Oxygenator change	2 (8.3%)	7 (10.6%)	>0.999
Pump malfunction	0	0	
Lower limb ischemia			
Distal perfusion	6 (25.0%)	17 (25.8%)	>0.999
Thrombectomy	1 (4.2%)	0	0.267
Fasciotomy	0	1 (1.5%)	>0.999
Amputation	1 (4.2%)	1 (1.5%)	0.464
Stroke	2 (8.3%)	3 (4.6%)	0.605
AKI requiring CRRT	1 (4.2%)	2 (3.0%)	>0.999
Overall incidence	11 (45.8%)	25 (37.9%)	0.627

seven (10.6%) patients in the heparin-free group required oxygenator changes due to thrombosis, there was no significant difference in the frequency of oxygenator changes between the two groups. ECMO pump malfunction was not observed in either group. The frequency of distal perfusion for the management of limb ischemia was not significantly different between the two groups. In the heparin-free group, there was only one case of critical limb ischemia requiring both fasciotomy and limb amputation. In the control group, one patient underwent limb amputation due to ischemia, while another underwent femoral arterial thrombectomy due to thrombosis. The overall incidence of thromboembolic complications was not significantly different between the two groups (45.8 vs. 37.9%, P=0.627, Table 2).

Discussion

Systemic anticoagulants should be routinely administered to patients on VA-ECMO with the primary goal of minimizing circuit thrombosis and preventing thromboembolic complications. The interaction between blood and the artificial surfaces of the ECMO circuit, including the oxygenator, activates both coagulation and inflammatory cascades, inducing a systemic pro-thrombotic state [1]. ECMO technology has been developed with a focus on the management of these inflammatory responses to non-biological surfaces of the ECMO circuit. Newly developed non-thrombogenic substances such as phosphorylcholine and 2-methoxyethyl acrylate are commonly used to coat ECMO circuits [2]. These coatings reduce clot formation in the ECMO circuit, resulting in lower levels of systemic anticoagulation requirement for the patients on ECMO [3]. With the development of these ECMO circuit coating, the incidence of circuit thrombosis is decreasing [4]. Given these technological advances, the use of conventional strict heparinization during ECMO support becomes questionable.

Several researchers have investigated the possibility of using a mild heparinization regimen. Buscher et al. reported a low complication rate despite low-dose heparinization and frequent discontinuation of anticoagulation in patients on ECMO [5]. Muellenbach et al. also demonstrated that long-term, non-heparinized ECMO support was feasible even in patients who initiated ECMO support without heparinization and received heparin 5 days after the initiation of mechanical support [6]. Some researchers have showed that ECMO support could be successfully performed even in patients who are not receiving anticoagulants at all [7,8]. However, most studies involved patients with trauma or patients on VV-ECMO, and there were only few reports involved patients on VA-ECMO for post-cardiotomy cardiogenic shock or ECPR.

At our institution, heparin infusion is liberally discontinued if deemed necessary during VA-ECMO support, after consideration of the risks and benefits of anticoagulation. In post-cardiotomy patients transferred to ICU with initiation of VA-ECMO in the OR, heparinization was not routinely initiated. Considering the residual effects of systemic heparinization during CPB, heparin administration was not prioritized within 24 h of completion of open cardiac surgery, and it was initiated only after confirmation of the absence of postoperative bleeding. For patients with active bleeding immediately after surgery, heparin was not used throughout the period of VA-ECMO support. We applied the same principle to cases of VA-ECMO initiated in the ICU because of post-cardiotomy cardiogenic shock. In cases of ECPR in particular, no bolus heparin was initially administered, and continuous infusion was not routinely initiated either. Heparinization was initiated only after the possibility of active bleeding due to CPR-related injury was completely ruled out. When this strategy was applied, the amounts of blood loss and RBC transfusion in the heparin-free group were not significantly different from those in the control group. Given that there was a significantly larger number of patients who needed re-exploration due to active bleeding in the heparin-free group, it would be reasonable to interpret that application of the heparin-free strategy effectively reduced the amount of blood loss in patients with massive bleeding in the heparin-free group.

A major concern when applying this strategy is sudden ECMO system malfunction requiring replacement of system components due to clots in the circuit, pump head, and oxygenator. The reported incidence of circuit thrombosis in patients on VA-ECMO is 15.6%, with oxygenator thrombosis accounting for 8.2% cases [9]. The frequency of VA-ECMO

malfunction due to circuit thrombosis during support without heparinization has been reported by only a few investigators. Lamarche et al. showed an oxygenator change rate of 9.4% in 32 patients with post-cardiotomy cardiogenic shock who were supported by VA-ECMO without anticoagulation for an average of 46.3 h [10]. Although Fina et al. demonstrated that oxygenator failure did not occur even without systemic anticoagulation, they included only six patients, and their mean ECMO duration was only 10 h [11]. In the present study, the mean VA-ECMO duration without heparinization was 79.8 h, and the rate of oxygenator change due to thrombosis was 10.6% in the heparin-free group. No pump malfunction occurred during VA-ECMO support in the heparin-free group. To the best of our knowledge, this study demonstrated that VA-ECMO could be safely maintained without heparinization for the longest period in the largest number of patients to date.

Another concern with the application of our heparin-free strategy is that it might increase the chance of developing thromboembolic complications such as limb ischemia and stroke. In the present study, only one patient (1.5%) in the heparin-free group experienced significant limb ischemia requiring surgical intervention; this is significantly lower than the 70% incidence of limb ischemia reported by Muehrcke et al [12]. Lamarche et al reported a limb ischemia of 16% [10], which was lower than that reported in previous studies; however, the incidence in our study was considerably lower. These results might be because our institution has been using NIRS monitoring for early detection and timely management of limb ischemia [13]. Our findings demonstrate that the incidence of limb ischemia does not significantly increase in patients on VA-ECMO, even after the long-term application of a heparin-free strategy with appropriate management of limb ischemia. The incidence of stroke was also comparable between the two groups in our study. The overall incidence of thromboembolic complications was relatively high in both groups (45.8 vs. 37.9%, P=0.627), although this was probably because all cases of distal perfusion were considered as cases of limb ischemia. With the exclusion of distal perfusion, the proportion of patients with thromboembolic complications was 25.0% in the control group and 19.7% in the heparin-free group (P=0.572).

This study has several limitations, and the results should be interpreted with caution. The relatively small number of patients and the retrospective design did not allow us to reach a definitive conclusion regarding the heparin-free strategy. A randomized study with a larger sample size is necessary to confirm our findings. In addition, because brain imaging is very difficult to perform in patients on VA-ECMO, the incidence of stroke may be underestimated. Moreover, no autopsy was performed in the mortality cases at our institution. Given that approximately 50% of undiagnosed thromboembolic complications are found during the autopsy of patients who died while supporting by ECMO [14], it can be assumed that the probability of underestimation is high, particularly in the mortality cases.

Conclusion

We demonstrated that a heparin-free strategy during VA-ECMO support could be feasible and did not increase the risk of thromboembolic complications. We suggest that appropriate discontinuation of heparinization during VA-ECMO support could be a safe strategy for patients with active bleeding or a high hemorrhagic risk. Although anticoagulation during VA-ECMO support is necessary in principle, it should be adjusted according to the patient's clinical situation.

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Conflict of Interest

The authors have no conflict of interest.

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