Accuracy of Venous Filling Index on Standing (VFIst) and Pure Regurgitation Index (PRI), a Novel Index Obtained by Air Plethysmography, for Detecting Venous Reflux

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Objective: To evaluate the accuracy of venous filling index on standing (VFIst) and a new index named pure regurgitation index (PRI), obtained by air plethysmography, for detecting venous reflux.

Materials and Methods: One hundred and sixty-one healthy subjects (161 limbs) and 180 varicose vein patients (180 limbs) were investigated. All subjects underwent duplex ultrasonography for verifying venous reflux and air plethysmography to obtain hemodynamic parameters such as VFIst, VFI in the supine position (VFIsu), and the maximum arterial inflow rate. To evaluate the accuracy of VFIst and PRI (= (VFIst – VFIsu)/body mass index), receiver operating characteristics curves were created.

Results: The optimal cut-off value, sensitivity, specificity, and area under the curve, obtained from analyzing the receiver operating characteristics curves, of VFIst vs. PRI were 2.058 mL/s vs. 0.059 mL/m²/s·kg, 93.3% vs. 90.3%, 88.8% vs. 91.3%, and 0.954 vs. 0.964, respectively.

Conclusions: This study indicates that while both VFIst and PRI are highly accurate indicators of venous reflux, PRI, which is not affected by the arterial inflow rate and body mass index, is slightly superior to VFIst, especially in subjects with greater body mass index.

Keywords: venous filling index, pure regurgitation index, accuracy, air plethysmography, varicose veins

Introduction

Among the several parameters obtained by air plethysmography (APG), venous filling index on standing (VFIst) is considered an indicator for quantifying venous reflux. However, since VFIst is highly affected by the arterial inflow rate (AIR) and body mass index (BMI), it seems an insufficient indicator for quantifying venous reflux. With this in mind, the aim of this study was to create an original index, termed pure regurgitation index (PRI), which is not affected by AIR and BMI, and to evaluate and compare the accuracy of VFIst and PRI as indicators of venous reflux.

Materials and Methods

The normal group (NG) analyzed in this study comprised 161 ambulatory patients (161 right limbs; 37 men and 124 women; mean age [range], 63.3 [22–88] years) who visited the Shiraishi Vascular Surgery Clinic with various leg complaints from May 2012 to February 2015. These patients underwent physical examination, APG, and duplex ultrasonography (DS) to exclude arterial or venous diseases. Arterial disease was ruled out by palpation of the posterior tibial artery and dorsalis pedis artery. The absence of superficial and deep vein incompetence was verified using DS. The mean (range) BMI of the subjects was 23.6 (15.4–33.8) kg/m². The NG consisted of 32 patients who underwent varicose vein treatment for the left leg, 51 preoperative patients with saphenous type varicose vein in the left leg (no venous reflux in the right leg), 20 patients with orthopedic disease such as osteoarthritis, 33 patients experiencing leg dullness during standing work and evening edema, two patients with previous deep vein thrombosis in the left leg, 12 patients with metabolic syndrome, and 11 patients with only telangiectasias in the right leg. None of the patients had a history of deep vein thrombosis in the right leg.

Another 180 patients with unilateral axial reflux in the great saphenous vein assessed by DS were selected and defined as the varicose vein group (VG). The absence of arterial disease was verified by artery palpation. The VG included 180 patients (180 limbs; 70 men and 110 women; mean age [range], 67.9 [32–92] years; mean [range] BMI, 23.8 [16.5–38.9] kg/m²). There was no significant difference in age or BMI between the NG and VG (Table 1).
To evaluate the hemodynamic function and anatomical findings of the lower extremities, APG and DS were performed by a well-trained technologist at the first visit to our clinic in the NG, and before treatment in the VG. Oral informed consent was obtained from all patients before undergoing the noninvasive evaluations.

**Duplex ultrasonography**

All subjects were examined for chronic vein insufficiency using DS (HIVISION Avius; Hitachi, Japan). Evaluation of valve competence was performed with the squeezing maneuver. Reflux flow by squeezing the calf, persisting for more than 0.5 s, indicated venous incompetence.

**Air plethysmography**

Volume changes of the lower limbs were recorded with APG (APG-1000; ACI Medical LLC, San Marcos, CA, USA). The subjects were asked to rest in the supine position for 10 min. Subsequently, the subjects were placed in the supine position with the test leg (right leg in the NG and affected limb in the VG) externally rotated and enclosed from the ankle to knee in a 27.5-cm polyurethane sensing cuff, while the foot was elevated 15 cm and rested on a foam block with the knee slightly bent. A 10-cm wide pneumatic tourniquet was placed just proximal to the knee and connected to a rapid inflator (Venapulse® ACI Medical LLC). After calibration, the tourniquet was rapidly inflated to 70 mmHg. Increasing volume tracing was observed and gradually reached a stable plateau. The AIR was calculated from the linear slope of the volume just after tourniquet inflation. The venous filling index in supine position (VFIsu) was calculated by dividing the 90% venous volume by the 90% venous filling time.

**Pure regurgitation index (PRI)**

Since VFIsu is calculated as the sum of the venous regurgitant flow rate and arterial inflow rate, which are affected by BMI, our novel index for quantifying pure venous reflux, described below, was created. Since the venous filling rate is considered to be affected by venous tone and venous volume, VFIsu, which indicates the overall arterial inflow rate, was used instead of maxAIR.

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\text{Pure Regurgitation Index (PRI)} = \frac{(VFIsu - VFIsu)}{\text{BMI}} \ (\text{mL} \cdot \text{m}^2/\text{s} \cdot \text{kg})
\]

**Accuracy of VFIsu and PRI as indicators of venous reflux**

To evaluate the accuracy of VFIsu and PRI as indicators for venous reflux, the optimal cut-off values, sensitivities, and specificities were determined by analyzing receiver operating characteristic (ROC) curves for the NG (gold standard reflux negative) and VG (gold standard reflux positive).

Further, concerning the influence of BMI on the accuracy of VFIsu and PRI, 20 cases each with the highest, intermediate, and lowest BMI values from the NG and VG were extracted and defined as G1, G2, and G3, respectively, and the sensitivity and specificity of VFIsu and PRI for detecting venous reflux were calculated for each group (G1–G3) based on the optimal cut-off value for each group.

**Statistical analysis**

Data were entered into a Microsoft Excel® spreadsheet. The paired or unpaired t-test was used for the statistical analyses by using ystat2013.xls, which is a type of Excel® file. A P value less than 0.01 was considered statistically significant. ROC curves were created and analyzed using EZR™ (Easy R) (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Characteristics of the hemodynamic parameters in the NG**

The mean values (range) of maxAIR, VFIsu, and VFIsu were 1.16 (0.20–3.41) mL/s, 1.426 (0.300–5.19) mL/s, and 0.74 (0.03–2.53) mL/s, respectively. A very strong correlation was observed between maxAIR and VFIsu (r = 0.95),
Since the main purpose of the treatment for varicose veins is to prevent venous reflux, it is necessary to accurately evaluate the amount of venous reflux for assessing the outcome of the treatment. Although VFInst has been considered an index of venous reflux, the accuracy of this index for detecting reflux has not been investigated yet. In addition, we have previously reported that increasing AIR leads to increasing VFInst, which may cause false positive results in detecting venous reflux.

Great VFInst without venous reflux is sometimes observed in patients with inflammation due to infection or non-bacterial cellulitis, and in obese patients. Our results regarding the relationship between hemodynamic parameters in the NG indicate that VFInst needs to be corrected by BMI and AIR in order to assess the pure amount of regurgitation. Thus, a new index of PRI was created.

Figure 4 shows the distribution of sensitivity and specificity for each extracted group (G1–G3) calculated based on the optimal cut-off value. The mean (range) BMIs (kg/m²) of the NG and VG in G1, G2, and G3 were 18.1 (15.4–19.5) vs. 18.3 (16.5–19.5), 23.0 (22.6–23.5) vs. 23.4 (23.0–23.8), and 30.2 (28.1–33.8) vs. 31.0 (28.0–38.9), respectively. There were no significant difference in BMI between the NG and VG except in G2 (p <0.001). Although both the sensitivity and specificity of PRI were over 80%, the specificity of VFInst was markedly reduced to 70% in G3.

### Discussion

Since the main purpose of the treatment for varicose veins is to prevent venous reflux, it is necessary to accurately evaluate the amount of venous reflux for assessing the outcome of the treatment. Although VFInst has been considered an index of venous reflux, the accuracy of this index for detecting reflux has not been investigated yet. In addition, we have previously reported that increasing AIR leads to increasing VFInst, which may cause false positive results in detecting venous reflux.

Great VFInst without venous reflux is sometimes observed in patients with inflammation due to infection or non-bacterial cellulitis, and in obese patients. Our results regarding the relationship between hemodynamic parameters in the NG indicate that VFInst needs to be corrected by BMI and AIR in order to assess the pure amount of regurgitation. Thus, a new index of PRI was created.

It has been previously reported by other investigators that the arterial inflow rate depends on the size of the leg. However, although it is reasonable to correct the VFInst, VFIsu, and maxAIR according to the leg size, the exact size at any given time depends on the posture of the subject,
Fig. 2 Correlations between various parameters in the normal group. maxAIR, VFIst, and VFIsu showed very strong correlations with each other (top) and strong correlations with BMI (bottom). maxAIR: maximum arterial inflow rate; VFIst: venous filling index on standing; VFIsu: venous filling index in supine position; BMI: body mass index

Fig. 3 Dot charts of VFIst (left) and PRI (middle) in the normal group (NG) and varicose vein group (VG). The respective mean values are connected by the dotted line. Receiver operating characteristics curve (right): Dots A and B indicate the optimal cut-off values for VFIst (2.058 mL/s) and PRI (0.059 mL · m²/s · kg), respectively. VFIst: venous filling index on standing; PRI: pure regurgitation index
and measuring the actual size of the leg is difficult. On the other hand, BMI, which is not affected by posture, is easy to measure and is a more versatile indicator than leg size for representing physique. In our previous study, higher correlation coefficient values were found among VFIst, VFIsu, maxAIR, and BMI compared to body surface area; thus, in the present study, BMI was used for correction rather than the size of the leg.

To compare the accuracy of the two indices, ROC curves were created using EZR. The ROC curve is known as a fundamental tool for diagnostic and/or index parameter evaluations. In ROC curves, the true positive rate, which is known as sensitivity, is plotted as a function of the false positive rate, which can be calculated as (1 – specificity), at various threshold settings. The AUC value is considered to indicate the diagnostic performance of a certain parameter for a disease. The comparison of two AUCs induced from ROC curves is a useful means for determining the superiority of two different indicators. AUC values over 0.9 indicate high accuracy; although our results suggested that both VFIst and PRI show high accuracy to detect venous reflux, the AUC of VFIst was slightly lower than that of PRI, which is considered to be caused by the low specificity of VFIst in cases of great BMI, such as in G3 in this study.

Although some investigators have reported that the clinical severity of varicose vein legs depends on increasing venous reflux flow, as assessed by VFIst, considerable overlap of the VFIst values is found between the clinical classifications. Welkie et al. described that once brawny edema and hyperpigmentation occur, ulceration generally develops without additional deterioration of the venous hemodynamics. In fact, varicose vein legs with skin lesions but without much venous regurgitation are often found. Hence, since the involvement of increased arterial inflow has been pointed out as a factor associated with worsening of venous congestive syndrome, it is important to remove the effect of the arterial inflow rate from VFIst to investigate the relationship between the amount of venous reflux and clinical severity. We are currently investigating this problem further using PRI instead of VFIst. These results will be reported in the near future.

**Limitations**

Although there are differences in the arterial inflow rate and venous tone of the lower extremities between the supine position and on standing, we assumed that there was no major difference in these values in the present study, and this may be a potential limitation. In Fig. 2, the difference in the incline between the two graphs is likely caused by the difference of posture and how the load was applied. Although both the VFIsu and maxAIR were measured under a load of constant pressure (70 mmHg) in the supine position, the VFIst was measured under hydrostatic pressure due to gravity on standing. Since it is impossible to measure the arterial inflow rate by the venous obstruction method on standing, such a difference in incline seems unavoidable.

In this study, all subjects in the VG had axial reflux in the great saphenous vein, with or without reflux in the deep vein and back flow from an insufficient perforator. Conversely, all subjects in the NG had no reflux anywhere in the low extremities. Since VFIst and PRI are used for assessment of the total amount of venous regurgitation flow in the calf on standing, I believe that the main issue is not the location of the valve insufficiency but rather whether there is regurgitation or not. Hence, I did not mention Boyd’s and Cockett’s perforators in the present study.

**Conclusion**

A new index for detecting venous reflux, named Pure Regurgitation Index (PRI), was created. According to the ROC curve analyses, even though VFIst and PRI both showed high accuracy, PRI, which is not affected by the AIR and BMI, is recommended for use as an indicator of venous reflux for the diagnosis and assessment of hemodynamic venous function.

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**Disclosure Statement**

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