



Letter to the Editor

The heart and coronary arteries as primary target in severe allergic reactions: Cardiac troponins and the Kounis hypersensitivity-associated acute coronary syndrome



Nicholas G. Kounis^{a,*}, Andreas Mazarakis^b, Constantinos Bardousis^b, Nicholas Patsouras^c

^a Department of Medical Sciences, Southwestern Greece Highest Institute of Education and Technology, Patras, Achaia, Greece

^b Department of Cardiology, "Saint Andrews" State General Hospital, Patras, Achaia, Greece

^c Department of Cardiology, University of Patras Medical School, Rio, Patras, Achaia, Greece

ARTICLE INFO

Article history:

Received 21 June 2015

Accepted 27 June 2015

Available online 2 July 2015

Keywords:

Acute myocardial infarction

Allergy

Anaphylaxis

Angioedema

Kounis syndrome

Troponins

Cardiac troponins T, I and C are cardiac regulatory proteins that constitute a complex able to control the calcium mediated interaction between actin and myosin. Troponin T binds the troponin components to tropomyosin, troponin I inhibits the interaction of myosin with actin, and troponin C contains the binding sites for Ca^{2+} that helps initiate contraction. Specific genes code the cardiac forms of troponins that are theoretically unique to the myocardium. Monoclonal antibodies to troponin epitopes can detect troponins in the serum. These antibodies are highly specific for cardiac troponin and have negligible crossreactivity with skeletal muscle troponins. Furthermore, these proteins do not exist in smooth muscle cells. Recently, an upstream open reading frame peptide from the human troponin T gene has been suggested to improve cardiac troponin T specificity in myocardial infarction patients [1].

In the very important study published in *International Journal of Cardiology* by Lippy et al. [2], 31 patients admitted to the emergency department and suffering from anaphylaxis, angioedema, urticaria and urticaria–angioedema were found to have significantly increased

troponin I serum levels in comparison with 125 healthy controls. In the subgroup of anaphylaxis, which is life threatening severe allergic reaction, troponin I levels were higher than those of patients with milder allergic reactions. The authors suggested systematic troponin measurement in patients with acute allergic reactions in order to detect and treat potential myocardial injury. These findings might have profound clinical, therapeutic and pathophysiologic implications as far as anaphylaxis, myocardial injury and Kounis allergy-associated acute coronary syndrome [3] is concerned. The above study comes to support previous laboratory and clinical evidence that inflammatory mediators released locally and in the systemic circulation during allergic and anaphylactic reactions are causing myocardial damage implicated in anaphylactic cardiac shock and cerebral hypoperfusion. Indeed, biogenic amines such as histamine, enzymes such as the neutral proteases chymase, tryptase, cathepsin-D, peptides, proteoglycans, chemokines, cytokines, growth factors and arachidonic acid products such as leukotrienes, thromboxane, prostacyclin, platelet activating factor (PAF) and tumor necrosis factor- α are released during mast cell activation [4]. Histamine induces coronary vasoconstriction, induces tissue factor expression and activates platelets. Tryptase can activate matrix metalloproteinases that can degrade the collagen cap and induce plaque erosion and rupture and possesses thrombotic and fibrinolytic properties. Chymase and cathepsin-D can convert angiotensin I to angiotensin II, which is a major vasoconstricting substance. Leukotrienes are also powerful vasoconstrictors and their biosynthesis is enhanced in the acute phase of unstable angina. Thromboxane is a potent mediator of platelet aggregation with vasoconstricting properties and PAF, in myocardial ischemia, acts as proadhesive signaling molecule via activation of leukocytes and platelets to release leukotrienes or as a direct vasoconstrictor. Platelets bearing high and low affinity $\text{FC}\gamma\text{RI}$, $\text{FC}\gamma\text{RII}$, $\text{FC}\epsilon\text{RI}$ and $\text{FC}\epsilon\text{RII}$ receptors are also involved in allergic and anaphylactic reactions resulting in adhesion, activation and aggregation. All of the above can cause coronary spasm and coronary thrombosis leading to myocardial ischemia and myocardial injury. It is not surprising, therefore, why troponin was found elevated in such circumstances. The following experimental and clinical evidence supports our view that in allergic and anaphylactic reactions, the heart and especially the coronary arteries are the primary target of the released mediators

* Corresponding author at: Queen Olga Square, 7 Aratou Street, Patras 26221, Greece.
E-mail address: ngkounis@otenet.gr (N.G. Kounis).

that induce myocardial injury resulting in troponin raising and physicians should focused their attention on this matter:

- 1-. In experiments with ovalbumin sensitized guinea pigs it was found that, during anaphylaxis, the main findings were acute myocardial ischemia, decrease in cardiac output, initial raise in arterial blood pressure and increase in left ventricular end diastolic pressure indicating pump failure. The latter, according to the authors, definitely excludes peripheral vasodilatation as a cause of the registered anaphylactic cardiac damage [5].
- 2-. In similar experiments with ovalbumin sensitized guinea pigs it was shown that, after ovalbumin challenge, heart rate and left ventricular end diastolic pressure were markedly increased while coronary flow, aortic flow, left ventricular diastolic pressure and LVdp/dtmax were profoundly decreased. A specific PAF antagonist given before anaphylactic challenge inhibited all of the above [6].
- 3-. Other experiments with isolated guinea pig hearts undergoing anaphylaxis after an intra-aortic injection of antigen showed prompt and prolonged decrease in coronary blood flow, abrupt heart rate increase that peaked within 2 min, and transient increase in ventricular contractile force, followed by a prolonged decrease [7].
- 4-. Anaphylactic cardiac damage, in sensitized guinea pigs, may be dissociated temporarily into 2 sets of events: first, initial primary cardiac reaction caused by the intracardiac release of histamine and second a subsequent cardiovascular reaction secondary to the systemic release of mediators [8].
- 5-. In recent experiments with sensitized mice, it was found that anaphylactic hypotension is caused by a decreased in cardiac output via PAF and histamine and not by peripheral vasodilatation [9].
- 6-. In ovalbumin sensitized Wistar rats, the antigen administration induced decrease in coronary blood flow and in the maximum increasing rate of systolic left ventricular pressure (dp/dtmax) with an increased coronary vascular resistance as evidence of coronary spasm [10].

7. In the clinical setting there are several anecdotal reports according to which patients with anaphylactic cardiac collapse, manifesting as Kounis syndrome with increased serum troponin, do not respond to intravenous fluid administration and only inotropic therapy, but required coronary event treatment protocol. This denotes that the heart and especially the coronary arteries are the primary target of the allergic inflammatory mediators that induce coronary injury with increased troponin levels. Furthermore, troponin levels have been found increased in subclinical and clinical presentation of Kounis syndrome [11]. In *Int J Cardiol* there are also reports [12,13] confirming our view. For example, an atopic female nurse, with previous atopic eczema, asthma, and allergy to milk protein who suffered an anaphylactic reaction, her hemodynamic status was unresponsive to intravenous administration of fluids such as Ringer's acetate, antiallergic treatment with adrenaline and corticosteroids and her condition was complicated with pulmonary congestion and reduced ejection fraction. The patient, however, recovered with myocardial infarction protocol treatment. It was commented that hemodynamic disturbance was most probably due to myocardial stunning leading to reduced cardiac output rather than due to fluid extravasation.

In another patient with peri-operative anaphylactic shock due to gelofusine infusion and increased troponin, treatment with metaraminol and epinephrine not only worsened the hypotension but the cardiac output was vanished within 3 min. The patient recovered gradually with stopping gelofusine infusion, administration intravenous antihistamine and steroid and ongoing inotropic support.

All of the above show that, mediators released during allergic and anaphylactic episodes affect the heart and especially the coronary arteries leading to myocardial injury and raised troponin levels. In this respect, the suggestion of Lippi et al. [2] to measure cardiac biomarkers during anaphylaxis, in the absence of obvious myocardial ischemia, in order to identify and manage potential myocardial injury seems to be justifiable.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

- [1] J. Lee, J. Young, C.M. Frampton, S. Aldous, R.W. Troughton, M. Than, A.M. Richards, C.J. Pemberton, A novel troponin T peptide in humans: assay, biochemistry and preliminary findings in acute coronary syndromes, *Int. J. Cardiol.* 190 (2015) 68–74.
- [2] G. Lippi, R. Buonocore, F. Schirosa, G. Cervellini, Cardiac troponin I is increased in patients admitted to the emergency department with severe allergic reactions. A case-control study, *Int. J. Cardiol.* 194 (2015) 68–69.
- [3] N.G. Kounis, Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int. J. Cardiol.* 110 (2006) 7–14.
- [4] N.G. Kounis, N. Patsouras, N. Grapsas, G. Hahalis, Histamine induced coronary artery spasm, fish consumption and Kounis syndrome, *Int. J. Cardiol.* 193 (2015) 39–41.
- [5] S.B. Felix, G. Baumann, W.E. Berdel, Systemic anaphylaxis—separation of cardiac reactions from respiratory and peripheral vascular events, *Res. Exp. Med. (Berl.)* 190 (1990) 239–352.
- [6] A. Tosaki, M. Koltai, P. Braquet, L. Szekeres, Possible involvement of platelet activating factor in anaphylaxis of passively sensitised, isolated guinea pig hearts, *Cardiovasc. Res.* 23 (1989) 715–722.
- [7] R. Levi, Cardiac Anaphylaxis: Models, Mediators, Mechanisms, and Clinical Considerations, in: G. Marone, L.M. Lichtenstein, M. Condorelli, A.S. Fauci (Eds.), *Human Inflammatory Disease, Clinical Immunology*, vol. 1, Decker, Toronto, Canada 1988, pp. 93–105.
- [8] J.H. Zavec, R. Levi, Separation of primary and secondary cardiovascular events in systemic anaphylaxis, *Circ. Res.* 40 (1977) 15–19.
- [9] M. Wang, T. Shibamoto, M. Tanida, Y. Kuda, Y. Kurata, Mouse anaphylactic shock is caused by reduced cardiac output, but not by systemic vasodilatation or pulmonary vasoconstriction, via PAF and histamine, *Life Sci.* 116 (2014) 98–105.
- [10] Y. Kuda, Y. Kurata, M. Wang, M. Tanida, T. Shibamoto, Major contribution of vasospasm-induced coronary blood flow reduction to anaphylactic ventricular dysfunction assessed in isolated blood-perfused rat heart, *Cardiol. J.* 21 (2014) 11–177.
- [11] A. Mazarakis, N.K. Karogiannis, G.C. Almpanis, et al., Subclinical and clinical presentation of Kounis syndrome: another cause of troponin elevation? *Int. J. Cardiol.* 157 (2012) 258–260.
- [12] O.A. Kajander, M.P. Virtanen, S. Sclarovsky, K.C. Nikus, Iatrogenic inverted takotsubo syndrome following intravenous adrenaline injections for an allergic reaction, *Int. J. Cardiol.* 165 (2013) e3–e5.
- [13] G. Shah, G. Scadding, N. Nguyen-Lu, et al., Peri-operative cardiac arrest with ST elevation secondary to gelofusin anaphylaxis—Kounis syndrome in the anaesthetic room, *Int. J. Cardiol.* 164 (2013) e22–e26.