Letter to the Editor

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Response by Lorenzano et al to Letter Regarding Article, "Oxidative Stress Biomarkers of Brain Damage: Hyperacute Plasma F2-Isoprostane Predicts Infarct Growth in Stroke"

In Response:

We thank Kazushi Tsuda for his thoughtful comments on our article on oxidative stress biomarkers of brain damage.[1]

We absolutely agree with Tsuda that oxidative stress triggers biochemical cascades and signaling pathways that can negatively impact infarct progression in patients with ischemic stroke also through direct effects on the endothelial cells. In fact, oxidative stress represents a major cause of endothelial dysfunction in cerebral vessels, as suggested by several evidence, and this can be considered a common characteristic of neurovascular diseases.[2] Endothelial dysfunction can result from the reduced bioavailability of nitric oxide (NO) and increased oxidant excess. NO, produced from eNOS (endothelial NO synthase), 1 of the 3 isoforms of NOS present in the nervous system, diffuses to the underlying smooth muscle, stimulates soluble guanylate cyclase with subsequent increase of cyclic GMP levels, and causes smooth muscle relaxation and blood vessel dilation.[3] The NO release from eNOS soon after brain ischemia, which is a calcium-dependent process, can be protective because it can contribute to preserve the integrity of the blood-brain barrier and, in particular, maintain the cerebral blood flow and tissue perfusion not only by promoting vasodilation but also by inhibiting microvascular aggregation and adhesion. In the acute phase of an ischemic stroke, this can ameliorate blood flow in the areas of ischemic penumbra and improve collateral microcirculation[3] with potential subsequent lower chance of infarct growth. Therefore, endothelial dysfunction has been related to stroke physiopathology but also to clinical severity, outcome, and stroke subtype.[4]

In his letter, Tsuda mentioned the results of some studies showing an inverse correlation between levels of oxidative stress markers, such as plasma or urinary isoprostanes, and markers of endothelial dysfunction in subjects with or without hypertension or in patients with obstructive sleep apnea. Of note, all these studies were not performed in patients with acute ischemic stroke, and specific techniques for cerebral circulation, such as the cerebrovascular reactivity to L-arginine, a precursor of NO, determined by transcranial Doppler, were not used.

We agree that in our study increased plasma levels of F2-isoprostanes, infarct growth, and endothelial dysfunction could be linked. Unfortunately, we did not specifically measure endothelial function; hence, it can only be speculated that, based on the above mentioned evidence, the endothelial dysfunction related to oxidative stress in the acute phase of ischemic stroke could have contributed to brain damage and infarct growth in our cohort. However, it should be taken into account that it is not the only determinant. The biochemical processes triggered by oxidative stress are several, dynamic, and extremely complex, and each of them can have a detrimental effect on stroke progression. Moreover, stroke is a pathologically and etiologically heterogeneous disease. Further studies are needed to specifically evaluate the relationship between oxidative stress and endothelial dysfunction in the acute phase of ischemic stroke and their synergistic influence on infarct growth.

Disclosures

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References

1. Lorenzano S, Rost NS, Khan M, Li H, Lima FO, Maas MB, et al. Oxidative stress biomarkers of brain damage: hyperacute plasma F2-isoprostane predicts infarct growth in stroke. *Stroke*. 2018;49:630–637. doi: 10.1161/STROKEAHA.117.018440.
2. Roquer J, Segura T, Serena J, Castillo J. Endothelial dysfunction, vascular disease and stroke: the ARTICO study. *Cerebrovasc Dis*. 2009;27(suppl 1):25–37. doi: 10.1159/000200439.
3. Chrissobolis S1, Miller AA, Drummond GR, Kemp-Harper BK, Sobey CG. Oxidative stress and endothelial dysfunction in cerebrovascular disease. *Front Biosci (Landmark Ed)*. 2011;16:1733–1745.
4. Adachi U, Tsutsumi Y, Iijima M, Mizuno S, Uchiyama S, Kitagawa K. Differences in endothelial function between ischemic stroke subtypes. *J Stroke Cerebrovasc Dis*. 2015;24:2781–2786. doi: 10.1016/j.jstrokecerebrovasdis.2015.08.009.

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