Hyperglycemia in thrombolysed acute ischemic stroke patients

In a relatively small sample of acute stroke patients treated with intravenous tissue plasminogen activator (IV-tPA), Meurer *et al.* (1) found no association between admission hyperglycemia and clinical outcomes (death, disability and intracerebral hemorrhage (ICH)). These results are counter to the conclusions of several other studies of similar size (2–4) and one larger prospective cohort study that found a clear association between admission hyperglycemia and an increased risk of death, symptomatic ICH (sICH) and disability outcomes (5). Thus, these results may simply represent a type II error (accepting the null-hypothesis when it should be rejected).

However, other explanations for these results should be considered. Only in-hospital death was reported, while other studies have generally examined mortality at 30 or 90 days. This would presumably lead to fewer outcome events in the current study and potentially underestimate the association between hyperglycemia and death, assuming that hyperglycemia is associated with an increased risk of death beyond the early phase after stroke. Similarly, considering disability at discharge rather than at a later time point may mask an eventual divergence in functional outcome between hyperglycemic and nonhyperglycemic patients over time. The use of the European Cooperative Acute Stroke Study definition of sICH (parenchymal hematoma type 2), resulted in a lower overall sICH rate compared with the use of the National Institute of Neurological Disorders and Stroke IV-tPA trial definition, and this may have diluted the association between glucose and sICH in this study.

The rate of overall ICH (9·9%) was surprisingly low as compared with other studies (2, 5) and may help explain the absence of an association between hyperglycemia and ICH. It is also possible that the population studied was comprised of milder strokes (median baseline National Institutes of Health Stroke Scale (NIHSS) is not provided) or a preponderance of lacunar strokes, a sub-type for which hyperglycemia may be less deleterious – or even beneficial (6). We found no evidence, on examining our own data, of effect modification of hyperglycemia on poor outcomes by baseline NIHSS score or by the Oxfordshire Community Stroke Project stroke type. Akin to the Meurer study, one other group also found no association between isolated admission hyperglycemia and outcome. In that study, among a mixed cohort of thrombolysed and nonthrombolysed patients, only persistent hyperglycemia at 24 h was associated with worse outcome. Unfortunately, 24 h glucose values were not available in the Meurer study.

We believe that the association between admission hyperglycemia and worse outcome in acute stroke patients treated with IV-tPA is well established and real. The more important question is whether aggressively treating hyperglycemia can improve patient outcomes.

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References

1 Meurer WJ, Scott PA, Caveney AF *et al.* Lack of association between hyperglycaemia at arrival and clinical outcomes in acute stroke patients treated with tissue plasminogen activator. *Int J Stroke* 2010; **5:**163–6.
2 Demchuk AM, Morgenstern LB, Krieger DW *et al.* Serum glucose and diabetes predict tissue plasminogen activator-related intracerebral hemorrhage in acute ischemic stroke. *Stroke* 1999; **30:**34–9.
3 Bruno A, Levine SR, Frankel MR *et al.* Admission glucose level and clinical outcomes in the NINDS rt-PA stroke trial. *Neurology* 2002; **58:**669–74.
4 Alvarez-Sabín J, Molina CA, Montaner J *et al.* Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. *Stroke* 2003; **34:** 1235–41.
5 Poppe AY, Majumdar SR, Jeerakathil T *et al.* Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis. *Diabetes Care* 2009; **32:**617–22.
6 Uyttenboogaart M, Koch MW, Stewart RE, Vroomen PC, Luijckx GJ, De Keyser J. Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke. *Brain* 2007; **130:**1626–30.

Reply

Dear Editor

We thank Drs Poppe and Hill for insightful observations regarding our study. Our a priori belief when initiating this investigation was that we would confirm the relationship between elevated glucose and adverse outcomes reported previously by others. After our analysis did not confirm this relationship, we felt it was important to provide this observation in order to aid future researchers and increase the amount of data available for systematic reviews and meta-analyses.

The median NIHSS in our cohort was 13 – additional information regarding other characteristics of the patients has now been published, although TOAST sub-typing was not carried out (1). We did not collect data on 24 h glucose or 90 day disability. The longer term impact of glucose on mortality could be evaluated in our data as we had follow-up mortality data. Of the 273 patients in the cohort, 112 had died through the end of our study follow up in 2005. Based on the suggestion, we examined 90 day mortality using Cox's proportional hazards regression. The hazard ratio for

each 100 mg/dl increase in glucose was 1·71 (95% confidence interval 1·1–2·7), with NIHSS, age and smoking included in accordance with the methods of the final binary logistic regression models reported in our paper. Not surprisingly, this was very similar to our published estimate of the association between glucose and in-hospital mortality – with a tighter confidence interval that no longer includes one.

Of course, these findings may represent a type II error and/or a manifestation of either the design limitations we noted in our manuscript or those listed by Drs Poppe and Hill. Disagreement between these data and prior studies may also reflect a deeper problem. It may be that all retrospective observations of the association between initial glucose and outcome may over simplify a complex pathology that defies simple interpretations. After all, initial glucose is a snapshot of a time-varying signal that reflects a variety of pathologies and comorbidities, and can result in physiological responses that may differ from patient to patient.

Based on all available clinical and laboratory data, it is likely that glucose metabolism interacts with acute brain injury, but the nature of the interaction requires further exploration. Even the way that we examine the available clinical observational data and our prior assumptions may influence interpretation. For example, should glucose be modeled as a continuous variable or should it be dichotomized as in many prior studies? The statistician in me says that dichotomization is throwing away data. The clinician in me has a difficult time conceptualizing the adverse effects of one milligram per deciliter rise in blood glucose. Should we assume a linear response, or should we model a *U*-shaped or an other type of relationship? Ultimately, we share Drs Poppe and Hill's inclination that hyperglycemia is adverse in brain injury; however, we also recognize the importance of keeping an open mind as data continue to emerge and theories are either confirmed or become more complicated. We strongly support prospective randomized trials of glucose-lowering strategies.

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Reference

1 Scott PA, Frederiksen SM, Kalbfleisch JD *et al.* Safety of intravenous thrombolytic use in four emergency departments without acute stroke teams. *Acad Emerg Med* 2010; **17:**1062–71.

A new ultrasound method for evaluating dysphagia in acute stroke patients

Dysphagia after stroke was a common and serious complication, and conventional methodologies of swallowing evaluation had several limitations. Here, we examined tongue movement during the swallowing process in order to evaluate dysphagia with our unique ultrasound examination, the Tongue and Oral Function test with Ultrasound (TOFU).

For 100 acute stroke patients (65 men, 72·2 ± 10·7 years) in who swallowing status had been evaluated by the modified water swallowing test and the food test, we performed TOFU in addition to videofluoroscopic swallowing study (VFSS). Dysphagia was defined as abnormal swallowing on VFSS. In TOFU, a patient was requested to swallow saliva in the 30° head-up position. Tongue surface was visible as a bright narrow line on an M-mode image (Fig. 1) (1–5). We measured the downward (Vd) and upward movement velocities (Vu) of tongue in the swallowing phase, and the distance from the caudally depressed to the cranially elevated positions (D). We assessed differences in various TOFU findings between the 24 patients with dysphagia and 76 patients without, and configured a ROC curve for Vu.

Vd and Vu were slower in the patients with dysphagia than in those without (Vd, 38·01 ± 21·42 vs. 47·98 ± 20·75 mm/s, $P = 0·007$; Vu, 57·04 ± 16·24 vs. 85·43 ± 24·74 mm/s, $P < 0·001$), and D was shorter (11·63 ± 3·19 vs. 13·49 ± 3·55 mm, $P = 0·027$). With a cut-off value of Vu of 63·55 mm/s, the sensitivity for the detection of dysphagia was 83·3% and the specificity was 88·2%.

A notable finding was that a cut-off value of Vu of 63·55 mm/s could accurately predict dysphagia. The TOFU is not only an easy way at the

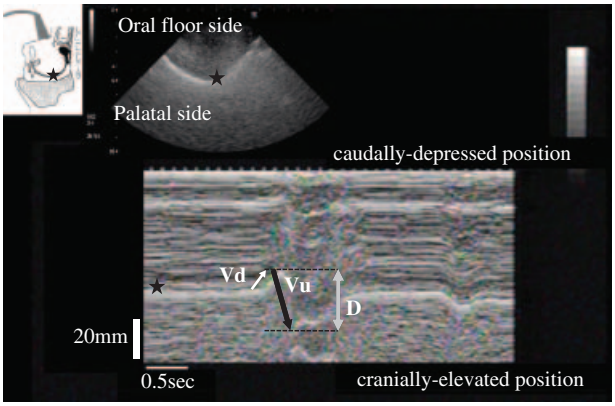

Fig. 1 A representative sagittal B-mode and M-mode ultrasound image of the swallowing process observed in a stroke patient without dysphagia. The viewing point of the tongue, marked by black star, was recognizable by its horizontal trace during the preparatory phase on an M-mode image. It was recognizable by the downward movement (Vd, white arrow), and then the upward movement (Vu, black arrow) in the swallowing phase. The distance from the caudally depressed to the cranially-elevated position was measured (D, gray double-headed arrow).