Risk factors for severe lower extremity ischemia following venoarterial extracorporeal membrane oxygenation: an analysis using a nationwide inpatient database

Akira Honda, Nobuaki Michihata, Yoichi Iizuka, Kazuaki Uda, Kojiro Morita, Tokue Mieda, Eiji Takasawa, Sho Ishiwata, Tsuyoshi Tajika, Hiroki Matsui, Kiyohide Fushimi, Hideo Yasunaga, Hirotaka Chikuda

ABSTRACT

Objectives Venous extracorporeal membrane oxygenation is increasingly being used as a life-saving modality in critically ill patients. Despite its necessity, severe lower extremity ischemia associated with venous extracorporeal membrane oxygenation remains a potentially devastating complication. We aimed to investigate the incidence and risk factors for severe lower extremity ischemia requiring fasciotomy or amputation following venoarterial extracorporeal membrane oxygenation.

Methods All patients who received venoarterial extracorporeal membrane oxygenation during hospitalization were identified in a Japanese national inpatient database from July 1, 2010 to March 31, 2018. The primary outcome was occurrence of severe lower extremity ischemia that required fasciotomy or amputation. We used cause-specific proportional hazard models to examine the associations between potential risk factors and outcomes. We also performed a competing-risk analysis to estimate the cause-specific HR for severe lower extremity ischemia using a multivariable competing-risk Cox proportional hazard model with adjustment for potential risk factors.

Results A total of 29,231 patients who underwent venoarterial extracorporeal membrane oxygenation during hospitalization were identified. Of these, 98 patients (0.3%) had lower extremity ischemia requiring fasciotomy or amputation. The young group (<18 years) had a significantly higher proportion of severe lower extremity ischemia cases than the adult (19–59 years) and elderly (≥60 years) groups (1.4%, 0.5%, and 0.2%, respectively; p<0.001). In a multivariable competing-risk Cox proportional hazards regression model, younger age (HR 3.06; 95% CI 1.33 to 7.02; p<0.008) and consciousness disturbance on admission were possible risk factors for severe lower extremity ischemia.

Conclusion In this study using a nationwide database, younger age and consciousness disturbance on admission were associated with higher risk of severe lower extremity ischemia following venoarterial extracorporeal membrane oxygenation.

Level of evidence Level III—prognostic and epidemiological.

Key messages

What is already known on this topic

- Lower extremity ischemia is one of the potentially devastating complications associated with venoarterial extracorporeal membrane oxygenation (VA-ECMO).
- Fasciotomy or amputation may require when acute compartment syndrome occurs following VA-ECMO of the affected limbs.

What this study adds

- Our study revealed that 1.4% of young patients required invasive treatment following VA-ECMO in Japan.
- Younger age and consciousness disturbance on admission were possible risk factors for severe lower extremity ischemia.

How this study might affect research, practice or policy

- Understanding the possible risk factors might help better management of VA-ECMO therapy and reduce invasive treatment, especially in younger patients.

BACKGROUND

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly being used as a life-saving modality in critical patients with refractory cardiopulmonary failure that is potentially reversible or treatable cardiac disease.1 2 During the past decade, the annual numbers of ECMO procedures in the USA and Germany have increased by more than threefold.1 3 Despite its pivotal role as a life-saving modality, VA-ECMO has grave complications including bleeding, acute kidney injury, and vascular structure insult.3 4

Lower extremity ischemia (LEI) is one of the potentially devastating complications associated with VA-ECMO. LEI can lead to acute compartment syndrome that requires emergency fasciotomy or—in more severe conditions—amputation of the affected limb.4 5 6 In previous studies, the proportions of fasciotomy and amputation following VA-ECMO were 9%–13% and 2%–3.9%, respectively.6–9 However, the risk factors for LEI following VA-ECMO remain largely elusive. Prior
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studies indicated potential risk factors such as young age, female sex, diabetes mellitus, respiratory disease, and atherosclerotic disease; however, their sample sizes were insufficient to draw solid conclusions.

To address this issue, we conducted an observational study using a nationwide inpatient database in Japan. The aims of the present study were to: (1) investigate the occurrence of severe LEI following VA-ECMO requiring fasciotomy or amputation and (2) examine its risk factors.

METHODS

Data source

We used the Diagnosis Procedure Combination database, which covers approximately 90% of all tertiary-care emergency hospitals in Japan. The database includes national administrative claims data and discharge data for all inpatients at >1000 participating hospitals. The database includes the following patient information: age and sex, body weight and height, diagnosis, comorbidities at admission, complications after admission, medical procedures, length of hospital stay, discharge status, and in-hospital death. Diagnosis, comorbidities, and complications are recorded using International Classification of Diseases, Tenth Revision (ICD-10) codes. Dates of hospital admission, surgery, bedside procedures, drugs administered, VA-ECMO initiation, weaning from VA-ECMO, and hospital discharge are recorded using a uniform data submission form. The validity of diagnoses and procedures in the database has been established. The specificity and sensitivity for diagnoses and procedures in the database has been established.19 The specificity and sensitivity for diagnoses were 96% and 50%-80%, respectively, while the specificity and sensitivity for procedures were both >90%.19

Participants

We included all patients who received VA-ECMO during hospitalization from July 1, 2010 to March 31, 2018 (figure 1). We excluded patients who: (1) were admitted with pneumonia, (2) had multiple injuries, (3) underwent fasciotomy or amputation prior to VA-ECMO, or (4) were admitted with diabetes mellitus-related gangrene. We excluded patients who were admitted with pneumonia because venovenous (VV)-ECMO is the first choice of treatment in these patients, and we were unable to distinguish between VA-ECMO and VV-ECMO in the present data. The primary outcome was occurrence of severe LEI that

Figure 1 Flow chart of the study. Patients who were admitted with pneumonia, had multiple injuries, underwent fasciotomy or amputation prior to venoarterial extracorporeal membrane oxygenation, or were admitted with diabetes mellitus-related gangrene were excluded. VA-ECMO, venoarterial extracorporeal membrane oxygenation.
required fasciotomy or amputation. We identified complications of LEI and compartment syndrome using ICD-10 codes (M62.2, T79.6) and fasciotomy, amputation, or disarticulation using Japanese original codes.

Baseline variables included age, sex, body mass index (BMI), diabetes mellitus (E10–14), chronic lung disease (J40–47), history of cerebrovascular disease (I60–69), history of cardiac disease (I60–69), pre-ECMO cardiac arrest, use of anticoagulation (heparin, nafamostat, and argatroban) at the start of VA-ECMO, Charlson Comorbidity Index,20 hospital volume, consciousness disturbance on admission, and ambulance use. We divided the eligible patients into three groups according to age: ≤18 years (young group), 19–59 years (adult group), and ≥60 years (elderly group). BMI was categorized into underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), and overweight (≥25.0 kg/m²). Hospital volume of VA-ECMO was categorized into tertiles (low, medium, and high) such that the numbers of patients in the three categories were almost equal. We used the Japan Coma Scale (JCS) score (0, alert consciousness; 1–3, dizziness; 10–30, somnolence; 100–300, coma) to categorize consciousness disturbance on admission into binomial valuations of alert (JCS score, 0) or not (JCS score >0).21 JCS status is well correlated with Glasgow Coma Scale scores.22

Statistical analysis

We used a t-test for comparisons of continuous variables, and the χ² test or Fisher’s exact test for categorical variables. Patient demographic data were compared between the young (≤18 years), adult (19–59 years), and elderly (≥60 years) groups. The log-rank test was used to compare cause-specific hazard functions among the groups. We further carried out cause-specific proportional hazard models to examine the associations between potential risk factors and outcomes.23 24 In the present study, occurrence of in-hospital death was regarded as a competing risk for fasciotomy or amputation. We therefore estimated the cumulative incidences of severe LEI and competing risk using a cause-specific hazard function.23 24 The cumulative incidence was defined as the probability of experiencing the outcome within a certain time and not experiencing a competing event within the same period. We compared the cumulative incidence using the log-rank test. We also performed a competing-risk analysis to estimate the cause-specific HR for severe LEI using a multivariable competing-risk Cox proportional hazard model with adjustment for potential risk factors.24 25 The following sensitivity analyses were performed. First, because it was difficult to completely remove the bias arising from the competing risk of death, we performed a sensitivity analysis on surviving patients who were discharged. Second, to make the indications for VA-ECMO clearer, we excluded patients who were weaned from ECMO within 2 days, were aged <12 years, or died within 2 days after admission. Third, we excluded patients who did not receive anticoagulants at the start of VA-ECMO. Fourth, we excluded patients who underwent cardiac surgery, as there may have been an option for central cannulation. All statistical analyses were performed with STATA V.15 software (StataCorp, College Station, Texas, USA). A two-tailed significance level of p<0.05 was used in all analyses.

RESULTS

We identified 29 231 eligible patients who received VA-ECMO from July 1, 2010 to March 31, 2018 (males, 71%; mean age±SD, 62±18 years). The average annual number of patients who received VA-ECMO was 2.9 per 100 000 inhabitants (online supplemental table S1). Cardiogenic shock was the most common diagnosis at admission (85%). Table 1 shows the demographic characteristics of the patients. In the sample, 948 patients (3.2%) were in the young group, but the majority of patients (65%) were in the elderly group. The young group was less likely to have consciousness disturbance on admission than the adult and elderly groups (online supplemental table S2).

Table 2 shows the outcomes according to age categories. The proportions of overall in-hospital death and 30-day death were 70% and 61%, respectively. A total of 98 patients (0.3%) received fasciotomy or amputation. Seven patients (0.7%) in the young group underwent amputation. Regarding age categories, the young group had significantly lower occurrence of death than the adult and elderly groups (overall in-hospital death, 55%, 66%, and 72%, p<0.001; 30-day death, 36%, 59%, and 64%, p<0.001), higher proportion of severe LEI (1.4%, 0.3%, and 0.2%, p<0.001), longer duration of VA-ECMO (4 days, 1 day, and 1 day, p<0.001), and longer hospital stay (72 days, 29 days, and 25 days, p<0.001).

Figure 2 shows the cumulative incidences of severe LEI and competing risk among the age categories. Overall, median observation period was 11 days (IQR, 2–35 days). During the observation period, 17 911 patients (61%) died. The majority of fasciotomy or amputation procedures were performed within 1 week after starting VA-ECMO (median, 6 days; IQR, 2–19 days). Data for the observational period, timing of fasciotomy or amputation after starting VA-ECMO, timing of death after starting VA-ECMO, proportion of patients who underwent leg intervention during ECMO, and proportion of patients who underwent cardiac surgery are shown in online supplemental table S3.

Table 3 shows the multivariable competing-risk Cox proportional hazards regression model for severe LEI. Younger age (HR, 3.06; 95% CI, 1.33 to 7.02; p=0.008) and consciousness disturbance on admission (HR, 2.53; 95% CI, 1.60 to 3.99; p<0.001) were significantly associated with higher likelihood of severe LEI. The sensitivity analyses produced similar results to those in the main analysis (online supplemental tables S4–S9).

DISCUSSION

The present study using a nationwide inpatient database revealed that severe LEI requiring fasciotomy or amputation occurred in 0.3% of patients who received VA-ECMO. Notably, 1.4% of young patients required invasive treatment including amputation because of severe LEI. After adjustment for patient demographic and clinical characteristics, younger age and impaired consciousness on admission were risk factors for severe LEI.

To the best of our knowledge, this is the first nationwide study to focus on the risk factors for severe LEI in patients who received VA-ECMO during hospitalization. In previous nationwide studies, the annual incidence of VA-ECMO was 4.4 per 100 000 inhabitants in the USA26 and 3.5 per 100 000 inhabitants in Germany.4 Consistent with these studies, our study revealed that the average annual incidence of VA-ECMO was 2.9 per 100 000 inhabitants and increased by almost threefold from 2010 and 2017 (online supplemental table S1). Despite the pivotal role of VA-ECMO as a life-saving modality, its mortality rate remains high, and its risk of severe complications should be acknowledged.

Severe LEI has been increasingly recognized as a devastating complication following VA-ECMO, particularly in those with refractory cardiogenic shock after cardiac surgery.8 10–12 In previous studies, the reported proportions of severe LEI following...
VA-ECMO in adult and pediatric patients ranged from 8.6% to 33%6–12 27 and from 9.5% to 19%,28–30 respectively. However, these prior studies lacked a unanimous definition of severe LEI and were mostly associated with small sample sizes or conducted in limited settings. Conversely, our results showed that severe LEI occurred in <1% of patients who received VA-ECMO. This marked difference may be attributable, at least in part, to increased recognition of this complication and improved management of VA-ECMO. In Japan, ultrasound-guided cannulation11 12 and monitoring of lower extremity blood flow using near-infrared spectroscopy (NIRS)33 have been widely used for ECMO and management of LEI. NIRS is used to determine whether distal perfusion catheter is needed.

The precise mechanism and risk factors for LEI following VA-ECMO remain unclear. Previous reports have proposed two mechanisms for severe LEI: peripheral circulation insufficiency on the same side as the cannulation6 and raised intracompartment pressure within a fascial or osteofascial compartment caused by

### Table 1  Demographic data of patients who received venoarterial extracorporeal membrane oxygenation

| Demographic data | Patient age | Overall (n=29,231) | Young (≤18 years) (n=948) | Adult (19–59 years) (n=9,195) | Elderly (≥60 years) (n=19,088) | P value |
|------------------|-------------|------------------|---------------------------|-------------------------------|-----------------------------|---------|
| Sex, n (%)       |             |                  |                           |                               |                             | <0.001  |
| Male             | 20,860 (71) | 520 (55)         | 6955 (76)                 | 13,385 (70)                   |                             |         |
| Female           | 8,371 (29)  | 428 (45)         | 2,240 (24)                | 5,703 (30)                    |                             |         |
| Body mass index (kg/m²), n (%) |             |                  |                           |                               |                             | <0.001  |
| Underweight (<18.5) | 2,585 (11) | 625 (78)         | 566 (8.0)                 | 1,394 (9.1)                   |                             |         |
| Normal weight (18.5–24.9) | 13,172 (57) | 143 (18)         | 3,496 (50)                | 9,488 (62)                    |                             |         |
| Overweight (≥25) | 7,413 (32) | 29 (3.6)         | 2,974 (42)                | 4,410 (29)                    |                             |         |
| Comorbid conditions at admission, n (%) |             |                  |                           |                               |                             | <0.001  |
| Diabetes mellitus | 4,904 (17) | 8 (0.8)          | 1,198 (13)                | 3,698 (19)                    |                             | <0.001  |
| Hypertension     | 5,058 (20) | 20 (2.1)         | 1,337 (15)                | 4,501 (24)                    |                             | <0.001  |
| Chronic lung disease | 566 (1.9)  | 18 (1.9)         | 116 (1.3)                 | 432 (2.3)                     |                             | <0.001  |
| Cerebrovascular disease | 1,145 (3.9) | 11 (1.2) | 262 (2.8) | 872 (4.6) | <0.001 |
| Cardiac disease  | 18,300 (63) | 159 (17)        | 3,432 (37)                | 5,472 (29)                    |                             | <0.001  |
| Atherosclerotic disease | 6,649 (23) | 24 (2.5)       | 1,639 (18)                | 4,966 (26)                    |                             | <0.001  |
| At least one comorbidity | 21,571 (74) | 477 (50)       | 6,465 (70)                | 14,629 (77)                   |                             | <0.001  |
| Episode of arrest at admission, n (%) | 4,150 (14) | 75 (7.9)       | 1,612 (18)                | 2,463 (13)                    |                             | <0.001  |
| Use of anticoagulants, n (%) | 19,617 (67) | 424 (45)       | 6,824 (74)                | 12,369 (65)                   |                             | <0.001  |
| Charlson Comorbidity Index update category, n (%) |             |                  |                           |                               |                             | <0.001  |
| ≤2               | 27,476 (94) | 931 (98)        | 8,776 (95)                | 17,769 (93)                   |                             |         |
| ≥3               | 17,555 (60) | 17 (1.8)        | 4,19 (4.6)                | 13,119 (6.9)                  |                             |         |
| Consciousness on admission, n (%) |             |                  |                           |                               |                             | <0.001  |
| Alert            | 13,624 (47) | 596 (63)        | 3,406 (37)                | 9,626 (50)                    |                             |         |
| Disturbance      | 15,607 (53) | 352 (37)        | 5,789 (63)                | 9,466 (50)                    |                             | <0.001  |
| Ambulance use, n (%) | 20,141 (69) | 425 (45)       | 7,021 (76)                | 12,695 (67)                   |                             | <0.001  |
| Hospital volume (per year), n (%) |             |                  |                           |                               |                             | <0.001  |
| Low (0.75–17.4)  | 10,146 (35) | 214 (23)        | 3,165 (34)                | 6,982 (36)                    |                             |         |
| Medium (17.5–41.4) | 9,884 (34) | 389 (41)       | 3,081 (34)                | 6,414 (34)                    |                             |         |
| High (≥41.5)     | 9,201 (31)  | 345 (36)        | 3,009 (33)                | 5,847 (31)                    |                             |         |

### Table 2  Adverse outcomes among age categories

| Adverse outcomes | Patient age | Overall (n=29,231) | Young (≤18 years) (n=948) | Adult (19–59 years) (n=9,195) | Elderly (≥60 years) (n=19,088) | P value |
|------------------|-------------|------------------|---------------------------|-------------------------------|-----------------------------|---------|
| In-hospital death, n (%) |             |                  |                           |                               |                             | <0.001  |
| Died within 30 day, n (%) |             |                  |                           |                               |                             | <0.001  |
| Severe lower extremity ischemia, n (%) | 98 (0.3) | 13 (1.4)       | 42 (0.5)                  | 43 (0.2)                      |                             | <0.001  |
| Fasciotomy       | 42 (0.1)   | 6 (0.6)         | 20 (0.2)                  | 16 (0.1)                      |                             | <0.001  |
| Amputation at any level | 60 (0.2) | 7 (0.7)        | 25 (0.3)                  | 28 (0.1)                      |                             | <0.001  |
| VA-ECMO duration (days), mean (±SD) | 2.9 (8.6) | 8.6 (19)      | 3.3 (12)                  | 2.4 (5.2)                     |                             | <0.001  |
| Length of hospital stay, (days), mean (±SD) | 28 (54) | 72 (125)       | 29 (61)                   | 25 (42)                       |                             | <0.001  |

VA-ECMO, venoarterial extracorporeal membrane oxygenation.
an increased volume within a fixed compartment size. Children and women were reported to be at high risk for LEI through immature development of arteries and collateral blood flow. Other conditions like diabetes mellitus, atherosclerotic disease, and respiratory disease were also reported as risk factors for LEI, presumably arising from degenerative changes to peripheral arteries and states of chronic hypoxia. In the present study, children and adolescent patients were at higher risk of severe LEI than adult or elderly patients. Prior studies showed that a relative lack of collateral circulation in young patients may accelerate ischemic compartment syndrome. Furthermore, McQueen et al. described that the stronger fascial structures, which the younger patients have, may lead to exacerbation of compartment syndrome. Because of the difficulties associated with proper cannulation of immature arteries, young patients are at risk of vascular structure insults (such as hemorrhage, vascular injury, mismatch between diameter of femoral artery and cannula size). However, many elderly people are also at risk because they have relatively small vessel diameters owing to calcification. Smaller catheters are routinely placed under ultrasound guidance when the vessel diameter appears small in patients such as young people, women, and elderly people with calcified vessels. Considering that ultrasound-guided cannulation is a relatively safe procedure, musculoskeletal structural reasons such as stronger fascia in younger patients, rather than difficulty in cannulation, may be a possible reason.

The present study showed that consciousness disturbance on admission was another factor associated with high risk of severe LEI. Presumably, patients with consciousness disturbance are likely to have more severe systemic conditions (such as severe cardiogenic shock) than those without consciousness disturbance. The lack of consciousness was presumably due to the severity and presence of shock on admission. Notably, in-hospital death was significantly higher in patients with consciousness disturbance on admission than in those without (online supplemental table S2). Such patients with more severe conditions are considered a priority for life-saving management regardless of their local condition, including suboptimal peripheral blood flow and leg ischemia. Although these patients are less likely to survive, closer attention should be paid to possible occurrence of severe LEI.

Several limitations should be acknowledged in the present study. First, we were unable to obtain data on the indications for VA-ECMO. In Japan, as in the USA and other Western countries, the indications for VA-ECMO are based on the Extracorporeal Life Support Organization guidelines. However, based on our sensitivity analysis, we believe that the indication bias may have had little influence on the evaluation of severe complications following VA-ECMO. Second, we were unable to obtain information on catheter size, insertion technique, side for catheter insertion, use of central cannulation, use of distal perfusion catheter, and whether VV-ECMO or VA-ECMO was performed. Although variations in technique may affect outcomes, a
previous large-population study found that percutaneous techniques had similar rates of limb ischemia to surgical techniques. As we adjusted for hospital volume of VA-ECMO and performed a sensitivity analysis, we believe that the insertion techniques had little influence on the outcomes. Third, even with the competing-risk analysis, the effects of confounding bias cannot be entirely adjusted, and therefore the risk of LEI may have been underestimated. Thus, we performed a sensitivity analysis on surviving patients only, and the results were confirmed to be robust. Fourth, the incidence of severe complications among younger patients was extremely low. Because of the anonymity of our database, we were unable to disclose the ages of the younger patients due to the low incidence of severe LEI. However, most of the patients who experienced severe LEI in the young group were aged >12 years, and their heights were almost equal to or taller than the average height of Japanese women. Finally, errors in data entry and coding may have occurred. However, we believe that miscoding is rare in the Diagnosis Procedure Combination database because the diagnoses are recorded by the attending physicians. Despite these limitations, we believe that the present study can provide an overview of the complications and interventions related to VA-ECMO and help to reduce this potentially disabling complication.

CONCLUSIONS
In this study using a nationwide database, younger age and consciousness disturbance on admission were associated with higher risk of severe LEI following VA-ECMO. The findings of the present study have important implications for better management of VA-ECMO.

Author affiliations
1Orthopaedic Surgery, Gunma University Graduate School of Medicine School of Medicine Faculty of Medicine, Gunma, Japan
2Health Services Research, Graduate School of Medicine, The University of Tokyo Graduate School of Medicine Faculty of Medicine, Tokyo, Japan
3Health Services Research and Development Center, University of Tsukuba Graduate School of Medicine Faculty of Medicine, Tsukuba, Ibaraki, Japan
4Global Nursing Research Center, The University of Tokyo Graduate School of Medicine Faculty of Medicine, Tokyo, Japan
5Clinical Epidemiology and Health Economics, The University of Tokyo Graduate School of Medicine Faculty of Medicine, Tokyo, Japan
6Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Tokyo, Japan

Table 3  Risk factors for severe lower extremity ischemia following VA-ECMO using a multivariable competing-risk Cox regression model

| Risk factor                     | Cause-specific HR | 95% CI       | P value    |
|---------------------------------|-------------------|--------------|------------|
| Age (years)                     |                   |              |            |
| ≤18                             | 3.08              | 1.34 to 7.07 | 0.008*     |
| ≥60                             | 0.57              | 0.36 to 0.92 | 0.021*     |
| Sex                             |                   |              |            |
| Female                          | Reference         |              |            |
| Male                            | 1.06              | 0.66 to 1.70 | 0.812      |
| Body mass index (kg/m²)         |                   |              |            |
| Normal weight (18.5–24.9)       | Reference         |              |            |
| Underweight (<18.5)             | 0.93              | 0.45 to 1.96 | 0.865      |
| Overweight (≥25.0)              | 1.26              | 0.78 to 2.04 | 0.352      |
| Comorbid conditions             |                   |              |            |
| Diabetes mellitus               | 1.21              | 0.70 to 2.10 | 0.498      |
| Atherosclerotic disease         | 0.64              | 0.36 to 1.18 | 0.152      |
| Episcope of arrest at admission | 0.82              | 0.43 to 1.59 | 0.564      |
| VA-ECMO duration (days)         | 0.97              | 0.93 to 1.01 | 0.166      |
| Consciousness on admission      |                   |              |            |
| Alert                           | Reference         |              |            |
| Disturbance                     | 2.50              | 1.58 to 3.95 | <0.001*    |

*P<0.05.
VA-ECMO, venoarterial extracorporeal membrane oxygenation.

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