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Do Prior Iodine Contrast Injections Affect Cerebral Blood Flow Measurement on CT Perfusion Studies of Patients with Large-Vessel Occlusions?

We read with great interest the recent study by Copelan et al[1] in which the authors concluded that recent administration (< 8 hours) of iodinated contrast renders infarct estimations inaccurate using a commercial CTP processing software. We believe that the conclusions suffer from unassessed confounders and misinterpretations deserving of clarification for the prospective reader.

First, the small cohort ($n = 38$) differs not only in the use of iodine, but also in presentation time and infarct size. The transfer patient group arrived approximately 3.2 hours later than the direct presenters. In our experience, this delay increases the likelihood of distal clot migration (eg, from the ICA terminus to the M1 or M2 segment), which may explain the reported core underestimation using CBF. It is unclear whether this confounder was excluded after comparison of the emergent large-vessel occlusion location on each patient's baseline and post-transfer CTAs.

Second, both core under- and overestimations are well-described limitations of CTP that are inherent to using perfusion as a surrogate of the core.[2] As shown in Fig 7,[1] the authors compared a delay-insensitive CTP processing method (RApid processing of PerfusIon and Diffusion [RAPID; iSchemaView]) with a delay-compensated (but not delay-insensitive) parametric CTP processing method (Advanced-Visualization Workstation; GE Healthcare). The apparent CBF reduction on the parametric deconvolution methods is not easily disambiguated from artifactual changes arising from delay-estimation and compensation errors between the arterial input function and the tissue. Prior studies have shown that CBF observed with delay-compensated deconvolution methods can be underestimated by as much as 40% for delays of 5 seconds.[2]

Third, CTP maps are derived from dynamic attenuation changes caused by the iodine bolus, relative to the prebolus baseline attenuation values. Provided that a reliable prebolus baseline attenuation measurement is obtained, any attenuation offset caused by persistent intravascular or extravascular tissue iodine (from preceding injections) is negligible. It is unclear if the authors' CTP acquisitions had an adequate baseline measurement. The authors also acquired their CTP in 2 sequential slabs, each with a separate bolus injection, to achieve the desired 80-mm coverage. This means that the second CTP slab is, by definition, a postcontrast scan in both patient groups. Thus, any confounding effects from prior iodine administration should be observed in the second CTP slab in both groups. However, when allowing at least 90 seconds between the 2 CTP acquisitions, we have not encountered such issues in our experience with either dual slab protocols or cases in which the CTA is acquired before the CTP. If leakage is the culprit (either first pass or at a steady-state from an earlier injection for the CTP or the outside CTA study), then this would affect CBV and, to a much lesser extent, CBF. Although the authors reference contrast leakage as a potential explanation for core underestimation, they did not report on whether, or to what extent, patients demonstrated contrast staining on their pre- and postcontrast head CTs.

Last, the authors state that "rather than delay the reporting of such a clinically relevant pitfall to augment our sample size, we thought it pertinent to alert our [...] colleagues to our finding." While the effort to bring urgent findings to the attention of the broader scientific community is laudable, doing so at the expense of scientific rigor is fraught with danger. On the basis of the reported number of cases, we are uncertain whether meaningful conclusions can be drawn regarding the association between CBF-derived core and the robustness of collaterals. Specifically, only 2 and 3 cases with "poor collaterals" were reported in the iodine and noniodine groups, respectively, while "intermediate collaterals" were reported only in 6 and 3 cases, respectively. Moreover, the initial power analysis was based on a 50% core overestimation, not underestimation. Therefore, we are concerned for the potential conflation of correlation with causality.

In summary, we thank Copelan et al[1] for sharing their findings and we agree with their conclusion that CBF can underestimate (or overestimate) core, and critically, that one should always cross-reference CTP with an unenhanced CT. We believe, however, that the authors' conclusions are excessively extrapolated and potentially without attention to well-recognized confounders. Several potential sources of bias may have had further influences upon the results, including the tendency to promote

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underestimation of the CBF core. Multiple prior studies, including post hoc analyses in large, prospectively collected cohorts and real-world populations with much larger numbers of patients, have documented accurate core estimations using the tested software, which included "transfer cases" with prior contrast.[3,4]

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