Angiographic characterization and clinical implications of specific anatomical features in human coronary arteries

Montero Cabezas, J.M.

1

General Introduction and Outline of Thesis

Like many other great advancements in the history of medicine, the story of coronary angiography began as result of pure chance. When in 1958, Mason Sones inadvertently injected contrast in a right coronary artery while performing a ventriculography[1], he started and amazing journey which evolved into the development of life-saving invasive techniques for the treatment of coronary artery disease (CAD), impacting the lives of millions of human beings in the next decades.

Shortly after its introduction, coronary angiography was broadly accepted and became soon the gold standard for assessing CAD. In 1977, the ground-breaking introduction of the percutaneous transluminal coronary angioplasty (PTCA) technique by Andreas Gruntzig changed forever the natural history of ischemic heart disease[2.3.4]. This major contribution was the starting point of the spectacular evolution of the field , with the subsequent introduction and refinement of novel techniques and technologies, together with expansion of the clinical indications (acute myocardial infarction, chronic coronary total occlusions, calcific disease, etc). All these innovations resulted in the creation of an entirely new sub-specialty, interventional cardiology, which continues today expanding its horizons towards new modalities of percutaneous treatments for coronary and structural heart disease[5,6,7]. Only four decades later, an annual median of 5131 diagnostic coronary angiographies and 2478 percutaneous coronary interventions per million people were reported in 2016 in Europe[8], which illustrates the major impact of these techniques in current clinical practice.

Diagnostic coronary angiography remains the core of cardiac catheterization. The goal of the procedure is to thoroughly characterize the coronary tree by injecting contrast is a number of pre-specified angiographic projections, aiming to evaluate all coronary segments and relevant pathological findings. With current use of high-resolution fluoroscopy, vessels up to 0.3 mm of diameter can be visualized[9]. Despite of the very well-known limitations of the technique and the development and improvement of non-invasive coronary imaging modalities such as computed tomography coronary angiography, invasive coronary angiography still remains as the cornerstone for risk stratification assessment in CAD[9]. Countless clinical decisions are taken on a daily basis based on angiographic findings. Angiography-derived tools, such as the SYNTAX score, have helped to standardize the evaluation of CAD complexity and have becoming a basic tool in helping clinicians in decision-making processes in coronary artery revascularization[10,11]. Needless to say, in patients undergoing percutaneous coronary artery revascularization, understanding angiographic coronary anatomy is indispensable to define the technical approach and the potential challenges derived from the procedure[9]. In addition, there are several angiographic anatomical or procedural related features that have been linked to patients prognosis, both immediate and long-term. For instance, in patients presenting with ST-segment elevation myocardial infarction, the presence of coronary no-reflow phenomenon complicating primary PCI has been linked to an increased mortality both at 1- and 5-years, independent of infarct size[12,13].

The standardization of coronary angiography interpretation, focused mostly on the ventricular coronary branches, has paid little attention to the coronary arterial branches supplying the atrial myocardium. The lack of consensus in the characterization of the angiographic anatomy of the atrial coronary branches has resulted is a confusing and heterogeneous mix of definitions, illustrating an evident gap of knowledge that remains nowadays[14]. Important clinical implications may be intimately related with the integrity of the atrial coronary circulation, such as the development of atrial arrythmias[15] or atrial structural and functional damage[16]. Likewise, the presence of coronary atrial branches in the vicinity of anatomical targets in atrial fibrillation ablation may impact negatively the effect of the procedure, highlighting the importance of a correct characterization of the coronary atrial branches anatomy in this clinical scenario[17].

Coronary ectasia was firstly described in 1812 by Bougon, and was considered many years as a rare pathological finding[18]. The advent and posterior universalization of coronary angiography made possible the diagnosis of this condition in living individuals[19]. Coronary angiography made possible the anatomic characterization and distribution of the abnormally dilated coronary segments, resulting in the identification of several phenotypes based on morphologic features (focal, diffuse) and extension, which important prognostic value[20,21,22]. In addition, coronary artery ectasia has been linked to particular diseases of clinical scenarios, such as inflammatory diseases, infections, trauma or atherosclerotic coronary artery disease[23]. The presence of coronary ectasia in patients requiring percutaneous coronary artery revascularization, particularly in acute coronary syndromes, is often a technical challenge with an important impact on procedural success and clinical prognosis. Despite of the existing evidence, a standardized, homogeneous, universal nomenclature and angiographic classification of coronary artery ectasia are lacking[24].

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated to cardiovascular complications, which are currently well known[25,26,27,28]. In early phases of the pandemic, little was known about the cardiovascular effects of COVID-19. The first data suggesting a hypercoagulable status in severely ill patients, with both venous and arterial thrombotic events[28], was rapidly followed by a number of reports of patients presenting with acute myocardial infarction due to coronary thrombosis with large thrombus burden[29,30,31]. Elevated cardiac biomarkers due to alternative cause of myocardial injury (myocarditis, Takotsubo cardiomyopathy, etc) were also described, requiring often the exclusion of acute coronary syndrome by coronary angiography[26]. Coronary angiography was therefore key in establishing the diagnosis, characterizing the pathological coronary findings and determining the percutaneous therapeutical strategy when indicated.

Coronary angiography is facing new challenges. As the burden of cardiovascular disease continues to increase globally[32], an increase of the number of diagnostic and therapeutic coronary procedures is expected. The impact of healthcare structures from an economic and a logistic perspective, may compromise both quality and timely access to care. In the past years, non-invasive computed tomographic coronary angiography has emerged as a valid alternative to invasive coronary angiography[33]. With a high negative predictive value, coronary computed tomography angiography allows to safely rule out coronary artery disease, decreasing significantly the number of patients referred for invasive evaluation. Despite of the refinements of the technique, poor image quality studies are not infrequent due to low resolution, motion, artifacts or suboptimal image acquisition to irregular or increased heart rate. These limitations compromise the diagnostic accuracy of CCTA, requiring diagnostic evaluation with invasive coronary angiography in all cases deemed positive[33]. Technical improvements in the next few years are warranted. For the moment, the announced downfall of invasive CAD is not yet effective. The promising development of technology based on artificial intelligence, with applications not only on image interpretation but also in other areas such as cath-lab logistics[34], may set the grounds for the next revolution in the field.

The journey still continues.

AIM AND OUTLINE OF THE THESIS

The objective of this thesis was to evaluate the role of invasive coronary angiography for risk stratification in patients presenting with myocardial infarction in specific clinical scenarios.

In **Part I**, we focused on the clinical impact of coronary flow impairment in coronary atrial branches. **Chapter 2** evaluated the impact of coronary atrial branch occlusion complicating a primary percutaneous coronary intervention in patients presenting with acute myocardial infarction. We defined the rate of this complication and its potential role in the occurrence of atrial arrythmias. In **Chapter 3**, we evaluated the impact of coronary flow limitation in the most developed coronary atrial branch, introducing the term of "atrial coronary dominance", and evaluating its potential role in the development of atrial arrythmias. **Chapter 4** studied the effects of atrial ischemia in both functional and structural remodelling of the left atrium in patients with acute myocardial infarction, by using serial advanced echocardiography techniques. Part II evaluated the prognostic value of coronary angiography in acute myocardial infarction in specific scenarios. **Chapter 5** focused in patients with coronary artery ectasia presenting with acute coronary syndromes, providing a systematic angiographic phenotypical classification and evaluating its impact in the occurrence of major cardiovascular events. Finally, in **Chapter 6** we evaluated the angiographic and clinical profile of patients with COVID-19 referred for invasive coronary angiography from an international registry, analysing as well the prognosis of this specific population.

REFERENCE LIST

1. Sones FM Jr, Shirey EK, Prondfit WL, Westcott RN. Cinecoronary arteriography. Circulation. 1959;20:773 (abstract)
2. Grüntzig AR, Myler RK, Hanna ES, Turina MI. Coronary transluminal angioplasty (abstract). Circulation. 1977;55-56(III):84
3. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet. 1978;1(8058):263
4. Grüntzig AR, Senning A Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med. 1979;301:61-8.
5. King SB III. The development of interventional cardiology. J Am Coll Cardiol 1998;31:64B
6. Ryan TJ. The coronary angiogram and its seminal contributions to cardiovascular medicine over five decades. Circulation. 2002 Aug 6;106(6):752-6
7. Bruschke AV, Sheldon WC, Shirey EK, Proudfit WL. A half century of selective coronary arteriography. J Am Coll Cardiol. 2009 Dec 1;54(23):2139-44
8. Barbato E, Noc M, Baumbach A, Dudek D, Bunc M, Skalidis E, Banning A, Legutko J, Witt N, Pan M, Tilsted HH, Nef H, Tarantini G, Kazakiewicz D, Huculeci R, Cook S, Magdy A, Desmet W, Cayla G, Vinereanu D, Voskuil M, Goktekin O, Vardas P, Timmis A, Haude M. Mapping interventional cardiology in Europe: the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Atlas Project. Eur Heart J. 2020;41(27):2579-2588
9. Moscucci M. Grossman & Baim's Cardiac Catheterization, Angiography, and Intervention. 8th ed. Wolters Kluwer. 2014
10. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. EuroIntervention. 2009 May;5(1):50-6
11. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009 Mar 5;360(10):961-72
12. Morishima I, Sone T, Okumura K, Tsuboi H, Kondo J, Mukawa H, Matsui H, Toki Y, Ito T, Hayakawa T. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. J Am Coll Cardiol. 2000 Oct;36(4):1202-9
13. Ndrepepa G, Tiroch K, Fusaro M, Keta D, Seyfarth M, Byrne RA, Pache J, Alger P, Mehilli J, Schömig A, Kastrati A. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. J Am Coll Cardiol. 2010 May 25;55(21):2383-9
14. Boppana VS, Castaño A, Avula UMR, Yamazaki M, Kalifa J. Atrial Coronary Arteries: Anatomy And Atrial Perfusion Territories. J Atr Fibrillation. 2011;4(3):375.
15. Alasady M, Shipp NJ, Brooks AG, Lim HS, Lau DH, Barlow D, Kuklik P, Worthley MI, Roberts-Thomson KC, Saint DA, Abhayaratna W, Sanders P. Myocardial infarction and atrial fibrillation: importance of atrial ischemia. Circ Arrhythm Electrophysiol. 2013;6(4):738-45
16. Aguero J, Galan-Arriola C, Fernandez-Jimenez R, Sanchez-Gonzalez J, Ajmone N, Delgado V, Solis J, Lopez GJ, de Molina-Iracheta A, Hajjar RJ, Bax JJ, Fuster V, Ibáñez B. Atrial Infarction and Ischemic Mitral Regurgitation Contribute to Post-MI Remodeling of the Left Atrium. J Am Coll Cardiol. 2017;70(23):2878-2889.

17. Pardo Meo J, Scanavacca M, Sosa E, Correia A, Hachul D, Darrieux F, Lara S, Hardy C, Jatene F, Jatene M. Atrial coronary arteries in areas involved in atrial fibrillation catheter ablation. Circ Arrhythm Electrophysiol. 2010;3(6):600-5
18. Bougon CJJ. Observation sur un aneurisme d'une des arterieses coronaires ou cardiaques. Bibliothkque Medicale, 37: 85-90, 1812.
19. Hartnell GG, Parnell BM, Pridie RB. Coronary artery ectasia. Its prevalence and clinical significance in 4993 patients.Heart 1985;54:392-395.
20. Markis JE, Joffe CD, Cohn PF, Feen DJ, Herman MV, Gorlin R. Clinical significance of coronary arterial ectasia. Am J Cardiol. 1976 Feb;37(2):217-22
21. Rath S, Har-Zahav Y, Battler A, Agranat O, Rotstein Z, Rabinowitz B, Neufeld HN. Fate of nonobstructive aneurysmatic coronary artery disease: angiographic and clinical follow-up report. Am Heart J. 1985 Apr;109(4):785-91
22. Demopoulos VP, Olympios CD, Fakiolas CN, Pissimissis EG, Economides NM, Adamopoulou E, Foussas SG, Cokkinos DV. The natural history of aneurysmal coronary artery disease. Heart. 1997 Aug;78(2):136-41
23. Kawsara A, Núñez Gil IJ, Alqahtani F, Moreland J, Rihal CS, Alkhouli M. Management of Coronary Artery Aneurysms. JACC Cardiovasc Interv. 2018;11(13):1211-1223
24. Wang X, Montero-Cabezas JM, Mandurino-Mirizzi A, Hirasawa K, Ajmone Marsan N, Knuuti J, Bax JJ, Delgado V. Prevalence and Long-term Outcomes of Patients with Coronary Artery Ectasia Presenting with Acute Myocardial Infarction. Am J Cardiol. 2021 Oct 1;156:9-15
25. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N, Hochman JS. ST-Segment Elevation in Patients with Covid-19 - A Case Series. N Engl J Med. 2020 Jun 18;382(25):2478-2480
26. Sandoval Y, Januzzi JL Jr, Jaffe AS. Cardiac Troponin for Assessment of Myocardial Injury in COVID-19: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Sep 8;76(10):1244-1258
27. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020; 75: 2950-73.
28. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145-7.
29. Hamadeh A, Aldujeli A, Briedis K, Tecson KM, Sanz-Sánchez J, Al Dujeili M, Al-Obeidi A, Diez JL, Žaliūnas R, Stoler RC, McCullough PA. Characteristics and Outcomes in Patients Presenting With COVID-19 and ST-Segment Elevation Myocardial Infarction. Am J Cardiol. 2020 Sep 15;131:1-6
30. Choudry FA, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, Woldman S, Jain AK, Knight CJ, Baumbach A, Mathur A, Jones DA. High Thrombus Burden in Patients With COVID-19 Presenting With ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol. 2020 Sep 8;76(10):1168-1176.
31. Stefanini GG, Montorfano M, Trabattoni D, Andreini D, Ferrante G, Ancona M, Metra M, Curello S, Maffeo D, Pero G, Cacucci M, Assanelli E, Bellini B, Russo F, Ielasi A, Tespili M, Danzi GB, Vandoni P, Bollati M, Barbieri L, Oreglia J, Lettieri C, Cremonesi A, Carugo S, Reimers B, Condorelli G, Chieffo A. ST-Elevation Myocardial Infarction in Patients With COVID-19: Clinical and Angiographic Outcomes. Circulation. 2020;141(25):2113-2116

32. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021
33. Abdelrahman KM, Chen MY, Dey AK, Virmani R, Finn AV, Khamis RY, Choi AD, Min JK, Williams MC, Buckler AJ, Taylor CA, Rogers C, Samady H, Antoniades C, Shaw LJ, Budoff MJ, Hoffmann U, Blankstein R, Narula J, Mehta NN. Coronary Computed Tomography Angiography From Clinical Uses to Emerging Technologies: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;76(10):1226-1243.
34. Molenaar MA, Selder JL, Nicolas J, Claessen BE, Mehran R, Bescós JO, Schuuring MJ, Bouma BJ, Verouden NJ, Chamuleau SAJ. Current State and Future Perspectives of Artificial Intelligence for Automated Coronary Angiography Imaging Analysis in Patients with Ischemic Heart Disease. Curr Cardiol Rep. 2022;24(4):365-376