Veno-venous extracorporeal membrane oxygenation (V-V ECMO) in COVID-19 patients: is there room for bivalirudin anticoagulation?

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Introduction

In patients affected by severe ARDS due to COVID-19 infection V-V ECMO may be indicated[1], but a careful selection of patients is needed as patient age and comorbidities appear to influence outcomes[2]. Critically ill patients infected by SARS-CoV-2 often present an acute hyperinflammatory state or even true cytokine storm[3]. The inflammatory activation leads to a hypercoagulable state bearing an increased mortality rate[4]. Nevertheless, there is no clear evidence on the pathophysiology of these haemostatic changes, but different hypotheses have been proposed, such as hypercoagulability status[3,5], antiphospholipid antibody production[6], and possible heparin resistance[7]. V-V ECMO support requires adequate systemic anticoagulation which is often performed with unfractionated heparin (UFH), but this anticoagulation strategy in patients with COVID 19 might present some drawbacks. For example: low AT III levels – which could reduce UFH efficacy - have been reported[5], an over-expression of acute phase proteins may bind UFH reducing its effect and leading to UFH resistance [8], or hyperexpression of FVIII could influence *in vitro* coagulation tests resulting in normal PTT values thus masking the true heparin effect and leading a to risk of UFH overdose[7].

Materials and methods

During the COVID-19 pandemic (March 1st 2020 - April 30th 2021) 363 patients were admitted to ICU in our center; out of them 11 (3 %) required V-V ECMO support. Clinical data of these patients are reported in Table 1. In Case 6, V-V ECMO support was required two separate times, but these data were summarized. Three patients (27%) underwent a femoral-jugular (F-J) configuration. Two patients transitioned from a femoral-femoral (F-F) to F-J approach, due to high recirculation in one case and to cannula damage in the other. The F-F configuration was performed in all other cases. Initially, we decided for traditional anticoagulation management in three cases, using UFH infusion with daily control of PTT ratio (target 1.5-2.0 sec). High doses of UFH (>35.000 UI/die) were required, without adequate anticoagulation (PTT ratio under target). As a consequence, in these and following cases, we changed our anticoagulation protocol introducing a direct thrombin inhibitor (bivalirudin). Our protocol included continuous infusion (starting 0.02 mg/kg/h) without initial bolus, dose titration was based on PTT ratio (target 1.5-2.0 sec) with potential dosage variation of 0.02 mg/kg/h each time. We managed bivalirudin dosage reduction due to glomerular filtration rate (GFR) and continuous renal replacement therapy (CRRT) requirement. The risk of bleeding was constantly monitored,

with clinical evaluation and checking haemoglobin value variation. Clots, fibrin stands and machine pressure values were monitored routinely with every shift change and PTT laboratory draw. We collected demographic data (age, sex, weight), ECMO type, indication, and setting, UFH dose (expressed as UI/h), bivalirudine dose (expressed as mg/kg/h), GFR, haemoglobin level, fibrinogen, platelet count, aPTT, PT, dimers and AT III level. Data were collected in an Excel database.

Results

In all 11 patients requiring V-V ECMO support anticoagulation was efficiently performed using bivalirudin. In no cases a significant clotting of oxygenator or tubing, and consequent machine change, was required. The adjustment of bivalirudin dosage was required in patients with renal impairment and continuous renal replacement performed with regional citrate anticoagulation. Two cases were complicated with severe bleeding needing massive transfusion and angiographic treatment. No intracranial bleeding was detected.

Discussion

Our decision to use bivalirudin is based on the hypothesis that it may be an alternative to UFH as it is not subject to the disadvantages of UFH such as acute phase protein binding or FV III overexpression. Moreover, bivalirudin applicability during both V-V ECMO and V-A ECMO has been previously described[9,10], so we theorised its use would be feasible in patients with COVID-19. Conversely, during bivalirudin anticoagulation a strict monitoring of PTT is required especially in patients with acute kidney injury to minimize the risk of accumulation. Our brief experience has different limitations. For example, FVIII and FXa measurements were never performed respectively to confirm heparin resistance and to monitor antithrombotic activity, and there are not sufficient cases of anticoagulation performed with UFH compared to bivalirudin. Overall, in this limited case series, a satisfying clinical result with adequate anticoagulation was achieved.

BIBLIOGRAPHY:

1. MacLaren G, Fisher D, Brodie D. Preparing for the Most Critically Ill Patients With COVID-19: The Potential Role of Extracorporeal Membrane Oxygenation. *JAMA*. 2020;323(13):1245. doi:10.1001/jama.2020.2342;

2. Ramanathan K, Antognini D, Combes A, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med*. March 2020:S2213260020301211. doi:10.1016/S2213-2600(20)30121-1;

3. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome [published online ahead of print, 2020 Apr 17]. *J Thromb Haemost*. 2020;10.1111/jth.14854. doi:10.1111/jth.14854

4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847. doi:10.1111/jth.14768;

5. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in Intensive Care Unit. A Report of Thromboelastography Findings and other Parameters of Hemostasis [published online ahead of print, 2020 Apr 17]. *J Thromb Haemost*. 2020;10.1111/jth.14850. doi:10.1111/jth.14850;

6. Bowles L, Platton S, Yartey N, et al. Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19 [published online ahead of print, 2020 May 5]. *N Engl J Med*. 2020;10.1056/NEJMc2013656. doi:10.1056/NEJMc2013656

7. Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2 [published online ahead of print, 2020 Apr 20]. *Int J Lab Hematol*. 2020;10.1111/ijlh.13230. doi:10.1111/ijlh.13230

8. Young E, Podor TJ, Venner T, Hirsh J. Induction of the acute-phase reaction increases heparin-binding proteins in plasma. *Arterioscler Thromb Vasc Biol*. 1997;17(8):1568-1574. doi:10.1161/01.atv.17.8.1568

9. Netley J, Roy J, Greenlee J, Hart S, Todt M, Statz B. Bivalirudin Anticoagulation Dosing Protocol for Extracorporeal Membrane Oxygenation: A Retrospective Review. *J Extra Corpor Technol*.:6.

10. Seelhammer TG, Bohman JK, Schulte PJ, Hanson AC, Aganga DO. Comparison of Bivalirudin Versus Heparin for Maintenance Systemic Anticoagulation During Adult and Pediatric Extracorporeal Membrane Oxygenation. Crit Care Med. 2021 Apr 19.

	Range	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
Sex		Male	Male	Male	Female	Male	Male	Male	Male	Male	Male	Male
Age		59	27	47	59	54	44	58	57	47	62	53
Weight (kg)		94	90	80	75	100	100	110	65	70	90	85
ECMO duration		7	15	23	19	15	25	63	10	12	30	26
Setting		F-J	F-F	F-F	F-J	F-J	F-F	F-F/F-J	F-F/F-J	F-F	F-F	F-J
Size cannula (Fr)		24-18	26-23	24-22	22-18	24-18	24-23	28-22	24-21	24-21	23-24	18-28
BF (l/m)		4	3.5	3.5	3.5	4.5	3.2	3.96	4.27	4.12	3,62	3.9
aPTT (ratio) with Bivalirudin	1.00 (0.86-1.20)		1.47 (0.7-1.8)	1.89 (1-2.4)	1.82 (1.54-2.32)	1.86 (1.4-2.7)	1.84 (1.66-2)	2.27 (1.3-3.85)	1.93 (1.56-2.28)	2.43 (2.01-3.14)	2 (1.64-2.39)	1.92 (1.34-2.99)
aPTT (ratio) with UFH		1.25 (1.1-1.38)	0.89 (0.88-0.9)	0.99 (0.9-1.03)								
D-dimer (µg/mL)	<0.5	28.3 (9.6- >35)	26 (3.8->35)	4.7 (1.7-14.3)	11.4 (3.9-24.7)	27 (4->35)	22.6 (4.2-32.5)	14.11 (3.82-23.86)	6.2 (1.8-10.66)	3.09 (1.35-4.78)	23.20 (5.76-35)	4.84 (2.3-12.16)
Fibrinogen (mg/dL)	258 (165.0-350)	683.7 (445-832)	391 (350-480)	374 (142-396)	400.6 (231-567)	692 (532-889)	405 (226-613)	522.78 (231-866)	404.81 (316-506)	442.91 (368-493)	287.5 (76-582)	450 (333-652)
PLT (×10⁹/L)	265 (130-400)	195 (170-270)	197 (136-294)	241 (56-279)	83.7 (23-151)	129.5 (84-181)	144.7 (112-167)	102.3 (67-202)	166.9 (111-355)	140.53 (44-195)	144.27 (84-247)	122.2 (44-237)
AT III (%)	102 (82-122)	98.8 (93-108)	105 (87-127)	101 (85-146)	112 (77-134)	89 (74-116)	98.8 (72-133)	88 (88-88)	63 (57-67)	57 (55-59)	74.07 (53-94)	79.6 (64-90)
Bivalirudin (mg/kg/h)			0.17 (0.05-02)	0.1 (0.03-0.13)	0.07 (0.03-0.18)	0.03 (0.01-0.1)	0.1 (0.05-0.1)	0.059 (0.009-0.22)	0.05 (0.03-0.07)	0.13 (0.02-0.2)	0.06 (0.03-0.11)	0.06 (0.01-0.11)
UFH (UI/h)		957 (200-1600)	750 (300-1200)	1100 (800-1400)								
CRRT		No	No	No	No	Yes	No	Yes	No	No	Yes	Yes
GFR (mL/min/1.73m^2)		30	95	130	102	25	60	20	48	94	30	31
Severe bleeding		no	no	no	no	no	no	no	yes	no	no	yes
Machine change		No	No	No	No	Yes	No	Yes	Yes	No	Yes	Yes
ECMO outcome		weaned	dead	weaned	weaned	dead	weaned	dead	dead	weaned	weaned	dead
ICU outcome		dead		dead	discharged		discharged	dead	dead	discharged	discharged	dead

Table 1: Hemostasis parameters and drugs doses for the investigated case series. Data are presented as mean (max and min) referring to V-V ECMO days