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# Head down positioning before recanalization in acute ischemic stroke

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The pilot clinical trial of Trendelenburg position in acute ischemic stroke, recently published in *Nature Communications*,<sup>1</sup> showed promising results on disability and no serious concerns on patient safety. Although the primary outcome (modified Rankin scale [mRS] 0–2 at 3 months) was statistically neutral, the clinical relevance of the estimates should be considered (15% mean difference; adjusted OR 2.28; 95% CI 0.84–6.14;  $p=0.104$ ), together with all the positive secondary outcomes (mRS 0–1 at 3 months, adjusted OR 2.72; 95% CI 1.00–7.36;  $p=0.049$ ; mRS shift analysis, adjusted OR 3.15; 95% CI 1.44–6.92;  $p=0.004$ ; changes in the National Institute of Health Stroke Scale at day 12, adjusted OR  $-0.16$ ; 95% CI  $-0.26$  to  $-0.06$ ;  $p=0.002$ ).

The main aim of head down positioning (HDP) in acute ischemic stroke is to increase cerebral collateral flow, preserve potentially salvageable penumbral tissue and expand the time window for recanalization therapies. This key concept highlights one of the major limitations of this trial and, even more importantly, is needed to guide future trials in this field: the timing of HDP with regards to recanalization is likely to be an essential detail.

For its simplicity, low cost and feasibility, HDP represents a good candidate as a collateral therapeutic to be applied as soon as an acute ischemic stroke is suspected, even a few minutes after arterial occlusion, prior to recanalization therapies. A mechanism of action of HDP at the neurovascular unit level is not established. However, we propose that it may promote a local increase in the filling of collaterals surrounding ischemic brain areas, wherein both arterial cerebrovascular autoregulation and venous outflow are impaired.

Experimental studies from our group at the University of Milano Bicocca, Italy, showed that head down tilt 15° (HDT15) increased cerebral blood flow and improved functional outcome and infarct volume in 118 randomized rats subjected to middle cerebral artery occlusion followed by reperfusion.<sup>2</sup> Further experimental studies, in collaboration the University of Lyon 1, France, confirmed that HDT15 application for 60 min increased cerebral perfusion in the ischemic area, assessed by perfusion MRI, in 28 randomized rats using the same stroke model.<sup>3</sup> An

experimental study of HDT15 in a non-human primate stroke model, which includes reperfusion, has recently been funded and is currently in its early phase (DOWN-PRIME), within a research consortium including our academic institutions in France and Italy.

The HeadPOST trial, the largest clinical trial so far on head positioning in acute stroke, produced neutral results on clinical outcome comparing lying-flat versus sitting-up positions.<sup>4</sup> Besides the “low dose” (lying-flat), other significant limitations of the HeadPOST trial were a very low proportion of patients receiving recanalization therapies (approximately 10% intravenous rt-PA, nearly 1% endovascular thrombectomy) and late application (median 14 h).

An observational study, from the pre-thrombectomy era, showed better clinical outcome in the Trendelenburg position (0° to  $-15^\circ$ ) applied soon after stroke onset, compared to the standard position (0 to  $+30^\circ$ ), in 209 patients with acute ischemic stroke due to large vessel occlusion.<sup>5</sup> Notably, approximately 50% of these patients had been treated with intravenous rt-PA and the benefit of HDP was strongly associated with an effective recanalization (OR 7.47, 95% CI 1.29–43.18). So far, the study by Gauthier et al. represents the only available evidence of the hyperacute effect of HDP applied before recanalization.

The most valuable contribution of the recent trial by Chen et al. is definitely related to the safety of HDP in acute ischemic stroke. The Authors applied a “large dose” ( $-20^\circ$ ) for a prolonged period (median 15 h) and reported only minor adverse events (headache, anxiety).

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As far as efficacy, the promising results of this trial are likely to reflect the hemodynamic etiology of stroke in many participants (nearly 50% had no occlusion of the responsive vessel, but moderate or severe stenosis), which represents a relatively rare occurrence compared to embolic occlusion. The same limitations of the HeadPOST trial (no recanalization therapies; late time to positional treatment) apply to the recent trial by Chen et al., although the “high dose” ( $-20^\circ$ ) and the highly selected etiology apparently made a difference.

HDP is a simple, low cost intervention that could readily be applied as part of emergency treatment of stroke at a global level. However, a big gap in knowledge is yet to be filled: is HDP applied before recanalization therapies effective and safe in acute ischemic stroke?

Rigorously designed, multi-national clinical trials are needed to fully investigate this issue.

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All authors contributed to the concept, drafting and critical revision of the manuscript.

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