Reply:

We would like to thank Dr Wilmshurst for his comments on our article.[1] The distribution of the rash in the animals in which it occurred was around the cheeks, neck and thoracic region as well as the abdomen and thighs. In our preliminary experiments there was a theoretical possibility of backflow of air directly from the catheter positioned in the ascending pharyngeal artery into the external carotid artery, resulting in a rash in the flow area of this artery, namely the head and neck.[2] In our later experiment, in which we used a balloon catheter, shunting of air to the extra-cerebral circulation was less plausible. The total volume of air injected in these experiments was a mean of 5.6 ± 1.3 ml, consisting of repeated injections of 0.2–0.5 ml.[3] As a result, some of these animals showed severe impact on cerebral metabolism (increase of intracranial pressure and brain lactate) and rashes on the abdomen and thighs. As we stated in our article, we cannot rule out the possibility of gas bubbles migrating through the brain circulation (due to the associated hypertension) and re-entering the systemic circulation, resulting in the skin manifestations, but we speculate that the rapid onset of the rash after the introduction of air suggests a centrally mediated response.

We agree with Dr Wilmshurst that the animals that survived the acute experiments, after recovery from anesthesia, could possibly have had severe neurological deficits. In addition, based on results in our latest study, we also make a plea for improving the model by introducing clinical outcome measures.

Dr Wilmshurst questioned whether a systemic surge of catecholamines due to severe cerebral injury might be an alternative explanation for the observed rash, as seen in phaeochromocytoma patients. We agree with this hypothesis and postulate a mechanism in which bubbles or bubble-related effects give rise to the release of neuropeptides or catecholamines which, in turn, result in an inflammatory response in the skin. This possible mechanism has been described earlier[4,5] and very recently hypothesised in another paper in which it is speculated as a disruption of the brainstem vasomotor response by bubbles.[6]

In conclusion, although we cannot exclude recirculating bubbles resulting in peripheral skin embolization in our animal model, the hypothesis on cerebrally mediated *cutis marmorata* is plausible and needs further research to elucidate the exact mechanism.

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