelin is associated with left ventricular hypertrophy in untreated hypertension patients. J Transl Med 2015;13:290.

46. Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Established and emerging vascular risk factors and the development of aortic stenosis: an opportunity for prevention? Expert Opin Ther Targets 2008;12:809–20.

47. Duman H, Bahçeci I, Hamur H, Demirelli S, Ramazan Dilek A, Erdogan T, et al. The relationship between serum apelin levels and the severity of calcific aortic stenosis. Acta Cardiol Sin 2018;34:259–66.