Rev Esp Cardiol. 2021;74(2):124–125

Editorial

Cardiac microvasculature and adverse remodeling after acute myocardial infarction. New evidence on the use of VEGF as a therapeutic target

La microvasculatura cardiaca y el remodelado adverso tras el infarto agudo de miocardio. Nuevas evidencias sobre el VEGF como diana terapéutica

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Article history:
Available online 17 October 2020

Myocardial reperfusion by percutaneous coronary intervention (PCI) after acute coronary syndrome is clearly a major advance for restoring tissue perfusion and reducing progression of the infarcted area.[1] However, in-hospital mortality continues to be high, despite widespread use of the treatment and major technological advances.

Microvascular obstruction (MVO) is one of the factors present after acute myocardial infarction (AMI) and causes post-PCI myocardial perfusion impairment in more than half of patients undergoing epicardial reperfusion.[2] For this reason, considerable research is underway to investigate factors leading to the condition, as well as to develop effective solutions to restore myocardial perfusion or to minimize any defects.

Among other causes, the MVO phenomenon can be attributed to microvascular endothelial dysfunction after the inflammatory response arising during myocardial ischemia and to the formation of microemboli due to the presence of thrombotic or atherosclerotic material.[3] When myocardial perfusion is insufficient even after blood flow is restored, no-reflow phenomenon occurs and, therefore, greater efforts have been made in recent years to find new therapeutic strategies for this phenomenon.[4] These efforts also focus on new tools for reliable noninvasive diagnosis, beyond the techniques currently used to detect MVO.

In situations where ischemia is prolonged, the reperfusion process further enhances related damage. Reperfusion injury can cause microvascular dysfunction, and the lumen is occluded due to the accumulation of platelet-neutrophil aggregates, causing endothelial impairment when nitric oxide is not produced and vasoactive substances are altered, with large amounts of vasoconstrictor factors also synthesized.[5–7]

Angiogenesis, understood to be the formation of new vasculature from pre-existing vessels, is an essential post-AMI process, as it promotes the revascularization of damaged tissue and lessens the effects of MVO. At the molecular level, the underlying mechanisms inducing angiogenesis during reperfusion are not fully known, although activation of the transcription factor known as hypoxia-inducible factor (HIF) is key for the synthesis of several growth factors, predominantly vascular endothelial growth factor (VEGF), which has an isoform VEGF-A that mainly promotes the formation of new vessels to revascularize damaged myocardium.[8,9]

To date, there is significant evidence of the positive effect of VEGF-A on myocardial revascularization after ischemia. However, alternative messenger RNA processing of VEGF-A yields different isoforms. One of them, VEGF-A_{165}b, has been described as an antiangiogenic factor.[10] In particular, the harmful effects of VEGF-A_{165}b on patients with ST-segment elevation AMI (STE-AMI) have already been described,[11,12] although its role for diagnostic or therapeutic purposes has only been studied in observational studies.

The article by Ríos-Navarro et al.[13] recently published in *Revista Española de Cardiología* reported on the role of VEGF-A_{165}b in AMI, analyzing its serum concentration in a sample of patients with STE-AMI and in a mouse model of AMI with and without myocardial reperfusion; these studies have reported that postreperfusion VEGF-A_{165}b inhibition does have an effect, making it of particular interest due to its possible therapeutic use.

The study design is sound, as the authors have first determined that VEGF-A_{165}b is increased in the blood plasma and myocardial tissue of animals subjected to ischemia, for both the chronic and the postreperfusion acute variants. The release of the soluble form of VEGF-A_{165}b into the bloodstream and its increase in infarcted tissue, specifically in the endothelium, is related to significantly worsened ventricular function. The novelty of the study lies mainly in the mechanistic role suggested by the authors, who correlate VEGF-A_{165}b activity inhibition and subsequent heart function. It is interesting that only the reperfusion model showed positive effects from VEGF-A_{165}b blockade, with a net benefit on myocardial function, more precisely, preserving ejection fraction, reducing the size of the necrosed area, and of particular relevance, significantly increasing capillary density.

Additionally, the authors studied the serum VEGF-A_{165}b concentration at 24 hours post-AMI in 104 STE-AMI patients, using samples from 25 patients with no heart disease as a control group. The results obtained are comparable to those observed in animal models, where larger circulating amounts of VEGF-A_{165}b at 24 hours after STE-AMI were related to a lower ejection fraction at 6 months and to the occurrence of major cardiovascular adverse events.

The authors should be congratulated on the importance of their study, as it not only shows the direct implication of VEGF-A_{165}b in

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https://doi.org/10.1016/j.rec.2020.03.013

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https://doi.org/10.1016/j.rec.2020.07.019
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the clinical progress of postreperfusion AMI, but also opens the door to the development of new therapies combining coronary reperfusion and molecular blockade of VEGF-A_{165}b activity. The experimental design of the study by Ríos-Navarro et al.[13] uses the chronic and acute ischemia model to demonstrate the role played by VEGF-A_{165}b exclusively under coronary reperfusion conditions.

Angiogenesis is the main microvascular repair process undertaken after AMI is treated by primary PCI. Some authors indicate that, in the absence of reperfusion, arteriogenesis also participates in tissue revascularization due to the pressure difference between a donor artery and an occluded artery, inducing the conversion of small arteriolar anastomoses into functional arteries. However, this pressure difference does not occur during myocardial reperfusion because the artery is not occluded and, consequently, angiogenesis is the main tissue revascularization process.[8] The results of the study by Ríos-Navarro et al. are consistent with this premise, as promoting angiogenesis by blockade with an antiangiogenic agent is able to compensate for MVO while allowing postreperfusion tissue revascularization.[13] Likewise, the authors show the potential use of VEGF-A_{165}b as an early biomarker for poor AMI resolution and the occurrence of adverse cardiovascular events, a finding of utmost importance, as targeted treatments can thus be prescribed to avoid long-term sequelae. In the future, these results can lay the groundwork for new therapies aimed at promoting angiogenesis which, in combination with PCI with reperfusion, may prevent MVO sequelae.

CONFLICTS OF INTEREST

None declared.

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