



Correspondence

Clinical and subclinical leaflet thrombosis in bioprosthetic aortic valves: A manifestation of Kounis syndrome?



Nicholas G. Kounis^{a,*}, Nicholas Grapsas^b, George D. Soufras^b, Dimitrios Lianas^b,
Nicholas Patsouras^c, George Hahalis^c

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

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

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

ARTICLE INFO

Article history:

Received 20 February 2016

Accepted 19 March 2016

Available online 28 March 2016

Keywords:

Allergy

Bioprosthetic valves

Heart failure

Kounis syndrome

Thrombosis

Calcific aortic valve stenosis is the most prevalent valve disease for the elderly people and transcatheter aortic valve implantation has become, nowadays, new treatment option for inoperable patients. The rapid growth of this procedure has been spread worldwide, with the performance of more than 200,000 such procedures. However, very early, early, late and very late thrombotic complications may accompany this procedure. In the very interesting report published in the *International Journal of Cardiology* [1] an 81 year old male underwent transcatheter aortic valve implantation with a 31 mm CoreValve for the treatment of symptomatic severe aortic stenosis. Three years later the mean aortic gradient increased and transoesophageal echocardiography revealed that one of the three leaflets was completely immobile due to valve leaflet thrombosis. Following this, the patient suffered an ischemic stroke but recovered fully on treatment with rivaroxaban. This report raises important issues on causality, pathophysiology, timing, ischemic stroke, prevention and treatment of such thrombotic complications:

–Several causes and mechanisms of thrombus formation, associated with transcatheter aortic valve implantation have been incriminated so far. They include incomplete valve expansion, sub-optimal stenting, valve malposition, incomplete apposition, pertinent antithrombotic

treatment, inadequate antithrombotic therapy, prothrombotic conditions and coagulation disorders, hypersensitivity to device components, foreign body reaction and Kounis syndrome from drugs administered during the procedure [2]. Indeed, the structure composition of the various implanted aortic valves seems to play an important role in the pathogenesis of leaflet thrombosis. CoreValve (Medtronic, Minneapolis, Minnesota) porcine pericardium valve has nitinol (nickel-titanium alloy) stent, Portico (St. Jude Medical, Minneapolis, Minnesota) bovine pericardium valve has also nitinol stent and Edward Sapien (Edwards Lifesciences, Irvine, California) bovine pericardium valve has polyethylene terephthalate skirt and cobalt chromium stent. The latter has misleading term because it contains also nickel, titanium, molybdenum and iron. These metals and polymer are great sensitizers able to produce corresponding IgE antibodies [3]. In the United States, nickel, chromium and cobalt induce allergic reactions in 14%, 4% and 9%, while in Europe, in about 20%, 4% and 7%, respectively [4].

–As far as pathophysiology of leaflet thrombosis is concerned, the nitinol, an alloy composed of 45% titanium and 55% nickel that is contained in CoreValve and Portico valve could have played an important role. A “device syndrome” resembling Kounis syndrome [5] and consisting of chest discomfort, exertional dyspnea, asthenia, palpitations, worsening of migraine headaches, and mild leukocytosis, between postoperative days 2 and 3, have had encountered in patients with Amplatzer device implantation containing also nitinol [6]. All symptoms were resolved within one week with prednisone and clopidogrel administration. Interestingly, in the same report, 2 patients with negative skin patch testing had postoperative atrial fibrillation that was resolved with anti-arrhythmic treatment. Metals can release metal ions while are embedded in the aortic orifice and are directly in touch with the blood stream. Such anions can react with high affinity and low affinity IgE antibody receptors FCγRI, FCγRII, FCεRI and FCεRII, on platelet surface and trigger the thrombotic cascade. Implanted valves constitute, therefore, an ideal surrounding for endothelial damage and dysfunction, together with hemorheologic changes and turbulence as well as platelet dysfunction, coagulation and fibrinolytic disturbances [7].

–In the described patient the time of occurrence of transcatheter heart valve thrombosis had been 3 years after the procedure that is indeed a very late event. However, there are reports of such thrombosis occurring even 5 years after transcatheter valve implantation [8]. This

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

can be explained by the fact that hypersensitivity inflammation goes through three phases, the early phase which lasts minutes, the late phase which lasts from 2 h to 2 days and the chronic phase which follows a continuous, persistent, and repetitive allergen exposure and lasts as long as the allergen is present [9].

The described patient developed an ischemic stroke one month after transcatheter valve thrombosis with full recovery while he was under treatment with rivanoxaban. The incidence of cerebrovascular events following transcatheter aortic valve implantation seems to exceed that after any other cardiac intervention or valve surgery and has been attributed to particulate emboli dislodged by the procedure itself or as a result of thromboembolism [10]. However, it seems likely that stroke and valve thrombosis in transcatheter aortic valve implantation share the same pathophysiology. Kounis syndrome has been found to affect not only coronary arteries but also the cerebral arteries [11]. In the first randomized clinical trial (CHOICE trial) that compared different transcatheter heart valves in high-risk aortic stenosis patients at 5 experienced centers, the rate of stroke at 30 days was 2.6% with self-expandable valves and 5.8% with balloon expandable valves [12]. In another trial that took place in 4 experienced European centers, the 30-day incidence of stroke was 2.9% in the self-expandable valve and 1.0% in the balloon-expandable [13].

Since the reason for thrombus formation on these valves still remains obscure [8], we believe that further systematic studies are warranted to elucidate the exact cause of thrombotic and embolic events associated with transcatheter aortic valve implantation and to predict, prevent and treat this complication. Meanwhile, we suggest careful history of hypersensitivity reactions with monitoring of inflammatory mediators as well as lymphocyte transformation studies to detect metal hypersensitivity before implantation. Additionally, thrombus histology and searching for inflammatory cells such as eosinophils, mast cells, macrophages and T-lymphocytes will help to establish the cause and the manner of thrombosis. Such recommendations have been already issued by Food and Drug Administration and applied to coronary stent implantations [14].

Conflict of interest

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

References

- [1] S. Toggweiler, K. Schmidt, M. Paul, F. Cuculi, R. Kobza, P. Jamshidi, Valve thrombosis 3 years after transcatheter aortic valve implantation, *Int. J. Cardiol.* 207 (2016) 122–124.
- [2] D. Benedetto, P. Agostoni, F. de Waal, P.R. Stella, Kounis syndrome with cardiogenic shock during transfemoral transcatheter aortic valve replacement, *Coron. Artery Dis.* 26 (2015) 726–727.
- [3] J.P. Thyssen, T. Menné, Metal allergy – a review on exposures, penetration, genetics, prevalence, and clinical implications, *Chem. Res. Toxicol.* 23 (2010) 309–318.
- [4] G.C. Almpanis, G.G. Tsigkas, C. Koutsojannis, A. Mazarakis, G.N. Kounis, N.G. Kounis, Nickel allergy, Kounis syndrome and intracardiac metal devices, *Int. J. Cardiol.* 145 (2010) 364–365.
- [5] N.G. Kounis, Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int. J. Cardiol.* 110 (2006) 7–14.
- [6] G. Rigatelli, P. Cardaioli, M. Giordan, S. Aggio, M. Chinaglia, G. Braggion, Nickel allergy in interatrial shunt device based closure patients, *Congenit. Heart Dis.* 2 (2007) 416–420.
- [7] N.G. Kounis, S. Giannopoulos, G.G. Tsigkas, J. Goudevenos, Eosinophilic responses to stent implantation and the risk of Kounis hypersensitivity associated coronary syndrome, *Int J Cardiol* 156 (2012) 125–132.
- [8] D. Richardt, T. Hanke, H.H. Sievers, Two cases of heart failure after implantation of a CoreValve prosthesis, *N Engl J Med* 372 (2015) 1079–1080.
- [9] S.J. Galli, M. Tsai, A.M. Piliponsky, The development of allergic inflammation, *Nature* 454 (2008) 445–454.
- [10] J.P. Fanning, D.L. Walters, D.G. Platts, E. Eeles, J. Bellapart, J.F. Fraser, Characterization of neurological injury in transcatheter aortic valve implantation: how clear is the picture? *Circulation* 129 (2014) 504–515.
- [11] G.D. Soufras, G. Hahalis, N.G. Kounis, Thrombotic complications associated with transcatheter aortic valve implantation: the role of Kounis hypersensitivity-associated thrombotic syndrome, *Cardiovasc Pathol* 23 (2014) 383–384.
- [12] M. Abdel-Wahab, J. Mehili, C. Frerker, F.J. Neumann, T. Kurz, R. Tölg, et al., CHOICE investigators comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial, *JAMA* 311 (2014) 1503–1514.
- [13] A. Chieffo, G.L. Buchanan, N.M. Van Mieghem, D. Tchetché, N. Dumonteil, Latib, et al., Transcatheter aortic valve implantation with the Edwards SAPIEN versus the Medtronic CoreValve revalving system devices: a multicenter collaborative study: the PRAGMATIC Plus Initiative (Pooled-Rotterdam-Milano-Toulouse In Collaboration), *J. Am. Coll. Cardiol.* 61 (2013) 830–836.
- [14] Review of XIENCE V Everolimus Eluting Coronary Stent System and PROMUS Everolimus Eluting Coronary Stent System: P070015, Silver Spring, MD: Food and Drug Administration, 2008 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=p070015>.