REPLY:

We would like to thank Amukotuwa et al for their interest in our article,[1] their expertise in the technical aspects of CTP, and for their important contributions to the development of RApid processing of PerfusIon and Diffusion (RAPID) software and iSchemaView, the company that produces RAPID. Their efforts to automate the interpretation of CTP to facilitate early stroke interventions have been important for acute stroke therapy, and we wish them continued success with their products.

The underlying mechanism for the systematic underestimation of the core infarct by RAPID in patients who previously received intravenous contrast is of important academic interest. As neurointerventionalists and diagnostic neuroradiologists, our goal is to rapidly diagnose and appropriately treat patients with acute ischemic stroke. Using the RAPID software, our team repeatedly observed underestimation of the volume of core infarction in patients with persistent large-vessel occlusions and large MCA infarctions on unenhanced CT. We felt this specific limitation needed to be highlighted for the physicians reliant on such information when deciding to perform interventions. While we take exception to the authors' questioning our "scientific rigor," we will attempt to answer the potential issues raised by Amukotuwa et al point-by-point.

We agree that the sample size is a potential limitation of our study, as we stated in our Discussion. While 38 subjects met inclusion criteria, we excluded several subjects from the analysis who showed distal migration of thrombus. At the authors' request, we confirm that the original thrombus location remained the same on the follow-up posttransfer CTAs for all of the included subjects. In regard to the other covariates that were raised by Amukotuwa et al as potential confounders, our multivariate analysis was designed to account for the potential influence of these variables.

We agree that delay-insensitive and delay-compensated parametric processing methods may result in differing estimates of core infarction volume; however, that was not the point of Figs 3, 4, and 7. Rather, these figures exemplify that RAPID inaccurately calculated a small core infarct in a patient with a large complete MCA infarct and a persistent M1 occlusion, who had previously received iodinated contrast before the transfer to our facility. More specifically, Fig 3 shows a patient with a completed infarct in the right MCA territory with persistent occlusion of the right M1. RAPID correctly identified the prolonged transit time in that territory but estimated a core infarct volume of 0 mL (Fig 4). Figure 7 demonstrates that the underlying raw data were not the problem, but the methods used by RAPID resulted in a gross underestimation of core infarct volume. These figures illustrate the point of the article in its entirety, namely that the method used by RAPID, to a high statistical likelihood ($P = .04$), results in underestimation of core infarct volume in patients who recently received iodinated contrast.

We thank the authors for pointing out that CTP maps are derived from dynamic attenuation changes. We suggested contrast leakage as a potential mechanism for the observed error, but again, we are not certain. At the authors' request, we reviewed the prebolus CT scans and measured the attenuation manually. Our analysis showed the expected evolution of core infarct after transfer. As time progressed, the infarct became less attenuated (pair-wise *t* test, $P = .004$). We also evaluated the 12 patients who had a postcontrast CT obtained as part of the same study, and only 1 of the 12 had contrast enhancement. Again, the mechanism of the error remains unclear, but the data very clearly demonstrate an underestimation of the volume of core infarct in patients who had recently received iodinated contrast as part of a separate pretransfer examination ($P = .04$).

We thank the authors for again pointing out the perils of small sample sizes. It is a valid concern. We did have small samples in some of the statistical groups, and as such, the precision of our estimates was quite poor. For example, the 95% CI for the effect of grade III collaterals was 2.1–34.1. This nonetheless met the threshold of statistical significance ($P = .004$) and indicated the effect very likely exists. More samples are required to satisfactorily determine the true effect size of poor collaterals on CTP estimates produced by RAPID. We also thank the authors for pointing out our typographical error regarding the power analysis. Indeed, it should read "underestimation."

In the concluding paragraph, the authors reference 2 articles they and their colleagues with ties to iSchemaView have co-authored[2,3] as proof of real-world accuracy of RAPID. Overall, we agree that RAPID is an important addition to the diagnosis and treatment of patients with acute ischemic infarction. However, neither of the 2 referenced studies evaluated the accuracy of core estimate in patients with prior contrast administration versus patients who were contrast naïve. In the article by Sarraj et al,[3] a minority of the subjects were transfer patients (only 27 of 105), which is likely insufficient to affect the outcome of the study. In the article by Dehkharghani et al,[2] there was no mention of how many patients had previously received iodinated contrast.

Clinical practice demands that practicing neurointerventionalists and diagnostic neuroradiologists understand both the value and the limitations of software to determine the viability of brain tissue in patients with acute stroke. As scientists and physicians, it is our obligation to identify potential limitations and pitfalls, study them carefully, and report the results in the medical literature regardless of potential financial conflicts. Amukotuwa et al have great experience in CTP. As co-developers of RAPID, shareholders and consultants for iSchemaView (the company that produces RAPID), and in having relationships with the founders of iSchemaView,[4] we feel it is incumbent on them to publicly inform the user community of both the advantages and limitations of their products. As inventors, we thank them for making a product that has helped so many patients. As scientists, we challenge them to further explore the underestimation of core infarct by RAPID in patients who received iodinated contrast as part of a prior study. Should they confirm our findings, we hope they will inform physicians who rely on their software of the pitfalls of prior contrast administration on the estimate of core infarction provided by RAPID and make improvements to the platform for patients in whom contrast has recently been administered.

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