Author's response to reviews

Title: The effect of short-term high versus normal protein intake on whole-body protein synthesis and balance in children following cardiac surgery: A randomized double-blind controlled clinical trial

Authors:

Vincent G Geukers (v.g.geukers@amc.uva.nl)
Monique E Dijsselhof (m.e.dijsselhof@amc.uva.nl)
Nicolaas JG Jansen (N.J.G.Jansen@umcutrecht.nl)
Johannes MPJ Breur (H.Breur@umcutrecht.nl)
Dewi van Harskamp (d.vanharskamp@amc.uva.nl)
Henk Schierbeek (h.schierbeek@amc.uva.nl)
Johannes van Goudoever (h.vangoudoever@amc.uva.nl)
Albert P Bos (a.p.bos@ziggo.nl)
Hans P Sauerwein (h.p.sauerwein@planet.nl)

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REVIEWERS' COMMENTS

REVIEWER 1

Major Compulsory Revisions

Q1. The authors need to clearly state the potential negative impact of high protein intake in these patients.

Possible side effects of high protein intake are azotemia, hypertonic dehydration and acidosis [Klein C, et al. J Am Diet Ass, 1998;98(7):795–806]. In our study, we reported higher protein oxidation rates and BUN in the HP group compared to the NP group [7.1 (4.4 to 11.7) and 4.0 (2.7 to 5.6) mmol•L⁻¹, respectively, p<0.05] (Table 4, page 35).

Transient azotemia, as a distinct entity from acute kidney failure, in adult hospitalized patients is independently associated with increased hospital mortality [Uchino S, et al. Nephrol Dial Transplant, 2010(25):1833-1839]. However, the transient (<72 hrs) rise in serum creatinine concentrations that can be observed in this clinical condition are the result of a temporarily disturbed kidney function, and should not be confused with a relative overload of renal clearance of nitrogenous compounds due to increased production as is the case in our study. We considered the observed higher oxidation rate and concomitant ureagenesis plausible explanations of the metabolic fate of surplus amino acids in the HP group (Discussion section; page 19, lines 378-380). Therefore, we considered the only moderately higher BUN in the HP group (maximum: 11,7
mmol•L⁻¹), compared to the NP group, as clinically irrelevant.

In a systematic review in low birth weight infants, Premji et al identified 5 studies that reported not only azotemia but also metabolic acidosis with high protein intakes of 4-6 g•kg⁻¹•d⁻¹ balanced protein, compared to age-related reference protein intake of 3 g•kg⁻¹•d⁻¹ [23]. Despite the fact that five of the included studies predating 1995, in a time in which the amino acid balance of feeding solutions did not meet present-day standards, we cannot rule out the possibility that metabolic acidosis has also occurred in our patients, since we did not routinely measure blood pH as part of the study protocol. We have inserted this remark in the Discussion section (page 19, lines 368-371). Also, we have changed the final sentences of the Conclusion section into (page 21, lines 406-409):

"We cannot rule out a possible detrimental effect of metabolic acidosis due to high protein intake in the HP group, since we did not routinely measure blood pH. Therefore, a high protein diet (5 g•kg⁻¹•d⁻¹) is not a meaningful, yet even potentially hazardous strategy in young children following cardiac surgery."

Minor Essential Revisions

Q1. Page 6; line 95: what do the authors mean by low complex congenital heart disease?

The Aristotle Basic Complexity (ABC) score has been used since 2002 both by The Society of Thoracic Surgeons and the European Association of Cardiothoracic Surgery to indicate complexity of cardiac surgical procedures (Aristotle Committee. The Aristotle score: a complexity-adjusted method to evaluate surgical results. Eur J Cardiothorac Surg. 2004 Jun;25(6):911-24). The score involves three components: the potential for mortality, the potential for morbidity, and surgical technical difficulty. The latter is influenced by anatomical factors, associated procedures, and age at procedure. The ABC score ranges from 1 to 4, with 4 being the most complex.

In our study, we have included patients with ventricular septal defect (VSD) and/or atrial septal defect (ASD), or partial atrioventricular septal defect (pAVSD) with CPB. These congenital defects are listed in the 1st and 2nd category of the ABC score.

For clarity, we have inserted a reference to the Aristotle Committee paper in the material and methods section (recruitment of subjects) (page 7, lines 106-108). Also, we specified pAVSD as a separate entity from ASD and VSD:

"Inclusion criteria were age 3-24 mos, and pending low-complex (Aristotle score 1-2 out of 4, [REF] surgical repair of ventricular septal defect (VSD) and/or atrial septal defect (ASD), or partial atrioventricular septal defect (pAVSD) with CPB."

Q2. There is no power analysis with the primary outcomes to state the required sample size that would show a difference in either direction.

The primary outcomes of our study were short-term (<48 hrs) effects on
whole-body valine kinetics and albumin synthesis rate, of high protein (HP; 5 g•kg\(^{-1}\)•d\(^{-1}\)) dietary intake, compared to normal protein diet (NP; 2 g•kg\(^{-1}\)•d\(^{-1}\)) (page 6, lines 94-97). As stated in the Statistical paragraph, in young children following cardiac surgery there are no available estimates of mean valine balance with standard deviation (SD), obtained from protein intakes of 2 and 5 g•kg\(^{-1}\)•d\(^{-1}\) (page 13, lines 255-257).

As an alternative estimate, we based our power calculations on correction to zero of the whole-body valine balance of \#0.65 (SD 0.56) \(\mu\text{mol}•\text{kg}^{-1}•\text{d}^{-1}\), that we had found in a previous study in young children following cardiac surgery with protein intake of 0.3 g•kg\(^{-1}\)•d\(^{-1}\). Also in the comparison of the effects of protein intakes of 2 and 5 g•kg\(^{-1}\)•d\(^{-1}\), we would have considered an statistically significant increase of valine balance by \#0.65 \(\mu\text{mol}•\text{kg}^{-1}•\text{d}^{-1}\) to be clinically relevant. We added this sentence to the Statistical paragraph (page 13, lines 262-264):

"Also in the comparison of the effects of protein intakes of 2 and 5 g•kg\(^{-1}\)•d\(^{-1}\), we consider a statistically significant increase of valine balance by \#0.65 \(\mu\text{mol}•\text{kg}^{-1}•\text{d}^{-1}\) to be clinically relevant."