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LETTER

Severity of endothelial dysfunction is associated with the occurrence of hemorrhagic complications in COPD patients treated by extracorporeal CO_2 removal

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Dear Editor,

In chronic obstructive pulmonary disease (COPD) patients extracorporeal CO_2 removal ($ECCO_2R$) has been associated with both hemorrhagic and thrombotic complications [1], which could be related to an endothelial dysfunction promoted in part by extracorporeal life support [2]. Moreover, endothelial dysfunction is a hallmark of severe COPD: an imbalance between repair capacity and endothelial damage has been reported in stable patients [3], with a changing profile during acute exacerbations [4]. We planned to rigorously study these points using a formalized $ECCO_2R$ register (NCT02965079) combined with a study project (Hector: Hemostasis and $ECCO_2R$).

We counted circulating endothelial cells (CEC) by CD146-coated beads and $CD34^+CD45^{dim}$ circulating hematopoietic progenitor cells (HPC) by flow cytometry according to the ISHAGE (International Society of Hematotherapy and Graft Engineering) protocol (see also ESM). We also quantified in plasma VEGF-A, a mobilizing factor of endothelial progenitor cells, and its main soluble receptor sVEGFR-2. Sixteen severe COPD patients were admitted and studied prior to $ECCO_2R$ initiation (Hemolung device, ALung, Pittsburgh, USA, and iLA Activve device, Xenios/Novalung, Heilbronn, Germany), then daily during the $ECCO_2R$ course and after $ECCO_2R$. We recorded severe hemorrhagic events (types 3–5 of the Bleeding Academic Research Consortium standardized classification) and thrombotic events [5]. Cell counts were compared to control values obtained from healthy subjects. Quantitative variables were summarized using mean with standard deviation. Quantitative variables determined to follow non-normal distributions are summarized using median presented with IQR and evaluated for associations using a nonparametric equality-of-medians test.

Demographics and cellular counts are presented in Table 1. We observed a high level of both CEC and $CD34^+CD45^{dim}$ prior to $ECCO_2R$ initiation as compared to controls, confirming previous results [4]. Daily CEC count during $ECCO_2R$ was not different in the whole group from CEC count prior to $ECCO_2R$ initiation. Daily $CD34^+CD45^{dim}$ count in the whole group was higher than $CD34^+CD45^{dim}$ count prior to $ECCO_2R$ initiation ($p=0.031$). A severe hemorrhagic event was observed in five patients. As compared to the mean daily count during the full $ECCO_2R$ therapy in the other patients, these patients exhibited higher mean CEC count, lower mean $CD34^+CD45^{dim}$ count and higher mean sVEGFR-2 plasma values during the period preceding the hemorrhagic complication (Table 1), along with longer $ECCO_2R$ duration and higher extracorporeal blood flows (Table ESM). We also present (ESM) daily counts according to the occurrence or not of hemorrhagic complications and to the $ECCO_2R$ devices. Thrombotic complications were

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Table 1 Main demographics and hematopoietic progenitor cell and circulating endothelial cell (CEC) counts in control subjects and in AE-COPD patients studied prior to and during $ECCO_2R$

	AE-COPD prior to $ECCO_2R$	Healthy volunteers	*p* value
n	16	81	NA
Age (years)	64 (14)	38 (8)	< 0.001
Male/female	7/9	37/44	0.99
SAPS2 at ICU admission	37 (11)	–	–
ICU length of stay	23 (14)	–	–
ICU survival	12 (75%)	–	–
CEC count (cells per mL)	51.4 (113.1)	10.1 (14.6)	< 0.001
$CD34^+CD45^{dim}$ count (absolute count)	6043.4 (8300.8)	2261.2 (1314.5)	0.016
VEGF-A (pg/mL)	23.94 (17.56)	–	–
sVEGFR-2 (pg/mL)	10,028.12 (4906.54)	–	–

	Severe hemorrhagic event during $ECCO_2R$	No severe hemorrhagic event during $ECCO_2R$	*p* value
n	5	11	NA
Mean daily CEC count (cells per mL)	45.9 (40.8)[a]	25.7 (36.6)[b]	0.009
Mean daily $CD34^+CD45^{dim}$ count (absolute count)	2110.7 (2274.4)[a]	5370.7 (5645.9)[b]	0.008
Mean daily VEGF-A (pg/mL)	12.62 (5.03)[a]	18.72 (19.02)[b]	0.372
Mean daily sVEGFR-2 (pg/mL)	13,247.58 (4329.53)[a]	9164.06 (3627.71)[b]	0.005

Results are expressed as mean (SD) or absolute number (%)

The upper part of the table indicates demographics and cell counts in AE-COPD patients before $ECCO_2R$ initiation and in controls. The lower part indicates mean daily cell counts during the period preceding the hemorrhagic complication in five AE-COPD patients suffering from severe hemorrhagic complication during $ECCO_2R$, as compared to mean daily cell counts during the full $ECCO_2R$ course in the remaining 11 AE-COPD patients

[a] Mean daily count and values from the first day after starting $ECCO_2R$ to the day immediately preceding the hemorrhagic complication

[b] Mean daily course during the full $ECCO_2R$ therapy

observed in four patients, without any association with endothelial dysfunction.

Our results confirm that CEC and $CD34^+CD45^{dim}$ counts are elevated in very severe COPD patients and suggest that an endothelial dysfunction, characterized by endothelial damage and insufficient mobilization of HPC, could be a marker of impending bleeding during $ECCO_2R$. We present (ESM) the sample size calculation for a validation study. Since we observed statistical links with extracorporeal blood flows and $ECCO_2R$ duration, it will be important to further study the effects of different devices on endothelial dysfunction. Comparing COPD and ARDS patients could help to identify the influences of the devices and the diseases on the endothelial dysfunction.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-020-06138-8) contains supplementary material, which is available to authorized users.

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Availability of data and material

Data are available from corresponding author on reasonable request.

Compliance with ethical standards

Conflicts of interest
Dr. Diehl reports grants and non-financial research support from ALung, non-financial research support from General Electric Healthcare and personal fees and non-financial research support from Xenios/Novalung (Fresenius Medical Care), all outside the submitted work. Other reported no conflicts of interests.

Ethics approval
Treatment with $ECCO_2R$ was performed as part of a specific registry (Registry on the EXperience of Extracorporeal CO_2 Removal in Intensive Care Units, NCT02965079), benefiting from an approval (07 March 2016) from the Ethics Committee of the French Intensive Care Society.

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References
1. Sklar MC, Beloncle F, Katsios CM, Brochard L, Friedrich JO (2015) Extracorporeal carbon dioxide removal in patients with chronic obstructive pulmonary disease: a systematic review. Intensive Care Med 41:1752–1762
2. Al-Fares A, Pettenuzzo T, Del Sorbo L (2019) Extracorporeal life support and systemic inflammation. Intensive Care Med Exp 7(S1):46
3. Tura-Ceide O, Pizarro S, García-Lucio J, Ramírez J, Molins L, Blanco I, Torralba Y, Sitges M, Bonjoch C, Peinado VI, Barbera JA (2019) Progenitor cell mobilisation and recruitment in pulmonary arteries in chronic obstructive pulmonary disease. Respir Res 20:74
4. Sala E, Villena C, Balaguer C, Ríos A, Fernández-Palomeque C, Cosío BG, Garcia J, Noquera A, Agusti A (2010) Abnormal levels of circulating endothelial progenitor cells during exacerbations of COPD. Lung 188:331–338
5. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J et al (2011) Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 123:2736–2747