Perioperative levels of neurofilament light (NFL) in serum and its association with postoperative delirium (POD) after cardiac surgery

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Background – Postoperative delirium (POD) is an important complication after cardiac surgery. It is associated with an increased morbidity and mortality. The pathophysiology of POD is not fully elucidated. In addition to perioperative episodes of cerebral hypoxia and/or hypoperfusion, neuroinflammation and a direct insult to the brain, induced by both anaesthesia and surgery may play o role.

In current clinical practice, the ideal biomarker, highly sensitive for brain injury, as well as highly specific for neuronal tissue, has not been determined yet.
Recently, much focus has been given to perioperative serum levels of neurofilament light (NFL), a subunit of neurofilaments.[1,2] These proteins are exclusively expressed by neuronal tissues, as they are part of the scaffolding of axons.

Goal of Study – We present the preliminary results of an ongoing study dedicated to analyse the perioperative kinetics of NFL in serum in adult cardiac surgery, and their potential association with POD.
We specifically analysed whether preoperative, as well as postoperative serum levels of NFL were higher in patients presenting POD, compared to those who did not experience POD.

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Materials and methods – This study is a pre-specified sub-analysis of an ongoing research project (NCT03706989).

Five iterative blood samples were collected perioperatively (before anaesthesia, 2 hours after admission in ICU, postoperative day 1, day 2 and day 5) in 30 adult patients undergoing a first elective cardiac surgery with normothermic cardiopulmonary bypass.
Quantitative determination of NFL in serum was performed using a single-molecule array method (Simoa®). One round of experiments was performed, using one batch of reagents. Results with a coefficient of variance > 20% were repeated.

POD was assessed in ICU using the CAM-ICU, after an evaluation of the level of consciousness by the RASS (Richmond Agitation and Sedation Scale). At the ward, the CAM, in combination with a flow chart review, were used to screen any episode of POD until hospital discharge.

Statistical analysis – Continuous variables are expressed as median (P_{25}-P_{75}). A Friedman Wilcoxon test was used to analyse paired NFL levels in patients with or without POD, followed by a Bonferroni post-hoc analysis. The difference between groups was significant at level 0,05 if the endpoint's P value was <0,005 (0,05/10). A Mann-Whitney U-test was used to compare continuous variables between patients with or without POD.

Results – NFL levels increased up to 5 days in all patients, although this increase was not statistically significant in POD(+) group (Figure 1).

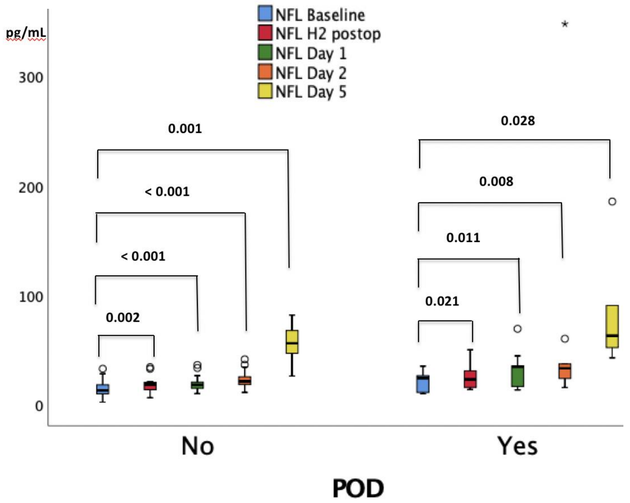

Figure 1 -Within patient analysis of perioperative serum NFL levels

NFL levels at baseline increased significantly with age (p= 0,001); and patients who experienced POD were significantly older and had higher levels of Euroscore II (Table 1).
However, there was no statistically significant difference in NFL levels at baseline between POD (+) and POD (-) patients. Besides, patients who experienced POD had higher levels of NFL in serum at postoperative day 1 and day 2 (Table 2).

	POD (+) (n=9)	POD (-) (n=21)	p
Age, y	81 (65-82)	68 (48-74)	**0.02**
Euroscore II, %	3.7 (2.6-7.78)	1.88 (0.94-2.76)	**0.02**
Serum creatinin (mg/dl)	1.04 (0.90-1.37)	0.93 (0.83-1.12)	0.365
CPB time (min)	123 (102-129)	102 (65-125)	0.189
Surgical time (min)	246 (210-253)	206 (177-262)	0.287
Aortic cross-clamp time (min)	91 (73-102)	78 (49-109)	0.441

Table 1 - Characteristics of the population

	POD (+) (n=9)	POD (-) (n=21)	p
NFL baseline (pg/ml)	24.1 (11-26.4)	12.8 (9.7-18)	0.1
NFL H2 (pg/ml)	22.9 (15.7-30.8)	18.3 (13.6-20.3)	0.14
NFL D1 (pg/ml)	34.6 (16.5-35.3)	18 (14.9-20.4)	**0.03**
NFL D2 (pg/ml)	33.2 (23.8-37.1)	21.2 (18.2-25.3)	**0.05**
NFL D5 (pg/ml)	62.9 (52-90.5)	55.9 (46.8-67.6)	0.32

Table 2 – Perioperative NFL levels in serum - Results in median (P_{25}-P_{75})

Conclusion – These preliminary results allow to suggest that there is a perioperative increased release of NFL in serum and that NFL could be a potential biomarker of POD in cardiac surgery.

References: 1. Evered L. JAMA Neurol 2018;75:542-547, 2. Casey CP. Brain 2020;143(1):47-54