Editorial

Research on the Development of Collaterals from Occluded Internal Mammary Arteries and Refractory Angina: Where are we in 2019?

Refractory Angina (RA) is an increasingly-prevalent issue worldwide. With increasing age, the number of patients who might not undergo conventional myocardial revascularization with Coronary Artery Bypass Grafting (CABG) or Percutaneous Coronary Interventions (PCI) is increasing steadily. The exact number of such patients has been ignored; but it has been estimated that, in Europe, there are about 75,000 new cases annually [1], while in the United States, the reported incidence stands at roughly 50,000 new cases/year and prevalence from 600,000 to 1,800,000 overall [2]. Due to limits in treatment, these patients have been called “no-option” patients, their most common cause of unsuitability for CABG or PTCA being diffuse coronary disease, either associated or not associated with small vessel disease. Comorbidities, excessively-old age, and the combination of these two factors are further causes [3]. Apart from second- and third-line anti-anginal medications - like Nicorandil, ivabradine, ranolazine, trimetazidine, perhexiline, allopurinol, molsidomine, and fasudyl/hydroxyfasudil - several non-pharmacological methods have been developed over the last 20 years. These include laser trans-myocardial revascularization, shockwaves, spinal cord stimulation, stellate ganglion block, pro-angiogenic gene therapy, lipoprotein apheresis, stem cells, external counter-pulsation and, quite recently, coronary sinus reducer devices [4]. Many of these techniques represent old ideas and methods of revascularization, abandoned soon after the advent of cardiopulmonary bypass and coronary surgery, and resurrected with modern technologies [5]. Two further options existed in the past, both involving the potential of Internal Mammary Arteries (IMAs) to develop collaterals; and both surgical. One dates back to Arthur Vineberg, a Canadian surgeon who developed a technique to implant an IMA into an intra-myocardial tunnel [6]. This allowed for neo-angiogenesis in the heart, next to the site of the mammary artery implant, with the development of collaterals visible by coronary angiography. This technique, after about 15 years of satisfactory results, was abandoned for some decades. Recently, a suggestion was made to resurrect it as a way to address refractory angina [7].

Another old method involving the IMAs consisted of occluding them by ligature. This technique was invented by Davide Fieschi, in 1939 [8], and reproduced by Cesare Battezzati [9, 10] and Robert Glover [11] in the fifties. The principle behind this approach is that, if an IMA is ligated distal to its pericardiophrenic branch, blood flow might be redirected towards the heart through a microvascular anastomotic network. This technique initially exhibited encouraging results, though conflicting opinions existed [12, 13]. However, all discussions about this approach were abandoned, as well as Vineberg’s procedure, following the advent of the heart-lung machine [14-16] and on-pump coronary surgery.

After 50 years of silence, since 2010, it has been proposed that ligating the IMA to develop collaterals, by occluding it distal to the pericardiophrenic branch, could be adopted for patients with RA [17]. By the same year, it was suggested that this could be achieved surgically, with or without the help of Vascular Endothelial Growth Factors (VEGF), or alternatively by endovascular occlusion [18, 19]. An experimental study on dogs published in 2012, which included both a surgical approach and the injection of VEGF, though inconclusive due to the high mortality rate among the dogs, opened the way to rediscovering therapeutic IMA occlusion [20]. Subsequently, greater emphasis was placed upon IMA occlusion and, ultimately, a Swiss team adopted this concept and has since published two papers, in 2014 and 2017, describing interesting results achieved in humans. In the first study, they occluded the IMAs via balloon angioplasty, while simultaneously occluding the coronary vessels for a short period of time [21]. In the second study, they caused persistent occlusion of the right internal mammary artery for six weeks [22]. They disclosed that, in patients with IMA occlusion, there were improvements in the collateral flow index, fractional flow reserve, ECG intracoronary ST segment, and anginal symptoms. This improvement occurred ipsilaterally, meaning that occluding the left IMA generated improvements if the left anterior descending artery was involved; as well, occluding the right IMA resulted in improvement if the right coronary artery was involved. Conversely, the circumflex coronary artery exhibited no benefit from occlusion of both the right and left IMAs. The investigators concluded that IMA occlusion could increase extracardiac ipsilateral coronary supply to the point of reducing ischemia in the dependent but not contralateral myocardial region. What is remarkable is that these conclusions are practically identical to those reported by Italian authors in 1939 and 1955.

Despite these modern demonstrations, occluding IMAs for therapeutic purposes is only a slowly-advancing concept within the scientific community. In a recent editorial, this field of discovery was called an “undiscovered country” [23], and the author of the current editorial certainly agrees [24]. The microvascular network that connects extra-cardiac vessels to the coronary artery [25, 26], and the potential roles of IMA occlusion [27], remain almost ignored fields of research. As a result, in 2019 the road towards therapeutic IMA occlusion for refractory angina [28], although re-opened after years being dormant, certainly requires further studies and remains far from being an established therapeutic option.

Keywords: Angiogenesis, collaterals, internal mammary artery, occlusion, refractory angina, Coronary Artery Bypass Grafting (CABG).
REFERENCES


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