



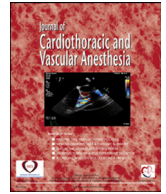
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Original Article

Eleven Years of Venovenous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: From H1N1 to SARS-CoV-2. Experience and Perspectives of a National Referral Center

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Objective: Despite growing expertise and wide application of venovenous extracorporeal membrane oxygenation (VV ECMO) treatment for acute respiratory distress syndrome (ARDS) of different origin and during pandemics (H1N1 Influenza A virus and SARS-CoV-2), large reports are few and pertain mostly to multicenter registries, and randomized trials are difficult to perform. The aim of this study was to report outcomes, trends, and innovations of VV ECMO treatment over the last 11 years.

Design, Setting, and Participants: Observational study on 142 patients treated at the IRCCS San Raffaele Hospital in Milan from June 2009 (year of the H1N1 pandemic) to May 2020 (SARS-CoV-2 pandemic).

Interventions: None.

Measurements and Main Results: The main causes of ARDS were H1N1 pneumonia in 36% of patients, bacterial pneumonia in 17%, and SARS-CoV-2 in 9%. Seventy-two percent of patients were centralized from remote hospitals, of whom 33% had implanted VV ECMO before transport. The most common cannulation strategy was the dual-lumen catheter cannulation system (55%), and anticoagulation was performed with bivalirudin in most patients (79%). Refractory hypoxia was treated with intravenous beta-blockers (64%), nitric oxide (20%), and pronation (8%). Almost one-third of patients (32%) were extubated while on ECMO. Forty-nine percent of patients were discharged from the intensive care unit, and hospital discharge was 46%; survival was lower in patients requiring VV ECMO for more than three weeks compared with shorter support duration (23% v 56%, $p = 0.007$). Anticoagulation with bivalirudin was associated with higher survival, compared with heparin (55% v 31%, $p = 0.03$), and lower thrombocytopenia incidence (69% v 35%, $p = 0.003$).

Conclusion: VV ECMO is the pivotal rescue treatment for refractory ARDS—timely treatment and optimal care are needed to optimize therapy, as duration of support is associated with outcome. Anticoagulation with bivalirudin may improve outcome.

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Keywords: acute respiratory distress syndrome; venovenous extracorporeal membrane oxygenation (VV ECMO); H1N1 Influenza A; SARS-CoV-2; mortality

ACUTE RESPIRATORY distress syndrome (ARDS) is a severe clinical manifestation of heterogeneous origin that still is burdened with high mortality (up to 65%, with great

variability among statistics).^{1,2} Over the last two decades the therapy of this syndrome has evolved significantly; in particular, with the temporary replacement of lung function by venovenous extracorporeal membrane oxygenation (VV ECMO) in patients refractory to conventional ventilation technique.^{1,3}

Despite high initial mortality rate,^{3,4} interest in VV ECMO has increased continuously after technical and clinical

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progress, and it represented a fundamental rescue therapy even during the H1N1 influenza A pandemic^{5,6} and SARS-CoV-2 pandemic. The use of such an invasive and demanding therapy in critically ill patients requires high expertise level, 24/7 availability, and optimal clinical management.⁷ To date, VV ECMO effects on survival remain controversial compared with conventional mechanical ventilation, and no definitive survival benefits have been demonstrated in randomized trials. Randomized trials are nevertheless difficult to implement due to complicated ethical and logistical issues.^{8,9} A recent systematic review of the literature analyzed data from 33 studies with more than 100 VV ECMO patients (32 observational studies and one randomized controlled trial) despite the great amount of data (12,860 patients); however, most information came from international registries that did not collect contemporary data.² Furthermore, the number of patients treated in each center was limited, and data reported in different studies were few and not consistent, making comparison of patients populations and management very difficult.

The aim of this study was to report outcomes, trends, and innovations in the management of VV ECMO treatment in a large population of patients treated over the last 11 years in a national referral center.

Materials and Methods

All adult patients treated with VV ECMO due to refractory ARDS at IRCCS San Raffaele Scientific Institute in Milan from June 2009 to May 2020 were included in the study.

Criteria for VV ECMO treatment eligibility and exclusion criteria have been reported previously and were consistent over the years.¹⁰ In case of refractory hypoxia in ARDS patients, physicians in remote hospitals were put in contact with the ECMO center via a national phone number, where an ECMO specialist was available for case discussion in order to optimize therapy and decide whether to centralize the patient to the referral center.¹¹ VV ECMO was implanted by the ECMO team either before or after transport to the referral center. The decision to implant VV ECMO before transport was undertaken by the ECMO team in the case of patients deemed at immediate risk of death and too ill and hypoxic to be transferred without extracorporeal support.¹¹ The authors performed percutaneous cannulation with the Seldinger technique; since 2012, the authors' first-line preferred approach was with bilumen cannulae, as an alternative to femorojugular or femorofemoral approach.¹¹ The causes of ARDS were classified as follows: H1N1 Influenza A virus, bacterial pneumonia, viral pathogens other than Influenza A (including Influenza B and SARS-CoV-2 virus), and other causes (including medical causes of ARDS such as pancreatitis, postsurgical ARDS as in cases of abdominal surgery, polytrauma, sepsis of undetermined origin, autoimmune disease, etc). All patients were administered intravenous (IV) anticoagulation to achieve target activated partial thromboplastin time of 55-to-60 seconds; primary anticoagulation was performed with heparin until 2011 and with the direct thrombin inhibitor bivalirudin from 2011 to the present.¹²⁻¹⁴ Sequential Organ Failure

Assessment (SOFA) Score, Simplified Acute Acute Physiology Score (SAPS), Acute Physiology And Chronic Health Evaluation (APACHE) II and III scores, and the VV ECMO-specific ECMOnet score¹⁵ were calculated. Hemorrhagic complications were recorded according to the ELSO definitions. Major bleeding was defined as clinical bleeding with a decrease in hemoglobin of at least 2 g/dL/24 h; a transfusion requirement of one or more 10 mL/kg red blood cells transfusions over 24 hours; and retroperitoneal bleeding, pulmonary, or bleeding that involved the central nervous system or required surgical intervention.¹⁶ Right ventricular failure secondary to ARDS was treated with IV inotropes, nitric oxide, and, if needed, intraaortic balloon pump (IABP).¹⁷

Refractory hypoxia in spite of VV ECMO (60-80 mL/kg/min) has been managed with nitric oxide and pronation and, since 2011, with intravenous short-acting beta-blockers administration.^{18,19} In addition, a continuous infusion of esmolol was administered in case of persisting severe hypoxemia (peripheral O₂ saturation <91% or PaO₂/fraction of inspired oxygen (F_IO₂) <100 mmHg despite ECMO treatment) and concomitant high cardiac output (>7 L/min) as measured by pulmonary artery catheter, and titrated to an SpO₂ >92%.¹⁸

Data were collected from patients' medical records and anonymously stored in an Excel Database at the IRCCS San Raffaele Hospital. The study was in compliance with the Declaration of Helsinki and data were collected with the approval of the authors' local ethical committee.

Categorical variables are reported as numbers (percentage), whereas continuous variables are expressed as mean \pm standard deviation (SD) or as median (interquartile range) according to the Kolmogorov-Smirnov test.

Results

Study Population

One hundred forty-two patients were treated in the study period (June 2009-May 2020). Baseline data are shown in [Table 1](#): 93 were men (65%), mean age was 54 \pm 14 years, and body mass index 28 \pm 7.

The main causes of ARDS were H1N1 pneumonia in 36% of patients, bacterial pneumonia in 16%, and SARS-CoV-2 infection in 9% of patients. The main comorbidities were obesity (23%) and immunosuppression (9.2%) ([Table 1](#)). Baseline PaO₂/F_IO₂ was 64 (52-77). Patients had high mortality risk according to risk scores: SOFA was 12 \pm 5, SAPS II was 66 \pm 25; APACHE II was 28 (22-35), APACHE III was 103 \pm 54, and the ECMOnet score 7 \pm 4. Variations of pre-ECMO respiratory parameters and cause of ARDS over the years under study are shown in Supplementary Figures 1 and 2, respectively.

Treatments

As shown in [Table 2](#), 93 of 129 patients (72%) were referred to the San Raffaele Hospital from another facility, and among these, 31 of 93 (33%) were implanted with VV ECMO before

Table 1
Patients' Characteristics

Characteristic	Values
Age, y	54 ± 14
Sex, male	93/142 (65%)
Height, cm	171 ± 10
Weight, kg	83 ± 20
BMI	28 ± 7
Cause of ARDS - n (%):	
Pneumonia	
H1N1, n	46/129 (36%)
Bacterial, n	22 /129 (17%)
SARS-CoV-2, n	12/129 (9%)
Other viral, n	5/129 (4%)
Other causes of ARDS, n	44 /129 (34%)
Obesity, n	30/129 (23%)
Pregnancy, n	2/129 (1.5%)
Immunodepression, n	13/129 (9.2%)
COPD/asthma, n	22/129 (17%)
Other comorbidities, n	84/129 (65%)
Pre-ECMO PaO ₂ /F ₁ O ₂	64 (52 -77)
Pre-ECMO PEEP, cmH ₂ O	12 ± 6
Pre-ECMO mechanical ventilation, d	2 (1-6)
SOFA	12 ± 5
SAPS II	66 ± 25
APACHE II	28 (35-22)
APACHE III	103 ± 54
ECMOnet	7 ± 4

NOTE. The data in the table are reported as mean ± standard deviation; median (interquartile range) and number (%) of patients. Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ECMOnet, ExtraCorporeal Membrane Oxygenation network score; H1N1, influenza A H1N1; PEEP, positive end- expiratory pressure; SAPS, Simplified Acute Acute Physiology Score; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SOFA, Sequential Organ Failure Assessment Score.

transport because they were considered at immediate risk of death if transferred without extracorporeal support. Notably, no cannulation-related issues were recorded. Median duration of VV ECMO treatment was nine (five-18) days, with a maximum of 75 days. The cannulation system was the dual-lumen jugular cannula in 71 of 129 patients (55%), the femorojugular

Table 2
ECMO-Related Parameters

Parameters	Values
Referred from other hospital, n	93/129 (72%)
VV ECMO implanted before transport, n	31/93 (33%)
VV ECMO - femorojugular, n	57/129 (44%)
VV ECMO - dual-lumen cannula, n	71/129 (55%)
VV ECMO - femorofemoral, n	1/129 (1%)
Duration VV ECMO, d	9 (5-18)

NOTE. The data in the table are reported as mean ± standard deviation; median (interquartile range) and number (%) of patients. Abbreviation: VV ECMO, venovenous extracorporeal membrane oxygenation.

Table 3
Administered Therapies

Parameters	Values
Anticoagulation	
Heparin, n	26/125 (21%)
Bivalirudin, n	99/125 (79%)
Management of right ventricular failure	
Inotropes, n	65/129 (50%)
IABP, n	25/129 (20%)
Other extracorporeal purification therapies	
CVVH, n	47/129 (36%)
Cytosorb, n	19/129 (15%)
Management of refractory hypoxia	
Beta-blockers, n	82/129 (64%)
NO, n	26/129 (20%)
Prone position, n	10/129 (8%)

NOTE. The data in the table are reported as mean ± standard deviation; median (interquartile range) and number (%) of patients. Abbreviations: IABP, intraaortic balloon pump; NO, nitric oxide; PLT, platelets; VV ECMO, venovenous extracorporeal membrane oxygenation.

in 57 of 129 (44%), and the femorofemoral in only one of 129 patients (1%).

Therapeutic management is shown in Table 3. Patients received intravenous anticoagulation with unfractionated heparin until 2011 (26/125, 21%), and bivalirudin thereafter (99/125, 79%). Half of the patients had need for support to the circulatory system with inotropes after ECMO implantation (65/129, 50%), and five of 129 patients (20%) also needed concomitant mechanical circulatory support with an intraaortic balloon pump. In 47 of 129 patients (36%), continuous venous hemofiltration was used, and the use of Cytosorb for blood purification was applied in 19 of 129 patients (15%).

Most patients (82/129, 64%) received IV beta-blocker continuous infusion due to refractory hypoxia despite VV ECMO support; therapy with nitric oxide was administered to 26 of 129 patients (20%) and ten of 129 patients were prone (8%). Moreover, 20 of 129 patients (15%) received platelet transfusions due to severe thrombocytopenia. Overall, 73 circuit exchanges were performed: 37 (51%) due to oxygenator signs of impaired performance or failure, and 36 (49%) due to activation of coagulation with the aim to prevent bleeding episodes.

Table 4
Ventilation and Mobilization

Parameters	Values
PSV or BIPAP, n	117/129 (91%)
Extubation, n	41/129 (32%)
Tracheostomy, n	45/129 (35%)
Mobilization, n:	
on the side, n	32/129 (25%)
in the armchair, n	19/129 (15%)

NOTE. The data in the table are reported as mean ± standard deviation; median (interquartile range) and number (%) of patients. Abbreviations: Bipap, biphasic positive airway pressure; ECMO, extracorporeal membrane oxygenation; PSV, pressure- support ventilation.

Table 5
Complications and Outcome

Parameters	Values
Major bleeding, n	28/129 (22%)
Peripheral ischemia, n	11/129 (8.5%)
Hemorrhagic stroke, n	6/129 (4.6%)
Ischemic stroke, n	2/129 (1.6%)
Sepsis, n	44/129 (34%)
MOF, n	39/129(30%)
Thrombocytopenia <50,000, n	53/129 (41%)
Thrombocytopenia <20,000, n	27/129 (21%)
DIC, n	9/129 (6.9%)
Other complications, n	21/129 (16%)
Weaned from ECMO, n	82/131 (63%)
Discharge from ICU, n	67/137 (49%)
Hospital discharge	63/137 (46%)
ICU, d	16 (32-9)
Hospitalization, d	23 (38-14)

NOTE. The data in the table are reported as mean \pm standard deviation; median (interquartile range) and number (%) of patients.

Abbreviations: DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MOF, multiorgan failure.

Ventilation and Mobilization

Thirty-two percent of patients (41/129) underwent extubation during VV ECMO support (“awake ECMO”), and 45 of 129 patients (35%) had a tracheostomy. Mobilization was an essential part of ECMO patients’ management strategies: 32 of 129 patients (25%) were mobilized on one side and 19 of 129 in the armchair (15%) (Table 4).

Complications and Mortality

Complications are reported in Table 5. Notably, no major complication related to cannulation procedure was recorded. Sepsis was recorded in 44 of 129 patients (34%), multiorgan failure in 39 of 129 patients (30%), and major bleeding was reported in 28 of 129 patients (22%)

Sixty-three percent of patients (82/129 patients) were weaned from ECMO, 49% (67/137 patients) were discharged from the intensive care unit (ICU), and 63 of 137 (46%) were discharged from the hospital. A trend toward increase in ICU survival rate over the years under study was observed, as shown in Supplementary Figure 3. Overall, patients were admitted to the ICU for 16 (nine-32) days while in the hospital, for an overall duration of 23 (14-38) days (Table 5). No baseline single parameter was found to be associated with outcome; patients who needed VV ECMO support for more than three weeks had a lower survival rate compared with patients who had VV ECMO treatment shorter than three weeks (23% v 56%, $p = 0.007$).

Subgroup Analysis

Patients who received anticoagulation with bivalirudin had a higher survival rate compared with patients treated with

heparin (ICU survival 55% v 31%, $p = 0.03$). In addition, incidence of thrombocytopenia with platelet count <50,000 per blood microliter during treatment was almost doubled in patients treated with heparin compared with bivalirudin (69% v 35%, $p = 0.003$) (Supplementary Table 1). A trend toward high ICU survival also was recorded in patients treated with beta-blockers compared with controls (53% v 41% $p = 0.2$), and in case of adoption of bilumen cannulation strategy compared with other strategies (53% v 43% $p = 0.3$), although these findings were not statistically significant. Outcome according to the cause of ARDS is reported in Supplementary Figure 4.

Discussion

VV ECMO represents a life-saving therapy in patients with ARDS refractory to conventional therapies and mechanical ventilation—patients who can be weaned from extracorporeal support in the first three weeks of treatment present a higher chance of survival. Over the years the authors have treated more severe patients (Supplementary Fig 1); despite this, survival rates progressively have increased (Supplementary Fig 3). The authors’ conclusions are strengthened by the consideration that they analyzed a large cohort of contemporary patients.

The recurrence of pandemic events over decades, together with technologic and clinical advances, have led to a rapid increase in the number of patients undergoing VV ECMO support, together with a consequent increase in centers capable of managing ECMO treatment, with particular reference to adult patients. In this regard, the authors’ study documented that they were able to deal with complex scenarios over years, such as pandemic outbreaks, and to manage even very critically ill patients with highpredicted mortality risk. The overall results of the study indicated that VV ECMO is applicable to patients in ARDS with different etiologies and that, despite the still numerous complications often associated with it, 63% of patients recovered from ARDS and were weaned from ECMO and, in 49% of cases, discharged from the ICU.

From the data collected, it can be seen that VV ECMO still is burdened by various complications; mainly sepsis, multiorgan failure, and hemorrhagic complications. However, as already highlighted in the past, it is complicated to determine whether the occurrence of such events can be reduced by improving ECMO or supportive therapy, or whether they are simply a consequence of the critical conditions of patients treated with ECMO.²⁰ Therefore, it should underscore the need for further dedicated studies to define its origin. Finally, it should be remembered that VV ECMO treatment still remains significantly invasive and applied in patients who, by definition, are severely compromised. In the light of these considerations, it seems logical that the next efforts toward reducing adverse events and complications will be particularly challenging. At the authors’ institution, for this reason, they implemented some strategies over the years with the aim to improve management and ultimately patients’ outcomes. Specifically, the authors focused on anticoagulation therapy (with

the use of direct thrombin inhibitors for systemic anticoagulation),¹²⁻¹⁴ on coupling hemodynamics and oxygenation (administering IV short half-life beta-blockers during VV ECMO),^{18,19} and on less-invasive cannulation strategies (after the availability of bilumen jugular cannulae).

During ECMO treatment, hemostasis modifications are complex and can cause both hemorrhagic and thrombotic events due to numerous alterations of the coagulative cascade. Contact of the blood with the nonendothelial artificial surfaces of the extracorporeal circuit causes hypercoagulability. This, in turn, can trigger a phenomenon of fibrinolysis with subsequent consumption of coagulation factors, platelet dysfunction, and a massive inflammatory response, leading to bleeding.^{21,22} As a matter of fact, anticoagulant therapy is fundamental to prevent these serious problems and the level of anticoagulation required for thrombosis prevention depends on many factors. As shown in Table 3, treatment with bivalirudin was applied as the first choice in the majority of patients in VV ECMO (79% of cases), and no longer as an alternative to heparin (used only in 21% of patients). Although no recommendation exists on the use of direct thrombin inhibitor as primary anticoagulation in patients on ECMO, the authors preferred this strategy in this extremely critically ill population and they gathered positive experiences with direct thrombin inhibitor for patients treated with extracorporeal circuits.¹²⁻¹⁴ Indeed, on one hand, direct thrombin inhibitor anticoagulant effect is more specific than heparin and easily can be monitored with activated partial thromboplastin time; while, on the other hand, low platelet count frequently is observed in critically ill patients,²³ and the risk of heparin-induced thrombocytopenia is higher in patients on extracorporeal support. Notably, transition from heparin to bivalirudin was accompanied by increase in survival rate (55% v 31%, $p = 0.03$) and reduced thrombocytopenia incidence in the bivalirudin group (69% v 35%, $p = 0.003$). Such results are in line with a recently published study on 295 VV ECMO patients, which documented higher one-year survival rate, fewer circuit thrombotic events, and decreased blood product administration in patients treated with bivalirudin compared to heparin.²⁴

Furthermore, it is the authors' practice also to administer intravenous short-acting beta-blockers during VV ECMO treatment. This innovative strategy was introduced for the first time by the authors in patients with refractory hypoxemia with high-flow ECMO and high-endogenous cardiac output, with the aim of improving peripheral oxygenation, and the preliminary experience was encouraging.^{18,19} Indeed, the ratio between VV ECMO-oxygenated blood and the patients' venous blood can be raised by decreasing the patients' cardiac output with short-acting beta-blockers (time to peak effect six-ten min, washout time nine min) reducing recirculation amount.

Even though this practice is not common among ECMO centers, the authors believe that it may be of great clinical benefit for two reasons: first, tachycardia correction is associated with improved survival, at least in non-ECMO patients,²⁵ and beta-blockers have shown beneficial effect on the septic heart²⁶; and second, endogenous cardiac output reduction produces an increase in arterial PaO₂ in VV ECMO patients.^{18,19}

Hypoxemia during ECMO may be ascribed mainly to the mixture between the blood fully oxygenated by ECMO with the patient's blood, the recirculation rate between the cannulae, and the inability of the native lung to provide further oxygenation, together with the shunt because of the bronchial circulation that may worsen arterial PaO₂. Therefore, the shunt between the blood fully oxygenated by ECMO and the patient's own venous blood can be modified in selected patients to provide clinical benefits.¹⁸ The authors are aware that other strategies exist and may be applied to improve oxygenation during VV ECMO treatment, including change in cannulation approach, multiple cannulations, or transition to VA ECMO; however, the feasibility and safety of the authors' preliminary findings encourage, in their opinion, a trial with esmolol during VV ECMO in ARDS patients with refractory hypoxia and hyperdynamic circulation with high cardiac output, before embracing the more invasive maneuvers in critically ill unstable patients.

In addition, single bilumen cannulation was adopted in more than half of the patients (55%) and became the authors' standard of care since 2012. Indeed, the authors managed VV ECMO patients to promote spontaneous breathing as soon as possible in order to avoid excessive work of breathing with the aim to preserve the best ventilation-perfusion match and reduce lung injury, reduce the need for sedatives, and promote rehabilitation, oral feeding, and recovery. In this clinical setting, bilumen cannulation was a key element, because this technique enabled early extubation in 32% of patients and a more practical and safer mobilization of the patient before ECMO removal (25% mobilization on one side and 15% in the armchair). Furthermore, it proved to be safe and easy to handle; cannulation at the bedside under transesophageal echocardiography guidance was successful in all patients, and postimplantation chest X-ray and bedside transesophageal echocardiography enabled cannula position controls over days of VV ECMO support, especially in mobilized patients. No increased recirculation or need for proning and adjunctive pharmacologic therapy were observed with this strategy.

Some limitations of this study should be acknowledged. First, the nature of the study was observational. However, conducting a randomized trial on ECMO is both clinically and ethically complex. As a matter of fact, the only two large randomized trials conducted on VV ECMO are the CESAR trial and the EOLIA trial.^{8,9} Despite these limitations, this study represents an important contribution in the analysis of the experience and outcomes of refractory ARDS VV ECMO patients, with significant effects in clinical practice. Second, some data were missing and could not be retrieved from record charts (especially pre-ECMO parameters and some specific circuit related issues). This study also showed that the main cause of ARDS found in patients admitted for VV ECMO implantation in 2020 was attributable to SARS-CoV-2 infection (12 patients out of 14 from February to May 2020). This observation highlights the fact that clinicians must be able to manage VV ECMO treatment not only as an established therapy for known pattern of ARDS, but also must be ready to face outbreaks of new diseases with different patterns. For

example, it has been highlighted that SARS-CoV-2 pneumonia should be considered a specific disease with particular phenotypes.²⁷ Although this input is extremely interesting, the authors' study was underpowered to provide relevant information of this subgroup of patients and to provide comparisons with other patients' subgroups.

In conclusion, this study contributed to the complex debate about VV ECMO as a treatment in patients with severe ARDS who are refractory to conventional mechanical protective ventilation. The authors' experience proved that treatment with VV ECMO is effective and might be life-saving in a relevant percentage of patients, thus confirming previous findings.¹¹ Duration of extracorporeal support has impact on clinical outcome. The choice of medical therapies during VV ECMO treatment (anticoagulants above all) arguably has a crucial role to reduce complication and improve outcomes.

Conflict of Interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1053/j.jvca.2021.09.029](https://doi.org/10.1053/j.jvca.2021.09.029).

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