

Gut microbiota and myocardial infarction

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This commentary refers to ‘Is *Escherichia coli* involved in the myocardial infarction?’, by A. Zullo et al., 2020;41:2220.

We thank Zullo et al.¹ for the interesting comments regarding our recent report where we showed that circulating lipopolysaccharides (LPS) are increased in patients with myocardial infarction (MI) and concentrate in coronary thrombi, where they can facilitate thrombosis via leucocyte cathepsin G-mediated platelet activation.² This hypothesis was corroborated by experiments in mice where

thrombus growth was enhanced by LPS from *Escherichia coli* injection.² Zullo wonders as to whether LPS translocate in the peripheral blood as consequence of increased gut permeability by aspirin use. Gut permeability may be a sort of ‘physiologic process’ as LPS increase in the blood after fat food intake.³ Alternatively, gut permeability increases as consequence of gut dysbiosis or circulatory disturbances, which may damage the tight junctions and favour LPS translocation in the circulation (Figure 1).⁴ Aspirin is prevalently absorbed in the upper small intestine and, to a minor extent, in the

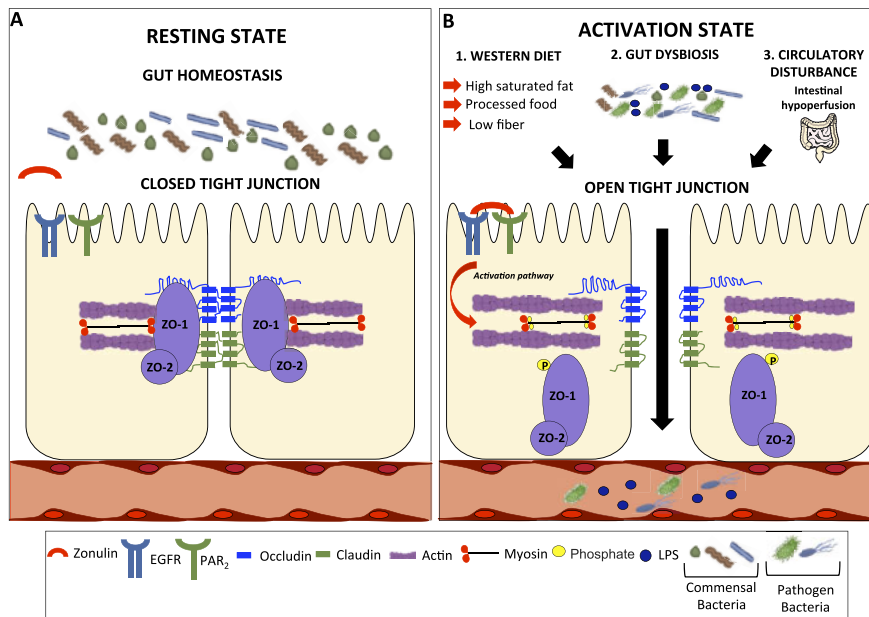


Figure 1 (A) Resting state: microbiota plays a role in the maintenance of the intestinal barrier, which is essential for homeostasis and functionality of the gut. In this condition, tight junction (TJ) proteins are engaged in protein–protein interactions that keep TJ in a competent state closed. (B) Activation state: several factors such as (1) western diet, (2) dysbiotic microbiota characterized by altered composition, reduced diversity and stability as well as increased amount of LPS-containing bacteria, and (3) circulatory disturbances (hypoperfusion), favour zonulin activation that transactivates epidermal growth factor receptor (EGFR) through proteinase activated receptor 2 (PAR2). The phosphorylation of zonula occludens 1 (ZO-1) and myosin, and actin polymerization cause the displacement of ZO-1 and zonula occludens 2 (ZO-2) from the junctional complex so opening intestinal TJ.

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gastric tube; its absorption is usually rapid and almost complete even if it cannot be fully excluded that it may reach the colon and eventually favour LPS translocation upon epithelial damage. Analysis of gut permeability seems to be against this hypothesis as, despite all patients with acute or chronic coronary heart disease were on aspirin treatment, patients with MI had higher levels of zonulin, a marker of gut permeability, compared to stable angina patients.²

Zullo also wonders if it is conceivable to eradicate bacteria such as *E. coli*, which contribute to synthesize physiologic molecules, to prevent cardiovascular disease. We believe that this issue is of particular relevance also in view of the fact that, as outlined in our report, *E. coli* is unlikely to be the only gut microbiota responsible for LPS elevation. Accordingly, increase of gut microbiota such as Proteobacteria (57.7%) or Actinobacteria (25.7%) has been detected in MI.⁵ Thus, we absolutely exclude eradication of *E. coli* or other gut microbiota as tool to counteract MI; conversely, it would be interesting to investigate if antibodies against circulating LPS may reduce the thrombotic risk. In the meantime, having identified the mechanism through

which LPS promote thrombosis, i.e. TLR4, it might be of clinical interest to assess the efficacy of blocking TLR4 in the acute phase of coronary thrombosis.

Conflict of interest: none declared.

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