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Adequacy of nutrition support during extracorporeal membrane oxygenation

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22 **Abstract**

23 *Background.* The use of veno-venous extracorporeal membrane oxygenation (vv-ECMO) is
24 increasing in adults with severe respiratory failure. Observational data suggest that there
25 are significant challenges to providing adequate nutritional support for patients on vv-
26 ECMO. We aimed to describe firstly the nutritional support practices in a large single-centre
27 providing vv-ECMO to adults and secondly any association with clinical outcome.

28 *Methods.* We conducted a retrospective review of patients receiving vv-ECMO on the
29 Intensive Care Unit (ICU) of a large London teaching hospital. Adult patients admitted to the
30 ICU with severe respiratory failure between December 2010 and December 2015 were
31 included. Daily energy and protein delivery were compared with estimated targets and
32 reasons for feeding interruptions were collected from electronic medical records. Adequate
33 feeding was defined as 80-110% of estimated targets.

34 *Results.* We analysed 203 eligible patients. Median duration of ICU stay was 21.0 (IQR,
35 15.0–33.0) days and vv-ECMO 10.0 (IQR, 7.0–16.0) days. Although median energy (89.8%
36 (IQR, 80.5–96.0%)) and protein (84.7% (IQR, 74.0–96.7%)) delivery was adequate,
37 underfeeding of either energy or protein occurred on nearly third (28.3%) of nutrition
38 support days. A higher admission severity of illness score was associated with inadequate
39 protein delivery ($p=0.040$). Patients with more severe organ dysfunction on the first day of
40 vv-ECMO received inadequate energy ($p=0.026$). The most common reasons for
41 interrupted feeding were medical procedures (39.1%) followed by poor gastric motility
42 (22.8%).

43 *Conclusion.* Adequate energy and protein delivery during vv-ECMO is possible but
44 underfeeding is still common, especially in those who are more severely ill or who have
45 more severe organ dysfunction. Patients with inadequate energy or protein intake did not
46 differ in ICU and 6-month survival. Prospective studies investigating optimal feeding in this
47 patient cohort are required.

48

49 **Introduction**

50 Veno-venous extracorporeal membrane oxygenation (vv-ECMO) is a temporary life support
51 system that removes blood from the central venous circulation and returns oxygenated
52 blood to the right atrium (1). The use of vv-ECMO in adults with severe respiratory failure is
53 increasing, particularly since the H1N1 influenza pandemic of 2009 and 2010 (2, 3). The
54 use of vv-ECMO has led to improved survival among patients with H1N1 (1-3), and
55 importantly has been shown to do so without severe disability at six-months when
56 compared with conventional management (4). However, the overall benefit of ECMO on
57 mortality is inconclusive (5).

58 In general, patients on the Intensive Care Unit (ICU) are commonly underfed, with
59 data reporting around 50-70% of energy and protein targets are received (6-8).
60 Observational studies demonstrate an association between underfeeding and worse
61 outcomes, including mortality (9, 10). However, these results have not been confirmed in
62 prospective randomised controlled trials (RCTs) over the first week of ICU admission (11-
63 13).

64 Nutrition support is likely of great importance during vv-ECMO given these patients
65 are some of the most severely ill, are more likely to have a prolonged stay on ICU and may
66 have raised nutritional requirements due to increased protein catabolism secondary to
67 inflammation and acute illness (14). However, despite the rapid increase in use of vv-
68 ECMO since 2010, there remains little information regarding optimal nutritional
69 management of these patients. Guidelines on nutritional support in general critical illness
70 recommend early (within 24–48 hrs) feeding using the enteral route as the first line (15-17).
71 However, there are no specific nutritional guidelines during ECMO; the guidelines by
72 Extracorporeal Life Support Organization simply mention that 'full energy and protein
73 support is essential' (18).

74 To our knowledge, only seven studies have been undertaken investigating nutrition
75 support practices in patients receiving ECMO (19-25). Their findings indicate that despite

76 timely commencement of enteral nutrition, nutrition deficits are common (19, 20, 22, 24,
77 25). However, there are important limitations in these studies; some do not report energy
78 and protein intakes separately (19, 20), some data include veno-arterial ECMO (20, 22, 24,
79 25), whilst other studies include non-ECMO days in their data analysis (24, 25).

80 Gastrointestinal (GI) intolerances (26) are common causes of underfeeding in the
81 general ICU population and this is also found in patients on ECMO with 50-73% of patients
82 requiring ECMO receiving prokinetic medication (20, 23, 25), however whether this is a
83 result of the severity of illness or due to an effect of ECMO itself is not known.

84 Our aim was to describe nutritional practices in a single-centre providing vv-ECMO
85 to assess the timing and adequacy of energy and protein delivery through gastric, jejunal
86 and parenteral routes, GI complications during vv-ECMO therapy, and the difference in
87 delivery of energy and protein during and after vv-ECMO. Further, we aimed to investigate
88 the association of nutritional support adequacy with clinical outcome.

89

90 **Methods**

91 A retrospective observational study of patients receiving vv-ECMO was undertaken on our
92 tertiary mixed medical and surgical intensive care unit which provides the ECMO referral
93 service for 43 hospitals in South East England. The need for informed consent was waived
94 and the study approved by our institutional review committee (reference number 2216).

95

96 *Inclusion and exclusion criteria*

97 Patients admitted to the ICU with severe respiratory failure requiring vv-ECMO between
98 December 2010 and December 2015 were included if they were age ≥ 18 years at the time
99 of admission and received ≥ 72 hours and no more than 6 months of vv-ECMO support.

100 Patients were identified from a prospectively held database and patient records were
101 searched from our electronic intensive care patient information system (ICIP, Philips,
102 Netherlands). Patients were excluded if there was no documentation of calculated

103 nutritional targets or if they were able to eat and drink for the entire duration of ECMO
104 support.

105

106 *Nutrition support protocol*

107 Patients on vv-ECMO commenced nutrition support according to the same protocol as
108 general ICU patients which advocates commencing gastric feeding within 24–48 hours of
109 admission, following which individualised nutritional targets were calculated by the ICU
110 dietitian within 48-72 hours of admission. Energy targets were calculated using 25-30
111 kcal/kg/day during vv-ECMO or during periods of no mechanical ventilation (27), and the
112 Modified Penn State equation (28) was used during periods not on vv-ECMO, but still
113 receiving mechanical ventilation. Protein requirements were calculated using a minimum of
114 1.2 g/kg/day, with increases depending on clinical condition (e.g. continuous renal
115 placement therapy). For patients with body mass index (BMI) ≥ 25 kg/m², ideal body weight
116 (IBW) and adjusted body weight (ABW) were used to calculate protein and energy
117 requirements, respectively.

118 Gastric residual volumes (GRVs) were assessed every four hours by nursing staff.
119 Clinical guidelines recommended prokinetic therapy be considered after two GRV >300 ml,
120 and then reducing the rate of feeding after three consecutive GRV >300 ml. If high GRV
121 persisted for more than 72 hours, jejunal feeding (unless contraindicated) followed by
122 parenteral nutrition (PN), was considered. Nasojejunal feeding tubes were placed by
123 nursing staff or ICU dietitian at the bedside using an electromagnetic device (Cortrak,
124 Halyard, UK).

125

126 *Data collection*

127 All data was retrospectively searched from our electronic patient records (IntelliVue Clinical
128 Information Portfolio, ICIP, Release F.01.00, Philips Healthcare, USA). Age, weight, height
129 and BMI were recorded at the time of admission to the ICU. Severity of critical illness was

130 calculated using APACHE II (Acute Physiology and Chronic Health Evaluation II) and
131 recorded on the day of ICU admission (29) and the degree of organ failure was calculated
132 using SOFA (Sepsis-related Organ Failure Assessment) and was recorded for the first day
133 of both ICU admission and vv-ECMO therapy (30). Other data collected included gender,
134 principal diagnosis and outcomes such as duration of vv-ECMO therapy, ICU stay, and ICU
135 and six-month survival.

136 The energy and protein delivered daily for each patient was collected for the days
137 they were on vv-ECMO (always on the ICU) as well for the days following decannulation
138 from vv-ECMO (data only recorded whilst on ICU). The first day of vv-ECMO and the day of
139 vv-ECMO cessation were treated as the first and final day on vv-ECMO, respectively. Data
140 were collected until both oral nutrition commenced and artificial feeding was either ceased,
141 intentionally reduced to provide <100% requirements, or when a patient was discharged
142 from ICU at our institution.

143 Data on nutritional intake included energy and protein from EN, PN, intravenous (IV)
144 glucose and propofol during a one day period (starting 06:00, finishing 05:59). Energy from
145 propofol was included if it was running at a minimum rate of 10 ml/hr for six or more hours a
146 day. 10% IV glucose was included in energy intake recording if the administered volume
147 exceeded 1000 ml/day.

148 Daily energy and protein delivery were compared with the estimated target that day.
149 If targets were expressed as a range, the midpoint of the range was recorded. For the first
150 day on the ICU, nutritional targets were re-calculated as a proportion of a 24-hour period
151 based on the time of admission, in order to ensure correct data representation. Similarly, on
152 the patient's last day on the ICU, nutritional targets were re-calculated as the proportion of a
153 24-hour period based on the time of discharge or death.

154 The overall energy and protein targets for periods on vv-ECMO and post vv-ECMO,
155 were recorded as the mean of each period. The overall energy and protein delivery for
156 these periods was also recorded as the mean of each period.

157 Adequate delivery of nutrition was defined as 80-110% of the target of energy or
158 protein for that day, with underfeeding defined as <80% and overfeeding >110%. Although
159 the optimal energy and protein intake in critical illness is much debated (31), recent studies
160 have observed lower 60-day mortality when 80% of energy (32) and protein (8) targets
161 were achieved. The upper limit of 110% was chosen to account for inaccuracies in
162 estimated weight based targets. When analysing nutrition support days, patients who were
163 underfed either energy or protein (e.g. underfed energy/ adequate protein and underfed
164 energy/overfed protein) were categorised as underfed.

165 The time taken to reach adequate energy and protein delivery over a 24-hour period
166 was calculated from the time of admission to the first hour of the 24-hour period of
167 adequate delivery.

168 The main, second and third routes of feeding during vv-ECMO were recorded based
169 on the length of time a patient relied on any one route. The longest duration of any one
170 route was recorded as the main route. Special attention was paid to capture possible
171 reasons for underfeeding. The number, duration and main reason for feeding interruptions
172 during vv-ECMO were recorded. The main reason was defined as the reasons for the
173 longest interruptions. If EN was stopped or reduced due to GRV >300 ml, three preceding
174 values and name/dose of a prokinetic agent administered, were recorded.

175

176 *Statistical Analysis*

177 Data were analysed using SPSS, version 23 (IBM SPSS Software NY, USA). Categorical
178 data are presented as *n* (%), continuous data as mean (standard deviation [SD]) for
179 normally distributed data and median (interquartile range [IQR]) for non-normally distributed
180 data. Assumptions for normality were assessed using Kolmogorov-Smirnov One-Sample
181 test.

182 Categorical data were compared between two groups using Chi-squared test.

183 Continuous data, which was not normally distributed, were compared between two groups

184 using Mann-Whitney test and between three groups using Kruskal-Wallis test and
185 Bonferroni *post hoc* correction. Nutritional delivery during vv-ECMO and post vv-ECMO
186 were compared using the Wilcoxon Signed Ranked test or sign test (where distribution was
187 asymmetrical on inspection of a histogram). $P < 0.05$ was considered statistically
188 significant.

189

190 **Results**

191 241 patients received vv-ECMO between December 2010 and December 2015. Of the 241
192 patient records assessed for eligibility, 38 were excluded (18 <72h on vv-ECMO, seven no
193 estimated nutrition target, five <18 years of age, three received oral nutrition only, two had
194 incomplete nutrition delivery data, one incorrect medical number, one with oral nutrition
195 intake during vv-ECMO and supplementary or no artificial nutrition, and one > six months
196 on vv-ECMO) resulting in 203 patient records included in this analysis.

197 Two hundred and two patients were admitted for medical reasons and one was
198 admitted for surgery. Details of the demographic and baseline data of all included patients
199 are shown in Table 1.

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214 **Table 1.** Demographic and baseline clinical data of 203 patients.

Characteristics	Result
Age (year), median (IQR)	44.0 (33.0–55.0)
Gender, <i>n</i> (%)	
Female	91 (44.8)
Male	112 (55.2)
Weight (kg), median (IQR)	80.0 (65.0–100.0)
BMI (kg/m ²), median (IQR)*	27.0 (23.7–33.0)
Principal diagnosis	
Aspiration, <i>n</i> (%)	11 (5.4)
Asthma, <i>n</i> (%)	14 (6.9)
Influenza, <i>n</i> (%)	35 (17.2)
Pneumonia, <i>n</i> (%)	94 (45.3)
Sepsis, <i>n</i> (%)	12 (5.9)
Other infectious respiratory failure, <i>n</i> (%)	10 (4.9)
Other respiratory failure, <i>n</i> (%)	29 (14.3)
APACHE II score, median (IQR)	18 (15–21)
SOFA score on admission, median (IQR)	6 (4–11)
SOFA score on first day of vv-ECMO, median (IQR)	7 (4–11)
vv-ECMO duration (days), median (IQR)	10.0 (7.0–16.0)
ICU duration (days), median (IQR)	21.0 (15.0–33.0)
vv-ECMO survival, <i>n</i> (%)	172 (84.7)
ICU survival, <i>n</i> (%)	163 (80.3)
Six-month survival, <i>n</i> (%)	159 (78.3)
Estimated energy requirements (kcal/day), median (IQR)	1800 (1600–2000)
Estimated protein requirements (g/day), median (IQR)	87.0 (75.0–100.0)

**n*=202; BMI for one patient unknown

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; ICU: Intensive Care Unit; SOFA: Sepsis-related Organ Failure Assessment; vv-ECMO: veno-venous extra corporeal membrane oxygenation.

215

216

217 *Nutrient delivery and adequacy during vv-ECMO*

218 VV-ECMO support was provided on a total of 2989 days, which consisted of 2900 days of
219 artificial nutritional support (EN, PN). During these nutritional support days on vv-ECMO the
220 median energy delivered was 89.8% (IQR 80.5–96.0%) and protein 84.7% (IQR
221 74.0–96.7%) of targets (Table 2). However, underfeeding still occurred in a large proportion
222 of patients (Figure 1). Protein and/or energy intake was inadequate on approximately one
223 quarter of days (Table 2).

224

225

226 **Table 2.** Energy and protein intake from nutritional support and adequacy during vv-ECMO of all 203 patients
 227 included in the study.

	Outcomes
Energy intake whilst on vv-ECMO	
Overall intake (% of target), median (IQR)	89.8 (80.5–96.0)
Minimum – maximum (% of target)	37.0 -119.3
Energy from IV glucose, median (minimum – maximum) (kcal/patient)	0.0 (0.0 – 3692.4)
Energy from propofol, median (minimum – maximum) (kcal/patient)	0.0 (0.0–2290.9)
Cumulative energy balance whilst on vv-ECMO ^a (kcal), median (IQR)	–1625.6 (–4088.3 to –540.0)
Protein intake whilst on vv-ECMO	
Overall intake (% of target), median (IQR)	84.7 (74.0–96.7)
Minimum – maximum (% of target)	25.9-133.8
Cumulative protein balance whilst on vv-ECMO (g), median (IQR)	–117.1 (–222.9 to –22.1)
Adequacy of energy intake, n (%) days ^b	
Underfeeding	694 (23.9)
Adequate feeding	1830 (63.1)
Overfeeding	376 (13.0)
Adequacy of protein intake, n (%) days ^b	
Underfeeding	790 (27.2)
Adequate feeding	1439 (49.6)
Overfeeding	671 (23.1)
Adequacy of energy and protein intake, n (%) days ^b	
Underfeeding either energy or protein	822 (28.3)
Adequate feeding both energy and protein	1203 (41.5)
Overfeeding either energy or protein	875 (30.2)

228 ^a Balance calculated as the difference between estimated target and delivery

229 ^bTotal number of nutrition support days was 2900

230

231 A

232

233 B

234 **Figure 1. A: Distribution of mean intakes of prescribed energy (A) and protein (B) per**
 235 **patient during vv-ECMO. Feeding was considered adequate if 80-110% of estimated**
 236 **targets were met (highlighted in dark grey).**

237

238 The median time taken to start nutritional support was 13.5 hours (IQR, 9.0–23.5)
 239 and 197 patients (96.6%) received nutrition support within 48 hours. The median time to
 240 reach adequate intake of both energy and protein over a 24-hour period was 68.8 hours
 241 (IQR, 41.5–105.8), although 13 (6.4%) patients never achieved adequate intake. The

242 median time taken to reach adequate energy intake was 54.5 hours (IQR, 36.0–77.8) (five
243 (2.5%) patients excluded due to never achieving adequate intake) and for protein was 59.5
244 hours (IQR, 36.9–86.0) (11 (5.4%) patients excluded due to never achieving adequate
245 intake).

246

247 *Route of feeding*

248 The most common route of feeding during vv-ECMO was gastric (123 patients, 60.6%)
249 followed by jejunal (70 patients, 34.5%) and parenteral (10 patients, 4.9%). Jejunal feeding
250 was attempted in another 20 (9.9%) patients but was unsuccessful as the clinician was not
251 able to advance the tube post-pylorically and therefore, the gastric route was used. Two
252 patients were admitted with a long-term EN feeding tube – one percutaneous endoscopic
253 gastrostomy tube and the other percutaneous endoscopic jejunostomy tube.

254

255 *Nutritional adequacy and outcomes*

256 Patients whose median protein intake represented underfeeding (<80% requirements)
257 (n=78) had higher APACHE II score on ICU admission than those with adequate (n=111)
258 ($p=0.040$), and patients whose average energy intake represented underfeeding (n=48) had
259 higher SOFA score on the first day of vv-ECMO than those with adequate (n=150)
260 ($p=0.026$). Patients with inadequate energy or protein intake did not differ in the time taken
261 to start nutritional support or ICU and 6-month survival (Table 3). However, those with
262 adequate energy ($p<0.001$) and protein ($p=0.001$) delivery had longer duration of vv-ECMO
263 than those without (Table 3).

	Energy ^a		p value	Protein ^b		p value
	Adequate	Underfeeding		Adequate	Underfeeding	
	(80–110% of target)	(<80% of target)		(80–110 % of target)	(< 80 % of target)	
Number of patients, n (%)	150 (73.9)	48 (23.6)		111 (54.7)	78 (38.4)	
Disease severity scores, median (IQR)						
APACHE II score	18.0 (15.0–20.0)	19.0 (15.0–22.8)	0.113 ^a	18.0 (14.0–20.0)	19.0 (16.0–22.0)	0.040 ^c
SOFA score on admission	5.5 (4.0–11.0)	8.0 (4.0–11.0)	0.117 ^a	6.0 (4.0–11.0)	8.0 (4.0–12.0)	0.440 ^c
SOFA score on first day of vv-ECMO	7.0 (4.0–11.0)	9.0 (5.0–12.0)	0.026 ^a	7.0 (4.0–11.0)	8.5 (4.0–12.0)	0.201 ^c
vv-ECMO duration, median (IQR)	11.0 (8.0–18.0)	8.0 (6.0–10.0)	<0.001 ^a	11.0 (7.0–17.0)	8.0 (7.0–12.0)	0.001 ^c
ICU duration, median (IQR)	23.0 (15.0–36.8)	18.5 (11.3–38.8)	0.052 ^c	21.0 (15.0–33.0)	20.5 (14.0–30.3)	0.304 ^c
Survival						
Whilst on vv-ECMO, n (%)	124 (82.7)	43 (93.8)	0.129 ^c	92 (82.9)	67 (85.9)	0.577 ^d
Whilst on ICU, n (%)	119 (79.3)	39 (81.3)	0.773 ^c	88 (79.3)	62 (79.5)	0.972 ^d
At six-months, n (%)	116 (77.3)	38 (79.2)	0.790 ^c	86 (77.5)	61 (78.2)	0.906 ^d

^a Five patients, who were overfed energy (>110% of target), were excluded from analysis due to low numbers

^b Eleven patients, who were overfed protein (>110% of target), were excluded from analysis due to low numbers

^c Mann-Whitney test

^d Chi-squared test

APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive Care Unit, IQR: interquartile range; SOFA: Sepsis-related Organ Failure Assessment; vv-ECMO: veno-venous extra corporeal oxygenation

	Energy		p value	Protein		p value
	Adequate	Underfeeding		Adequate	Underfeeding	
	(80–110% of target)	(<80% of target)		(80–110 % of target)	(< 80 % of target)	
Feeding started from ICU admission (hr), median (IQR)	13.5 (8.9–23.5)	15.5 (10.1–23.1)	0.506 ^a	13.5 (8.5–24.0)	15.3 (10.5–23.5)	0.393 ^a
Time taken to reach adequate energy and protein intake over a 24-hr period (hr), median (IQR)	69.5 (43.6–105.0) ^e	70.5 (41.3–116.5) ^f	0.492 ^a	59.8 (38.1–97.4) ^g	81.5 (50.6–113.0) ^h	0.022 ^a

^a Mann-Whitney test

^e Nine patients never reached the target. Number of patients 141.

^f Three patients were never underfed. Number of patients 45.

^g Seven patients never reached the target. Number of patients 104.

^h Four patients never underfed. Number of patients 74.

APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive Care Unit, IQR: interquartile range; SOFA: Sepsis-related Organ Failure Assessment; vv-ECMO: veno-venous extra corporeal oxygenation

266 *Interruptions to feeding*

267 Feeding interruptions occurred in 184 (90.6%) patients at least once and 95 (46.8%)

268 patients had more than two interruptions. The median number of interruptions during vv-

269 ECMO was two (IQR, 1–4) and the median duration was 9 (IQR, 3.0–32.0) hours. The

270 main reason for interruptions to feeding are shown in Table 4.

271

272 **Table 4.** The frequency of the main reason for interrupting a feed during vv-ECMO.

Main reason for feed interruption	Number of patients (%) (total 184 patients)
Procedures (bedside and operating room)	72 (39.1)
GI intolerances	42 (22.8)
Vomit	19 (10.3)
Concerns over abdominal distention and constipation	12 (6.5)
High gastric residual volume	10 (5.4)
High stool output	1 (0.5)
No access or mechanical complications related to feeding ^a	28 (15.2)
Not documented	16 (8.7)
Investigations	15 (8.2)
GI bleed or blood in aspirate	5 (2.7)
In anticipation of feeding tube extubation	4 (2.2)
Other ^b	2 (1.1)

^a Mechanical complications such as unable to site feeding tube, feeding tube extubation, tube blockage

^b Other included hyperglycaemia and propofol syndrome

273

274 Prokinetic agents were used in 106 patients (52.2%). The most commonly used

275 agent was metoclopramide which was used in 104 patients (51.2%). Erythromycin was

276 used in 16 (7.9%) and domperidone was used in one patient (0.4%).

277

278 *Nutrient adequacy during vv-ECMO vs post vv-ECMO*

279 Overall, 166 patients remained in our ICU post-ECMO. The median energy target for these
280 patients during vv-ECMO was 1800 kcal/d (IQR, 1619–2024kcal/d) and after vv-ECMO
281 decannulation was 1888 kcal/d (IQR, 1650–2100 kcal/d) ($p<0.001$). The median protein
282 target during vv-ECMO was 88.8 g/day (IQR, 75.0–100.0 g/d), and post-vv-ECMO 88.1
283 g/day (IQR, 75.0–100.0 g/d) ($p=0.253$).

284 There was a small but statistically significant difference in the proportion of energy
285 and protein delivery between the vv-ECMO and post vv-ECMO periods, with median
286 energy delivery during vv-ECMO being 89.8% (IQR, 80.5–96.0%) and post vv-ECMO
287 being 93.4% (IQR, 80.7–101.0%)($p=0.05$), and for protein the values were 84.7% (IQR,
288 74.0–96.7%) and 91.2% (IQR, 74.0–100.6%) ($p=0.014$), respectively.

289

290 **Discussion**

291 To our knowledge, this is the largest study investigating the provision of nutrition support in
292 adults receiving vv-ECMO. Our results show that delivery of adequate energy and protein
293 is possible, but underfeeding remains common. Further, we found that a higher APACHE II
294 score on admission to our ICU was associated with lower protein delivery and a higher
295 degree of organ failure on the first day of vv-ECMO with lower energy delivery.

296 Previous observational studies have reported difficulty achieving nutritional targets
297 in patients receiving ECMO due to frequent feeding interruptions (20, 25). In our cohort,
298 we also report feeding interruptions to be frequent with over 90% of patients having their
299 feed interrupted at least once and almost half having at least two interruptions, for a
300 median duration of 9 hours. Similar to Ridley *et al.* (25) we found fasting for procedures
301 and GI intolerances to be the main reasons for these interruptions. Despite this, we found
302 the median delivery of energy to be 89.8% (IQR, 80.5–96.0%) and protein 84.7% (IQR,
303 74.0–96.7%) which, according to our *a priori* definition, is considered adequate at the

304 population level. However, the finding that patients were underfed energy or protein on
305 one in three days during their vv-ECMO highlights that energy and protein debt can still
306 occur, especially following prolonged and repeated feeding interruptions.

307 It is possible that our higher nutritional intakes compared with others are due to our
308 higher usage of post-pyloric feeding tubes which we have previously reported to be
309 successfully placed at the bedside using an electromagnetic device (33). Results may also
310 have been influenced by changes to our feeding protocol during the period of this study;
311 the protocol was updated to include a high protein enteral formula along with additional
312 dietetic staffing on the ICU allowing 'catch-up' feeding to be prescribed on an individual
313 basis as required.

314 There was an association between relative underfeeding and reduced length of stay
315 on ECMO. Our results are consistent with an Australian ECMO cohort (24) where
316 increased delivery of energy and protein was associated with longer vv-ECMO support. In
317 addition, we also found the same was true for increased delivery of energy, but not protein
318 and ICU length of stay. The reasons for this are unclear, but one contributing factor may
319 be that the patients who receive vv-ECMO for longer spend a smaller proportion of time
320 achieving a target feeding rate than those who receive vv-ECMO for a shorter time (we did
321 not adjust for duration of vv-ECMO when calculating delivery). Patients may also become
322 more medically stable and require fewer procedures and investigations the longer they
323 receive on vv-ECMO, thus allowing higher nutritional intake.

324 There was an association between increased severity of illness and adequacy of
325 nutrition, with statistically significantly higher SOFA and APACHE II scores, in the underfed
326 group. Although clearly retrospective observational data is not a demonstration of
327 causality, it is clinically plausible that increased severity of illness results in increased
328 gastric stasis and increased requirement for procedures to be performed.

329 We found an association between higher APACHE II and SOFA scores and
330 inadequate delivery of protein and energy, respectively. The nutrition risk of these patients
331 should not be discounted. A first glance at the variables contributing to a score such as
332 NUTRIC (age, APACHE II and SOFA) (39, 40) may lead the clinician to classify patients in
333 our cohort as low risk. However, given that the patients in the current study have a
334 prolonged stay both on ECMO and in the ICU, not counting the days in ICU prior to
335 retrieval for ECMO from referring centres, we feel these patients should be classified as
336 high nutrition risk and steps taken to enhance the delivery of nutrition support from ECMO
337 commencement. In addition, nutrition risk only determines mortality, with the effect on
338 muscle wasting and functional outcomes in ICU, on the whole, is currently unknown.

339 We did not find an association between the adequacy of energy and protein
340 delivery, and either ICU or six-month mortality. This is in contrast to others where an
341 association between improved energy and protein delivery ($\geq 80\%$ of targets) and lower
342 ICU mortality was found for patients on veno-arterial ECMO (27). This may reflect either
343 differences in the severity of illness or the underlying illness (cardiogenic shock compared
344 with acute respiratory distress syndrome) between patients receiving veno-arterial and vv-
345 ECMO.

346 As previously reported in observational studies of ECMO patients, we found GI
347 intolerances to be a common contributor to feeding interruptions. This was mainly
348 incidence of vomiting and concerns regarding abdominal distention and GI dysmotility
349 which may be a reflection of poor gut perfusion which has been mentioned by others (24).

350 We found a small, but statistically significant improvement in the delivery of energy
351 and protein in the patients who remained on our ICU post-ECMO, when compared with
352 their stay on ECMO which has been previously reported by others (20). These results may
353 reflect gradual recovery from critical illness and therefore improved GI function and less
354 requirement for procedures, rather than a result of no longer being on vv-ECMO *per se*.

355

356 *Limitations*

357 The current study has the limitations of being a single-centre, retrospective study. In
358 addition, because nutritional targets for the first day were re-calculated as a proportion of a
359 24-hour period based on the time of admission, the first day on vv-ECMO was not always
360 representing one whole day. Therefore, the adequacy of feeding expressed as a number
361 of days, may have been overestimated in some cases. Similarly, requirements for both
362 energy and protein are estimated using calculations and usually based on an estimated or
363 previous weight which may influence the results. It is possible that by using a weight-
364 based equation, we have significantly over or underestimated energy targets. Two
365 methods to measure energy expenditure using indirect calorimetry in this population have
366 been described (34, 35), and feeding to measured, rather than calculated, requirements
367 may be one approach to limiting underfeeding or overfeeding in the future. In addition, the
368 protein targets calculated for patients in this study are lower than those recently
369 recommended in the American Society for Parenteral and Enteral Nutrition guidelines.
370 Although the evidence for this recommendation is weak (17), it is entirely plausible that
371 providing higher protein targets for these patients may have resulted in higher protein
372 delivery and improved outcome. Lastly, we have defined adequate energy and protein
373 targets based on currently available evidence for the general critically ill population, but the
374 overall optimal feeding strategy for critically ill patients remains under debate.

375

376 *Conclusion*

377 Adequate energy and protein intake is possible in patients receiving vv-ECMO support but
378 underfeeding is still common especially in those patients who are more severely ill or have
379 more severe organ dysfunction. As on the ICU in general, not all patients requiring vv-
380 ECMO are the same, underscoring the need for focused research in this area. Studies

381 investigating the impact of underfeeding on outcomes such as complications and mortality
382 during vv-ECMO could help us to understand the nutritional needs of this patient group.

383

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387

388 **Statement of authorship**

389 LK contributed to the design of the research, collection and analysis of the data and
390 drafted the manuscript. DEB contributed to conception/design of the study, collection and
391 interpretation of data and also critically revised the manuscript. KW contributed to the
392 design of the study, supervision of the data collection, analysis and data interpretation,
393 and also critically revised the manuscript. ES, CEH, BS, DO and KD contributed to data
394 collection, interpretation of the data and revision of the manuscript. NAB contributed to the
395 design of the study, interpretation of the results and revision of the manuscript.

396

397 **Conflict of Interest**

398 DB has received speaker fees from Nutricia, Baxter, BBraun and Fresenius Kabi,
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408

409

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