Association of Admission Glucose Level and Improvement in Pulmonary Artery Pressure in Patients with Submassive-type Acute Pulmonary Embolism

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Abstract:
Objective The admission glucose level is a predictor of mortality even in patients with acute pulmonary embolism (APE). However, whether or not the admission glucose level is associated with the severity of APE itself or the underlying disease of APE is unclear.

Methods This study was a retrospective observational study. A pulmonary artery (PA) catheter was used to accurately evaluate the severity of APE. The percentage changes in the mean PA pressure (PAPm) upon placement and removal of the inferior vena cava filter (IVCF) were evaluated. We hypothesized that the admission glucose level was associated with the improvement in the PA pressure in patients with APE.

Patients A total of consecutive 22 patients with submassive APE who underwent temporary or retrievable IVCF insertion on admission and repetitive PA catheter measurements upon placement and removal of IVCFs were enrolled.

Results There was a significant positive correlation between the admission glucose levels and the percentage changes in the PAPm (r=0.543, p=0.009). A univariate linear regression analysis showed that the admission glucose level was the predictor of the percentage change in PAPm (β coefficient=0.169 per 1 mg/dL; 95% confidence interval, 0.047-0.291; p=0.009). A multivariate linear regression analysis with the forced inclusion model showed that the admission glucose level was the predictor of the percentage change in PAPm independent of diabetes mellitus, PAPm on admission, troponin positivity, and brain natriuretic peptide level (all p<0.05).

Conclusion The admission glucose level was associated with the improvement in the PAPm in patients with submassive-type APE.

Key words: admission glucose level, pulmonary embolism, inferior vena cava filter

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Introduction
Acute pulmonary embolism (APE) remains a fatal disease in the clinical setting. A previous study reported that the mortality rate of untreated APE is about 30% (1). Even with standard therapy, the in-hospital mortality rate of APE was reported to be 14% in the Japanese registry (2). Severe APE was reported to cause right ventricular (RV) dysfunction (RVD), leading to cardiogenic shock, and the mortality rate of APE with cardiogenic shock was up to 30% (2). Therefore, the accurate classification of the severity of APE is important. APE has been classically defined as having three types according to the hemodynamic status of the patient

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and the presence of RVD: massive type, submassive type, and non-massive type (3, 4). Recently, however, APE has been defined as having four types according to the hemodynamic status, presence of RVD, pulmonary embolism (PE) severity index, and cardiac laboratory biomarkers [elevated cardiac troponin (Tn) or brain natriuretic peptide (BNP) level]: high, intermediate-high, intermediate-low, and low (5).

Anticoagulant therapy is the initial therapy in all patients with APE who have no contraindications to anticoagulant therapy. More aggressive therapies, such as the use of a percutaneous cardiopulmonary support device or fibrinolytic therapy, are needed in some patients (6, 7). In addition, insertion of an inferior vena cava filter (IVCF) is an optional therapy to prevent the recurrence of APE. Preventing the recurrence of APE, particularly in the acute phase, is important, as a previous report demonstrated that 90% of deaths resulting from PE were due to the recurrence of APE, which mostly occurred within 1 week (8). Recently, in the PREPIC2 study, IVCF insertion was reported to have no additional benefit in patients with APE who could be treated with anticoagulant therapy (9). However, the mean time between randomization and attempted IVCF insertion was 1.5 days, and the severity classification of APE was mixed, including the non-massive type of APE, in the PREPIC2 study. We believe that the risk of APE recurrence is highest on the day of admission; therefore, IVCF insertion may be more beneficial the sooner it is performed after admission. Earlier IVCF insertion may have some benefits in patients with poor improvement in their pulmonary artery (PA) pressure (PAP) in the acute phase. However, even early IVCF insertion may have no marked benefit in patients with a low-risk status, such those with the non-massive type of APE. Therefore, whether or not patients with APE actually need IVCF insertion remains unclear.

The admission glucose level is a predictor of mortality in various diseases (10-15). Recently, some reports have shown the admission glucose level to be a predictor of mortality, even in patients with APE (16-18). However, whether or not the admission glucose level is associated with the severity of APE itself or the underlying disease of APE is unclear. Furthermore, while a PA catheter can accurately evaluate the severity of APE, no study has investigated the association between the admission glucose level and the PAP as determined by using a PA catheter.

The aim of the present study was to examine whether or not the admission glucose level was associated with the improvement in the PAP in patients with APE by investigating the association between the admission glucose level and the percentage change in the mean PAP (PAPm) determined using a PA catheter.

Materials and Methods

Patients

The present study was a retrospective observational study in patients with APE treated at Saiseikai Yokohamashi Nanbu Hospital from March 2010 through March 2016. We used temporary IVCFs (Neuhause Protect; Toray Medical, Tokyo, Japan) or retrievable IVCFs ( Günther Tulip; Cook Japan, Tokyo, Japan) aggressively in patients with massive- or submassive-type APE as soon as possible on admission to prevent the recurrence of APE and performed PA catheter (Swan-Ganz thermodilution catheter; Edwards Lifesciences, Irvine, USA) measurements repeatedly upon insertion and removal of IVCFs. Consecutive patients with submassive-type APE who underwent temporary or retrievable IVCF insertion were screened for eligibility. As which patients need IVCF insertion among those with submassive APE in the clinical setting remains unclear, and it is important to exclude the potential confounding factors influencing the severity of APE. We therefore limited the included patients to those with submassive-type APE. All patients were given intravenous unfractionated heparin (intravenous bolus dose of 5,000 international units, then a continuous intravenous infusion) adjusted according to the activated partial thromboplastin time (aPTT) so that the ratio of the patient’s value to the control value remained between 1.5 and 2.5 (19). The target ratio was reached within the first day in all patients.

APE was defined as the acute onset of symptoms suspicious of PE on the basis of the European Society of Cardiology guideline (5). Computed tomographic pulmonary angiography, pulmonary angiography, or lung scintigraphy was used to confirm PE. Massive, submassive, and non-massive types were defined as follows: massive type was APE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 min or requirement for inotropic support not due to reasons other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 beats per minute with signs or symptoms of shock); submassive type was APE without systemic hypotension (systolic blood pressure <90 mm Hg) but with RVD; and non-massive type was APE without systemic hypotension (systolic blood pressure <90 mm Hg) and RVD (4).

We also excluded patients with any of the following characteristics: (i) contraindications of the initial anticoagulant therapy; (ii) lack of repetitive PA catheter measurements; (iii) mechanical ventilation; and (iv) hemodialysis.

A total of consecutive 22 patients with submassive-type APE who underwent temporary or retrievable IVCF insertion met the eligibility criteria and were enrolled. A PA catheter was used to accurately evaluate the severity of APE. The percentage changes in PAPm upon placement and removal of IVCFs were evaluated, and we divided the patients into two groups according to the percentage change in...
PAPm: a good improvement group, comprising 11 patients with percentage change in PAPm <−28.8%; and a poor improvement group, comprising 11 patients with percentage change in PAPm ≥28.8%. Some previous reports demonstrated that the percentage changes in PAP with treatments by recombinant tissue-type plasminogen activator, nitric oxide, and pulmonary embolectomy were −27.3% (31±7 mmHg to 22±6 mmHg), −11.9% (32.9±1.3 mmHg to 29.0±1.4 mmHg), and −22.3% (44.9±5.7 mmHg to 34.9±7.1 mmHg), respectively (20-22). Therefore, our cutoff value of the percentage change in PAPm <−28.8% had clinical significance. The present study protocol was approved by the Saiseikai Yokohamashi Nanbu Hospital Institutional Review Board and complied with the provisions of the Declaration of Helsinki.

Statistical analysis

Continuous variables are expressed as the mean±standard deviation for parameters with a normal distribution and as medians (25th to 75th percentiles) for parameters with a skewed distribution. Differences between two groups were assessed using Student’s t-test for variables with a normal distribution, the Mann-Whitney U test for variables with a skewed distribution (HDLC cholesterol, the admission glucose level, HbA1c, D-dimers, hs-CRP, and BNP), and the chi-squared or Fisher’s exact test, as appropriate, for categorical variables. The correlation between the admission glucose level and the percentage change in the PAPm or aPTT level was determined using Pearson’s correlation coefficient. Univariate linear regression analyses and a multivariate linear regression analysis with forced inclusion variables (the admission glucose level, diabetes mellitus, PAPm on admission, TN positivity, BNP level) for the prediction of the percentage change in PAPm were performed. All statistical tests were two-tailed, and p<0.05 was considered to indicate statistical significance. All statistical analyses were conducted with the SPSS software program, version 18.0 (Statistical Package for Social Sciences, Japan, Tokyo, Japan).

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the two groups of patients according to the percentage change in PAPm. There were no significant differences between the two groups in baseline characteristics, including age, sex, coronary risk factors, methods of therapy, biomarkers, and medications (Table 1). Of the 22 patients, only 3 were administered not only intravenous unfractionated heparin but also oral warfarin, a vitamin K antagonist, before the IVCF removal. No patients were administered direct oral anticoagulant before the time of IVCF removal. Two patients were administered oral warfarin from day 2, and one patient was administered oral warfarin from day 4; the international normalized ratio of prothrombin time (PT-INR) of the 2 patients treated on day 2 were 1.91 and 1.31, respectively, and that of the 1 treated on day 4 was 1.60 at the time of IVCF removal.
removal. However, there was no significant difference between the two groups in the daily average of each aPTT ratio to confirm the effect of anticoagulant therapy during the acute phase (p=0.38). Only the admission glucose level tended to be higher in patients in the poor improvement group than in the good improvement group [143 (112-246) mg/dL vs. 133 (103-146) mg/dL, p=0.09]. The HbA1c level did not differ markedly between the two groups [5.7% (5.6-6.2%) vs. 5.8% (5.6-6.2%), p=0.54].

In addition, there were no significant differences between the two groups in the findings of 2DE or lower-limb venous ultrasonography (Table 2). The LVEF and the location of remaining DVT did not differ markedly between the two groups.

However, although there were no significant differences between the two groups in the baseline PA catheter findings, the PAPm at the time of IVCF removal was higher in patients in the poor improvement group than in those in the good improvement group (26±8 mmHg vs. 20±6 mmHg, p=0.04) (Table 3).

**Association between the admission glucose level and the percentage change in PAPm**

We then investigated the association between the admission glucose level and the percentage change in the PAPm. There was a significant positive correlation between the ad-

### Table 1. Baseline Clinical Findings.

| Variables                  | Good improvement group (n=11) | Poor improvement group (n=11) | p value |
|----------------------------|-------------------------------|-----------------------------|---------|
| Age, years                 | 65±9                         | 66±12                       | 0.77    |
| Male, n (%)                | 4 (36)                       | 3 (27)                      | 0.50    |
| Body mass index, kg/m²     | 24±4                         | 24±5                        | 0.99    |
| Current smoker, n (%)      | 3 (27)                       | 1 (9)                       | 0.29    |
| Hypertension, n (%)        | 4 (36)                       | 6 (55)                      | 0.39    |
| Dyslipidemia, n (%)        | 7 (64)                       | 5 (45)                      | 0.39    |
| LDL cholesterol, mg/dL     | 128±20                      | 112±29                      | 0.17    |
| HDL cholesterol, mg/dL     | 49 (38-56)                  | 54 (42-79)                  | 0.29    |
| Triglycerides, mg/dL       | 123±42                      | 107±61                      | 0.47    |
| Diabetes mellitus, n (%)   | 1 (9)                        | 1 (9)                       | 0.76    |
| Admission glucose, mg/dL   | 133 (103-146)               | 143 (112-246)               | 0.09    |
| Hemoglobin A1c, %          | 5.8 (5.6-6.2)               | 5.7 (5.6-6.2)               | 0.54    |
| Use of fibrolitic therapy, n (%) | 2 (18)  | 1 (9)                        | 0.50    |
| Use of temporary IVCF, n (%) | 10 (91)         | 11 (100)                    | 0.50    |
| Use of retrievable IVCF, n (%) | 1 (9)             | 0 (0)                       | 0.50    |
| Duration of IVCF use, days | 5.6±3.2                    | 4.6±0.9                     | 0.34    |
| Admission systolic blood pressure, mm Hg | 132±18          | 120±19                     | 0.15    |
| Admission heart rate, bpm  | 97±19                      | 106±16                      | 0.25    |
| White blood cell count, /μL| 8,245±2,382                 | 8,727±2,714                 | 0.66    |
| Hemoglobin, g/dL           | 14.3±1.8                    | 13.3±2.6                    | 0.34    |
| D-dimer, μg/mL             | 10.6 (6.8-14.1)             | 10.1 (7.2-28.2)             | 0.87    |
| Average APTT ratio         | 2.4±0.5                     | 2.7±0.8                     | 0.38    |
| hs-CRP, mg/dL              | 1.09 (0.32-2.19)            | 1.01 (0.36-1.52)            | 0.92    |
| eGFR, mL·min⁻¹·1.73 m⁻²    | 58±11                      | 52±19                       | 0.42    |
| Troponin positivity, n (%) | 5 (45)                      | 7 (64)                      | 0.25    |
| BNP, pg/mL                 | 221.4 (143.3-599.5)         | 209.7 (136.9-412.9)         | 0.97    |
| Medication on admission, n (%) |                      |                             |         |
| Aspirin                    | 2 (18)                      | 1 (9)                       | 0.50    |
| Thienopyridine             | 0 (0)                       | 0 (0)                       | 1.00    |
| Anticoagulant              | 0 (0)                       | 0 (0)                       | 1.00    |
| Beta-blocker               | 0 (0)                       | 2 (18)                      | 0.24    |
| ACE-I or ARB               | 1 (9)                       | 2 (18)                      | 0.50    |
| Statin                     | 2 (18)                      | 1 (9)                       | 0.50    |

Data are shown as the mean±standard deviation or number (percentage) or median (range).

Good improvement group: percentage change in PAPm < 28.8%. Poor improvement group: percentage change in PAPm ≥ 28.8%.

PAPm: mean pulmonary artery pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, IVCF: inferior vena cava filter, aPTT: activated partial thromboplastin time, hs-CRP: high-sensitivity C-reactive protein, eGFR: estimated glomerular filtration rate, BNP: brain natriuretic peptide, ACE-I: angiotensin-converting enzyme-inhibitors, ARB: angiotensin II receptor blockers.
mission glucose level and the percentage change in PAPm (r =0.543, p=0.009) (Fig. 1), which means that a high admission glucose level was associated with a poor improvement in the PAPm.

**Association between the admission glucose level and admission aPTT level**

We also investigated the association between the admission glucose level and the admission aPTT level. There was a significant negative correlation between the admission glucose level and the admission aPTT level (r=-0.568, p=0.006) (Fig. 2).

**Univariate and multivariate linear regression analyses for the prediction of the percentage change in PAPm**

We hypothesized that the admission glucose level was associated with the improvement of the PAP in patients with APE. To test this hypothesis, we conducted univariate linear regression analyses and a multivariate linear regression

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### Table 2. Ultrasonography Findings.

| Variables                                      | Good improvement group (n=11) | Poor improvement group (n=11) | p value |
|------------------------------------------------|------------------------------|------------------------------|---------|
| 2D-echocardiography on admission               |                              |                              |         |
| LVEF, %                                        | 62±4                         | 60±9                         | 0.50    |
| TRPG, mm Hg                                    | 59±18                        | 53±18                        | 0.43    |
| RVd/LVd                                       | 1.2±0.2                      | 1.3±0.3                      | 0.42    |
| 2D-echocardiography at the time of IVCF removal|                              |                              |         |
| LVEF, %                                        | 63±5                         | 61±7                         | 0.57    |
| TRPG, mm Hg                                    | 21±12                        | 27±23                        | 0.52    |
| RVd/LVd                                       | 0.9±0.2                      | 1.0±0.2                      | 0.30    |
| Lower-limb venous ultrasonography              |                              |                              |         |
| Proximal DVT, n (%)                            | 6 (55)                       | 4 (36)                       | 0.41    |
| Only distal DVT, n (%)                         | 4 (36)                       | 6 (55)                       | 0.39    |
| No DVT, n (%)                                  | 1 (9)                        | 1 (9)                        | 0.76    |

Data are presented as the mean±standard deviation.

Good improvement group: percentage change in PAPm <−28.8%. Poor improvement group: percentage change in PAPm ≥−28.8%

PAPm: mean pulmonary artery pressure, LVEF: left ventricular ejection fraction, TRPG: tricuspid regurgitation peak gradient, RVd/LVd: right ventricular diameter divided by left ventricular diameter, IVCF: inferior vena cava filter, DVT: deep vein thrombosis

### Table 3. PA Catheter Findings.

| Variables                                      | Good improvement group (n=11) | Poor improvement group (n=11) | p value |
|------------------------------------------------|------------------------------|------------------------------|---------|
| PA catheter on admission                       |                              |                              |         |
| PAPs, mm Hg                                    | 57±14                        | 54±15                        | 0.59    |
| PAPd, mm Hg                                    | 18±7                         | 17±5                         | 0.87    |
| PAPm, mm Hg                                    | 33±8                         | 31±7                         | 0.72    |
| CVP, mm Hg                                     | 5±5                          | 7±5                          | 0.35    |
| CI, L·min⁻¹·m⁻²                                 | 2.1±0.3                      | 1.9±0.5                      | 0.36    |
| PA catheter at the time of IVCF removal         |                              |                              |         |
| PAPs, mm Hg                                    | 35±10                        | 45±14                        | 0.07    |
| PAPd, mm Hg                                    | 11±5                         | 16±5                         | 0.03    |
| PAPm, mm Hg                                    | 20±6                         | 26±8                         | 0.04    |
| CVP, mm Hg                                     | 4±3                          | 7±4                          | 0.03    |
| CI, L·min⁻¹·m⁻²                                 | 2.7±0.3                      | 2.6±0.5                      | 0.64    |

Data are presented as the mean±standard deviation.

Good improvement group: percentage change in PAPm <−28.8%. Poor improvement group: percentage change in PAPm ≥−28.8%

PA: pulmonary artery, IVCF: inferior vena cava filter, PAPs: systolic pulmonary artery pressure, PAPd: diastolic pulmonary artery pressure, PAPm: mean pulmonary artery pressure, CVP: mean central venous pressure, CI: cardiac index
analysis with the forced inclusion model to predict the percentage change in the PAPm (Table 4). A univariate linear regression analysis showed that the admission glucose level was indeed a predictor of the percentage change in PAPm (β coefficient=0.169 per 1 mg/dL; 95% confidence interval, 0.047-0.291; p=0.009). Diabetes mellitus, PAPm on admission, Tn positivity, and BNP level were not predictors of the percentage change in PAPm independent of diabetes mellitus, PAPm on admission, Tn positivity, and BNP level (α=0.05).

Discussion

The present study showed that the admission glucose level had a significant positive correlation with the percentage change in the PAPm. Furthermore, the admission glucose level was a predictor of the percentage change in the PAPm independent of diabetes mellitus, PAPm on admission, Tn positivity, and BNP level. To our knowledge, this is the first study to demonstrate that the admission glucose level is associated with the improvement in the PAP in patients with APE.

Preventing the recurrence of APE is important. IVCF, which is an optional therapy aimed at preventing the recurrence of APE, is being increasingly used; however, there is no benefit to using IVCF routinely in patients with APE (5, 28, 29). Nevertheless, IVCF is effective in some patients (30, 31). It is therefore important to distinguish high-risk patients with APE who may need IVCF from low-risk patients with APE who may not need it. Although previous studies have shown that Tn and pro-BNP were useful for predicting the clinical outcome in patients with APE (32, 33), the present study showed that the admission glucose level was associated with the percentage change in the PAPm independent of diabetes mellitus, PAPm on admission, Tn positivity, and BNP level. Our results revealed that patients with high admission glucose levels might be at a risk of a poor improvement in the PAP.

Several previous studies showed that the admission glucose level was a predictor of the prognosis in patients with APE (16-18). The findings of these previous studies were consistent with our results; however, the reasons underlying the prognosis in patients with APE might be multifactorial, including cancer death (34). Although we believe that a poor improvement in the PAP itself leads to a poor prognosis in patients with high admission glucose levels, no previous studies have determined the precise hemodynamics using a PA catheter, as was done in the present study. To our knowledge, this is the first study to assess the precise hemodynamics repeatedly using a PA catheter to elucidate the predictors of improvement in the PAP in patients with APE. The present study did not have a large impact, but only a small impact on the clinical setting in terms of investigating the mechanism underlying the association between the admission glucose level and outcomes.

The admission glucose level is a predictor of mortality in various diseases (10-15). A high glucose level at admission reflects stress hyperglycemia caused by sympatheic nervous activity, which can trigger a hypercoagulable state and exacerbate the risk of overt thrombosis in some patients (35). In addition, hyperglycemia itself can induce thrombin activation, potentially inducing oxidative stress (36). The present study also demonstrated a negative correlation between the admission glucose level and the admission aPTT level, indicating that patients with a high admission glucose level were in a hypercoagulable status, as previously reported (23-25). Furthermore, hyperglycemia following hypoglycemia may activate thrombosis through oxidative stress production (37). These mechanisms might have caused a vicious cycle, leading to a poor improvement in PAP in patients with a high admission glucose level in the present study, although there
were no significant differences between the two groups in the severity of APE or PAP on admission.

**Study limitations**

Our study has several limitations. First, the present study included a small number of patients enrolled at a single center. Therefore, further studies are needed to draw definite conclusions. Second, we limited the present study patients to only those with submassive-type APE; however, which patients need IVCF insertion remains unclear, especially among those with submassive APE in the clinical setting. We therefore believe that our results have clinical significance. Third, we excluded patients on mechanical ventilation and hemodialysis; therefore, our results might not be applicable to those patients. However, it is difficult to precisely evaluate the data of PA catheterization in such patients.

**Conclusions**

The admission glucose level has a significant positive correlation with the percentage change in the PAPm. Furthermore, the admission glucose level is a predictor of the percentage change in the PAPm independent of diabetes mellitus, PAPm on admission, Tn positivity, and BNP level. The admission glucose level is associated with the improvement in the PAPm in patients with submassive-type APE.

The authors state that they have no Conflict of Interest (COI).

**References**

1. Barratt DW, Jordan SC. Clinical features of pulmonary embolism. Lancet 1: 729-732, 1961.

2. Nakamura M, Fujioka H, Yamada N, et al. Clinical characteristics of acute pulmonary thromboembolism in Japan: results of a multicenter registry in the Japanese Society of Pulmonary Embolism Research. Clin Cardiol 24: 132-138, 2001.

3. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. Eur Heart J 21: 1301-1336, 2000.

4. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 123: 1788-1830, 2011.

5. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 35: 3033-3069, 69a-69k, 2014.

6. Hashiba K, Okuda J, Maejima N, et al. Percutaneous cardiopulmonary support in pulmonary embolism with cardiac arrest. Resuscitation 83: 183-187, 2012.

7. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370: 1402-1411, 2014.

8. Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. N Engl J Med 326: 1240-1245, 1992.

9. Mismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. JAMA 313: 1627-1635, 2015.

10. Vendamuri S, Fulda GJ, Tinkoff GH. Admission hyperglycemia as a prognostic indicator in trauma. J Trauma 55: 33-38, 2003.

11. Mekazia A, Gayat E, Lassus J, et al. Association between elevated blood glucose and outcome in acute heart failure: results from an international observational cohort. J Am Coll Cardiol 61: 820-829, 2013.

12. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 355: 773-778, 2000.

13. Whitcomb BW, Pradhan EK, Pittas AG, Roghmann MC, Perencevich EN. Impact of admission hyperglycemia on hospital
Bozbay M, Uyarel H, Avsar S, et al. Admission glucose level predicts in-hospital mortality in patients with acute pulmonary embolism: experiences from the DIGAMI study. Cardiovasc Res 34: 248-253, 1997.

Bozbay M, Uyarel H, Avsar S, et al. Admission glucose level predicts in-hospital mortality in patients with acute pulmonary embolism who were treated with thrombolytic therapy. Lung 194: 219-226, 2016.

Scherz N, Labarere J, Aujesky D, Mean M. Elevated admission glucose and mortality in patients with acute pulmonary embolism. Diabetes Care 35: 25-31, 2012.

Tanabe Y, Obayashi T, Yamamoto T, Takayama M, Nagao K. Predictive value of biomarkers for the prognosis of acute pulmonary embolism in Japanese patients: results of the Tokyo CCU Network registry. J Cardiol 66: 460-465, 2015.

ICS Joint Working Group. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (ICS 2009). Circ J 75: 1258-1281, 2011.

Verstraete M, Miller GA, Bounameaux H, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation 77: 353-360, 1988.

Bottiger BW, Motsch J, Dorsam J, et al. Inhaled nitric oxide selectively decreases pulmonary artery pressure and pulmonary vascular resistance following acute massive pulmonary microembolism in piglets. Chest 110: 1041-1047, 1996.

Zarrabi K, Zolghadrasl A, Ali Ostovan M, Azimifar A, Malekmakan L. Residual pulmonary hypertension after retrograde pulmonary embolectomy: long-term follow-up of 30 patients with massive and submassive pulmonary embolism. Interac Cardiovasc Thorac Surg 17: 242-246, 2013.

Korte W, Clarke S, Lefkowitz JB. Short activated partial thromboplastin times are related to increased thrombin generation and an increased risk for thromboembolism. Am J Clin Pathol 113: 123-127, 2000.

Tripodi A, Chantarangkul V, Martinelli I, Bucciarelli P, Mannucci PM. A shortened activated partial thromboplastin time is associated with the risk of venous thromboembolism. Blood 104: 3631-3634, 2004.

Mina A, Favaloro EJ, Mohammed S, Kouats J. A laboratory evaluation into the short activated partial thromboplastin time. Blood Coagul Fibrinolysis 21: 152-157, 2010.

Fremont B, Pacouret G, Jacobi D, Puglisi R, Charbonnier B, de Labrille A. Prognostic value of echocardiographic right/left ventricular end-diastolic diameter ratio in patients with acute pulmonary embolism: results from a monocenter registry of 1,416 patients. Chest 133: 358-362, 2008.

Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141 (2 Suppl): e351S-e418S, 2012.

Bikdeli B, Wang Y, Minges KE, et al. Vena caval filter utilization and outcomes in pulmonary embolism: medicare hospitalizations from 1999 to 2010. J Am Coll Cardiol 67: 1027-1035, 2016.

Four-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d’Embolie Pulmonaire par Interruption Cave) randomized study. Circulation 112: 416-422, 2005.

Wallace MJ, Jean JL, Gupta S, et al. Use of inferior vena cava filters and survival in patients with malignancy. Cancer 101: 1902-1907, 2004.

Muriel A, Jimenez D, Aujesky D, et al. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. J Am Coll Cardiol 63: 1675-1683, 2014.

Constan tinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 106: 1263-1268, 2002.

Kucher N, Printzen G, Doernhoef er T, Windecker S, Meier B, Hess OM. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. Circulation 107: 1576-1578, 2003.

Meneveau N, Ming LP, Seronde MF, et al. In-hospital and long-term outcome after sub-massive and massive pulmonary embolism submitted to thrombolytic therapy. Eur Heart J 24: 1447-1454, 2003.

von Kanel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo. Eur J Haematol 65: 357-369, 2000.

Ceriello A, Giacomello R, Stel G, et al. Hyperglycemia-induced thrombin formation in diabetes. The possible role of oxidative stress. Diabetes 44: 924-928, 1995.

Ceriello A, Novials A, Ortega E, et al. Hyperglycemia following recovery from hypoglycemia worsens endothelial damage and thrombosis activation in type 1 diabetes and in healthy controls. Nutr Metab Cardiovasc Dis 24: 116-123, 2014.

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