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Discussion

Foretelling plaque disruption: Is the journey to Ithaca reaching destination?

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"Σα βγεις στον πηγαιμό για την Ιθάκη, να εύχεσαι νάναι μακρύς ο δρόμος, γεμάτος περιπέτειες, γεμάτος γνώσεις."

"When you set out for distant Ithaca, fervently wish your journey may be long, full of adventures and with much to learn." [1].

Constantine P. Cavafy, Ithaca, 1911

Plaque rupture with superimposed thrombus formation has long been identified as the predominant pathophysiologic hallmark of acute coronary syndromes and plaque progression [2]. Intensive research efforts over the last decades focused on the development of accurate prediction tools for those plaques which are more likely to undergo fibrous cap rupture in the future and trigger adverse vascular and clinical sequelae. The rationale underlying these complex, time-consuming and multidisciplinary endeavors is that a prompt yet precise characterization of plaques at increased risk of triggering future coronary events would justify the adoption of either systemic or localized prophylactic measures to prevent catastrophic clinical manifestations. Advanced morphological and functional assessment of coronary lesions has provided incremental insights into the complex natural history trajectory of atherosclerosis and the factors which may contribute to the formation of high-risk plaque. Detailed vascular imaging has become feasible via the development and implementation of various imaging modalities such as coronary angiography, intravascular ultrasound, backscatter radiofrequency intravascular ultrasound analysis, optical coherence tomography and near-infrared spectroscopy, each of which can be employed either alone or in combination [3]. Furthermore, information on the functional status of the various vascular segments is accomplished by molecular imaging and vascular profiling to assess local blood flow properties via computational fluid dynamics analyses [4,5]. A main caveat of these approaches is that they require invasive investigations at various time points and therefore they may not be directly applicable in real-life clinical scenarios in humans. The advent of non-invasive imaging technologies such as cardiac computed tomography angiography and magnetic resonance imaging (MRI) offers attractive potential alternatives for serial vascular imaging in the clinical setting with diminished risks and complications. Animal studies offer indispensable information into the molecular, cellular and vascular phenomena which are implicated in the transition of early plaques towards a high-risk phenotype and set the stage for more advanced and targeted human studies [6,7].

In this issue of *Atherosclerosis*, Pham et al. report the outcomes of an animal study employing serial MRI to investigate differential plaque parameters, which are associated with plaque progression and ultimate fibrous cap disruption [8]. Male New Zealand White rabbits were studied over a period of three months. Atherosclerosis was induced by a 1% cholesterol high fat diet for 8 weeks and aortic endothelial injury via a balloon catheter. Plaque disruption was pharmacologically triggered at three months with Russell Viper Venom and Histamine. The rabbit aortas were imaged with MRI at five time points throughout the study: baseline, one month, two months and three months pre- and post-triggering of plaque disruption. This study demonstrated that the plaques which finally disrupted had previously exhibited larger vascular dimensions as illustrated by a higher preceding remodeling ratio and larger vessel wall area at two months and at three months comparing to the stable non-disrupted plaques. Furthermore, disrupted plaques exhibited increased gadolinium uptake which is a surrogate of inflammation, neovascularization and vessel wall degradation as compared to the quiescent plaques [8].

This study elegantly demonstrates the importance of ongoing morphological plaque features as determinants of the future plaque

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behavior and builds upon the existing knowledge from previous studies which have shown that plaque morphology and composition assessed by intravascular ultrasound is associated with clinical events in humans [9,10]. By confirming the above relationships with non-invasive vascular imaging, this study can contribute towards a wider application of such research concepts and methods in large-scale patient populations.

However, as this is a pre-human study, the results should be approached with a degree of caution. The interpretation and clinical translation of the findings in human clinical settings is far from straightforward. Human coronary atherosclerosis evolves over a period of decades and is hard to be convincingly replicated in time-constrained animal models. The spatial resolution of MRI imaging in human coronary arteries does not currently allow an accurate segmentation of the lumen and wall borders and thereby a precise morphological characterization of plaque lesions. Also, an important consideration towards the formulation of a clinical risk-stratification scheme based solely on morphologic plaque features is that the natural history of plaques follows a highly diverse temporal course and only a small fraction of those plaques encompassing high-risk characteristics actually progress to induce a clinical cardiac event [9,11].

The addition of endothelial shear stress as a metric of ongoing inflammation in the morphological plaque prognostication models considerably increases their positive predictive value [5]. All the above pieces of evidence taken together suggest that a conceivable mechanistic explanation of the results of the current study may be that the positively remodeled plaque segments are likely the ones with the high gadolinium uptake and that a progressive vicious cycle may develop over time: the positively remodeled microenvironment (associated with the pro-inflammatory abnormally low endothelial shear stress) leads to progressive local inflammation, which in turn leads to more extensive vascular wall destruction and consequently an amplification of positive remodeling and hence exacerbation of the local pro-inflammatory local hemodynamic environment [6].

As an increasing number of vascular parameters affecting plaque behavior is recognized, it will be of critical importance to develop risk-assessment tools inclusive of the complex and heterogeneous plaque profiles along with the respective pathobiologic mechanisms and interactions [12]. A successful predictive plaque characterization scheme will likely need to include morphological predictors, such as lumen and wall dimensions and plaque constituents, biomechanical factors, such as blood flow profiles and structural stresses, as well as molecular imaging of bioactive mediators of inflammation within the lesions [13,14].

The scientific journey to a clinically efficient preventive strategy for adverse coronary syndromes via a comprehensive *in vivo* plaque assessment has been long yet exciting and full of challenges. In an analogy, this venture may resemble the epic voyage of Odysseus to his home island, Ithaca, which was arduous and treacherous but ultimately rewarding. As the imaging modalities become more sophisticated and mature, and the existing studies yield valuable knowledge and experience, our goals appear to become more attainable. There is still considerable distance to be covered and the "journey to Ithaca" still features substantial difficulties and uncertainties. However, the expected socioeconomic merits of a successful prediction and prevention of high-risk plaques well justify the perseverance and intensification of our efforts.

Conflicts of interest

None.

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References

[1] Poems by C. P. Cavafy, Translated, from the Greek, by J. C. Cavafy. Ikaros; 2003.
[2] V. Fuster, L. Badimon, J.J. Badimon, J.H. Chesebro, The pathogenesis of coronary artery disease and the acute coronary syndromes (1), N. Engl. J. Med. 326 (1992) 242–250.
[3] J.L. Fleg, G.W. Stone, Z.A. Fayad, J.F. Granada, T.S. Hatsukami, F.D. Kolodgie, J. Ohayon, R. Pettigrew, M.S. Sabatine, G.J. Tearney, S. Waxman, M.J. Domanski, P.R. Srinivas, J. Narula, Detection of high-risk atherosclerotic plaque: report of the NHLBI working group on current status and future directions, JACC Cardiovasc. Imaging 5 (2012) 941–955.
[4] W.J. Mulder, F.A. Jaffer, Z.A. Fayad, M. Nahrendorf, Imaging and nanomedicine in inflammatory atherosclerosis, Sci. Transl. Med. 6 (2014) 239sr1.
[5] P.H. Stone, S. Saito, S. Takahashi, Y. Makita, S. Nakamura, T. Kawasaki, A. Takahashi, T. Katsuki, S. Nakamura, A. Namiki, A. Hirohata, T. Matsumura, S. Yamazaki, H. Yokoi, S. Tanaka, S. Otsuji, F. Yoshimachi, J. Honye, D. Harwood, M. Reitman, A.U. Coskun, M.I. Papafaklis, C.L. Feldman, P. Investigators, Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study, Circulation 126 (2012) 172–181.
[6] Y.S. Chatzizisis, A.B. Baker, G.K. Sukhova, K.C. Koskinas, M.I. Papafaklis, R. Beigel, M. Jonas, A.U. Coskun, B.V. Stone, C. Maynard, G.P. Shi, P. Libby, C.L. Feldman, E.R. Edelman, P.H. Stone, Augmented expression and activity of extracellular matrix-degrading enzymes in regions of low endothelial shear stress colocalize with coronary atheromata with thin fibrous caps in pigs, Circulation 123 (2011) 621–630.
[7] Y.S. Chatzizisis, M. Jonas, A.U. Coskun, R. Beigel, B.V. Stone, C. Maynard, R.G. Gerrity, W. Daley, C. Rogers, E.R. Edelman, C.L. Feldman, P.H. Stone, Prediction of the localization of high-risk coronary atherosclerotic plaques on the basis of low endothelial shear stress: an intravascular ultrasound and histopathology natural history study, Circulation 117 (2008) 993–1002.
[8] T.A. Pham, N. Hua, A. Phinikaridou, R. Killiany, J. Hamilton, Early *in vivo* discrimination of vulnerable atherosclerotic plaques that disrupt: A serial MRI study, Atherosclerosis 244 (2016) 101–107.
[9] G.W. Stone, A. Maehara, A.J. Lansky, B. de Bruyne, E. Cristea, G.S. Mintz, R. Mehran, J. McPherson, N. Farhat, S.P. Marso, H. Parise, B. Templin, R. White, Z. Zhang, P.W. Serruys, P. Investigators, A prospective natural-history study of coronary atherosclerosis, N. Engl. J. Med. 364 (2011) 226–235.
[10] M.I. Papafaklis, S. Mizuno, S. Takahashi, A.U. Coskun, A.P. Antoniadis, M. Tsuda, C.L. Feldman, S. Saito, P.H. Stone, Incremental predictive value of combined endothelial shear stress, plaque necrotic core, and plaque burden for future cardiac events: a post-hoc analysis of the PREDICTION study, Int. J. Cardiol. 202 (2015) 64–66.
[11] T. Kubo, A. Maehara, G.S. Mintz, H. Doi, K. Tsujita, S.Y. Choi, O. Katoh, K. Nasu, A. Koenig, M. Pieper, J.H. Rogers, W. Wijns, D. Bose, M.P. Margolis, J.W. Moses, G.W. Stone, M.B. Leon, The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization, J. Am. Coll. Cardiol. 55 (2010) 1590–1597.
[12] P.H. Stone, A.U. Coskun, Conceptual new biomechanical approaches to identify coronary plaques at risk of disruption, JACC Cardiovasc. Imaging 8 (2015) 1167–1169.
[13] K. Toutouzas, Y.S. Chatzizisis, M. Riga, A. Giannopoulos, A.P. Antoniadis, S. Tu, Y. Fujino, D. Mitsouras, C. Doulaverakis, I. Tsampoulatidis, V.G. Koutkias, K. Bouki, Y. Li, I. Chouvarda, G. Cheimariotis, N. Maglaveras, I. Kompatsiaris, S. Nakamura, J.H. Reiber, F. Rybicki, H. Karvounis, C. Stefanadis, D. Tousoulis, G.D. Giannoglou, Accurate and reproducible reconstruction of coronary arteries and endothelial shear stress calculation using 3D OCT: comparative study to 3D IVUS and 3D QCA, Atherosclerosis 240 (2015) 510–519.
[14] R. Vergallo, M.I. Papafaklis, T. Yonetsu, C.V. Bourantas, I. Andreou, Z. Wang, J.G. Fujimoto, I. McNulty, H. Lee, L.M. Biasucci, F. Crea, C.L. Feldman, L.K. Michalis, P.H. Stone, I.K. Jang, Endothelial shear stress and coronary plaque characteristics in humans: combined frequency-domain optical coherence tomography and computational fluid dynamics study, Circ. Cardiovasc. Imaging 7 (2014) 905–911.