Clinical Trial/Experimental Study

Medicine

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Pilot study on the effect of grape seed proanthocyanidin extract on inferior vene cava blood flow in patients with chronic venous insufficiency using 4D flow MRI

Hyuk Jae Jung, MD, PhD[a], Ki Seok Choo, MD, PhD[b]

Abstract

Background: Four-dimensional (4D) flow magnetic resonance imaging (MRI) was used to objectively assess changes in blood flow velocity in patients with chronic venous insufficiency (CVI) who underwent stocking treatment alone and stocking combined with Grape seed proanthocyanidin extract (GSPE) treatment.

Methods: Patients diagnosed with CVI were recruited from August 31, 2018 to December 31, 2020. A total of 23 participants were selected, with 10 and 13 patients in the stocking treatment and stocking + GSPE treatment groups, respectively. The blood flow velocity (Th-plane peak and average velocities) was calculated using 4D flow MRI. A paired *t* test was used to evaluate the differences in blood flow velocity before and after treatment.

Results: In the stocking treatment group, The Th-Plane peak velocity increased by 2.48 ± 5.05 cm/s after treatment ($P = .16$). In the stocking + GSPE treatment group, the Th-Plane peak velocity increased by 4.85 ± 5.57 cm/s after treatment ($P < .001$).

Conclusion: The blood flow velocity on 4D flow MRI was significantly increased in participants who underwent GSPE, highlighting the potential of GSPE for CVI treatment.

Abbreviations: 2D = 2-dimensional, 3D = 3-dimensional, 4D = 4-dimensional, CVI = chronic venous insufficiency, GSPE = grape seed proanthocyanidin extract, IVC = inferior vena cava, MRI = magnetic resonance imaging.

Keywords: chronic venous insufficiency, 4-dimensional flow magnetic resonance imaging, grape seed proanthocyanidin extract

1. Introduction

Chronic venous insufficiency (CVI) is characterized by persistent ambulatory venous hypertension that affects the venous system of the lower extremities. The condition causes various pathologies, including pain, edema, skin changes, and ulcers,[1] as well as symptoms of telangiectasias (or spider veins), reticular veins, varicose veins, edema, pigmentation, eczema, lipodermatosclerosis, atrophie blanche, and venous ulceration.[2] Although the prevalence of CVI varies depending on the study population, anomalies of the lower extremity veins can be observed in approximately 50% of adults.[3–5] This not only generates high medical costs, but also negatively impacts the quality of life of affected individuals.[6,7] Risk factors for CVI include advancing age, family history of the disease, prolonged standing, obesity, smoking, sedentary lifestyle, lower extremity trauma, prior venous thrombosis, presence of an arteriovenous shunt, high estrogen levels, and pregnancy.[3,8,9] The prevalence of CVI in Korea is expected to increase due to underdiagnosis, increased prevalence of obesity, and aging of the population.[2] Currently, CVI is mainly diagnosed using ultrasound methods,[10] with reflux of ≥0.5 second in the superficial vein and ≥1 second in the deep vein. Nevertheless, an accurate diagnosis remains a challenge, as it is dependent on the equipment used as well as the experience of the operator and the clinician interpreting the results, and the subjective experiences of patients.[11]

Recently, a time-resolved 3-dimensional (3D) MRI called phase-contrast magnetic resonance imaging and 4-dimensional (4D) flow MRI have been developed and widely used for the clinical evaluation of blood flow.[12,13] This 3D measurement technique can assess the entire cardiovascular system, quantify the volume of blood flow at any angle, and conduct a retrospective

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analysis.[14] Unlike conventional 2-dimensional (2D) phase-contrast MRI, wherein precise selection of the plane is of crucial importance, 4D flow MRI can measure the entire vascular system simultaneously and perform a retrospective analysis.[15]

Vitis vinifera is a flavonoid polyphenolic compound extracted from grape seeds,[16] frequently called "Grape seed proanthocyanidin extract (GSPE)." Various effects of GSPE have been reported, such as the protection of early cerebrovascular injury caused by hypertension,[17] antioxidant activity, reduction of inflammation, inhibition of the progression of diabetic retinopathy,[16,18] and improvement of vascular elasticity.[19] In addition, Entelon® (Hanlim Pharm Co. Ltd, Seoul, Korea) is a GSPE-based venoactive drug available in Korea for the improvement of symptoms related to CVI.[20,21] GSPE increases venous tone and improves capillary hyperpermeability, fibrinolysis, and lymph and blood flow, thereby inhibiting leukocyte adhesion to endothelial cells and the transmigration of leukocytes into the venous wall.[20,21]

Therefore, this study used 4D flow MRI to objectively evaluate improvement in blood flow velocity in patients with CVI receiving GSPE-based treatment. To date, previous studies on the objective evaluation of patients with CVI have not reached uniform conclusions. This study used 4D flow MRI to compare changes in blood flow velocity before and after intervention between a group that underwent treatment with stockings alone and that which received GSPE in addition to stocking treatment.

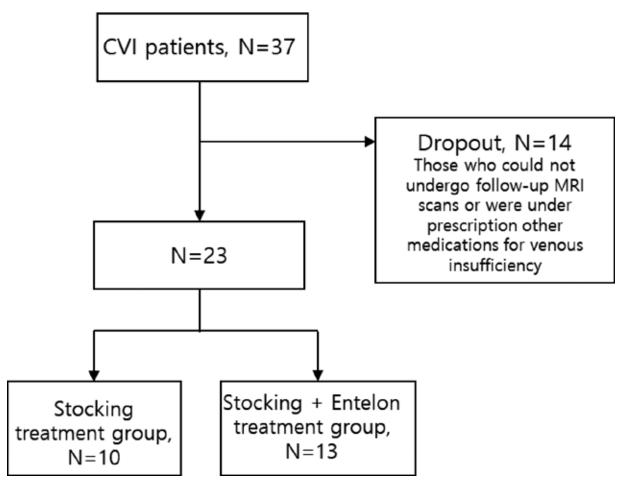

Figure 1. Flow chart for the selection of study participants. CVI = chronic venous insufficiency, MRI = magnetic resonance imaging.

2. Methods

2.1. Study participants

This prospective study was conducted on patients diagnosed with CVI with deep vein thrombosis and superficial vein regurgitation on Doppler ultrasonography after visiting the vascular surgery department between August 31, 2018 and December 31, 2020. Written consent was obtained from each study participant, and MRI scans were performed before and 90 days after treatment for comparative analysis. Those who could not undergo follow-up MRI or were prescribed other medications for venous insufficiency were excluded. The participants were randomly assigned to either the stocking treatment (20–40 mm Hg, below the knee stocking) or the stocking + GSPE treatment (150 mg bid.) groups using a random number table. A total of 14 of the 37 participants who dropped out of the study were excluded. Ultimately, 23 participants were included in the final analysis, with 10 and 13 participants in the stocking treatment and stocking + GSPE treatment groups, respectively (Fig. 1).

2.2. Measurement of blood flow velocity

To measure the blood flow velocity of the inferior vena cava (IVC), an 18-channel body coil was used in a MAGNETOM Skyra 3T MRI (Siemens Healthcare GmbH, Erlangen, Germany), and cross-sectional 3D phase-contrast images perpendicular to the IVC blood flow direction were obtained. The image parameters were as follows: time to repeat = 5.5 msec, time to echo = 3.9 msec, flip Angle = 7°, number of excitation = 2, field of view = 285 × 380 mm, acquisition matrix = 84 × 160, slice thickness = 2.5 mm, and receiver bandwidth = 495 Hz/pixel. Velocity encoding was set in the range of 30–40 cm/s to eliminate aliasing artifacts and was applied in all directions of the x-, y-, and z-axes. During the scan, 11 to 12 frame images were acquired for every cycle, with a time resolution of 50 to 55 msec, using prospective gating that was synchronized to the peripheral pulse, and the scan time was 12 to 14 minutes depending on the patient's cardiac cycle (Fig. 2). The acquired data were analyzed using prototype software (4D Flow version 2.4, Siemens Healthcare GmbH, Erlangen, Germany). A section through

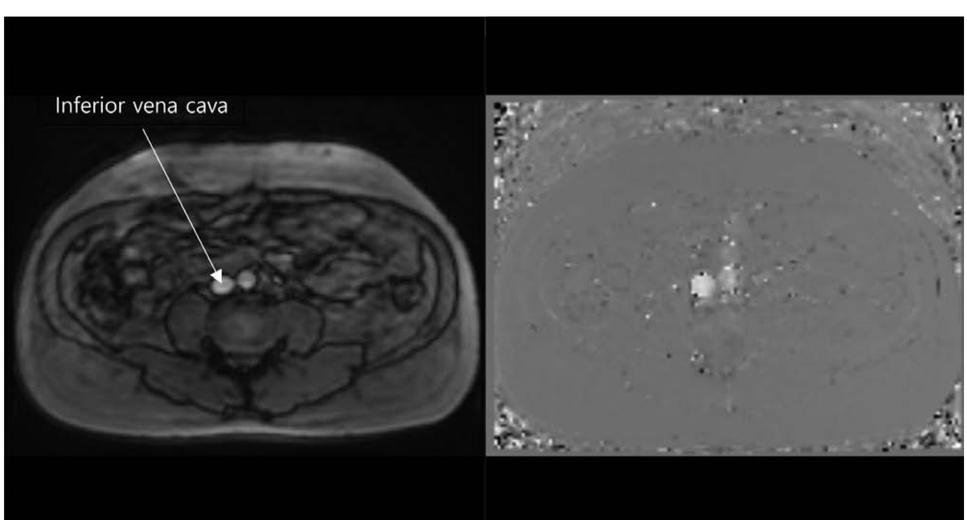

Figure 2. The image plane in the infrarenal Inferior Vena Cava (left: magnitude image; right: velocity image).

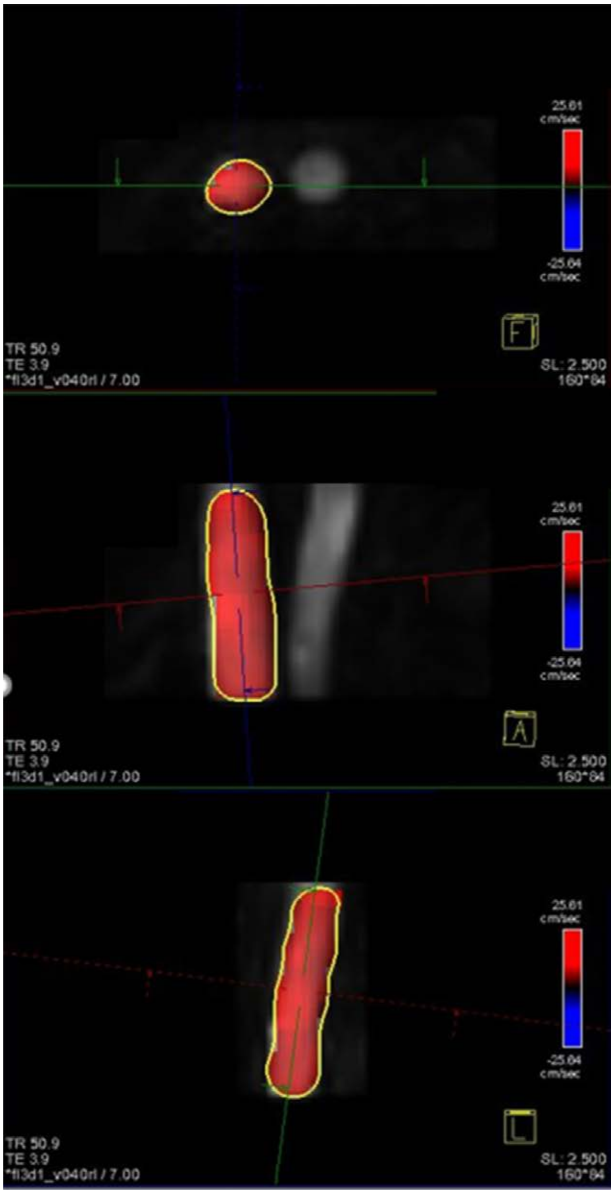

Figure 3. Vessel segmentation and region of interest (ROI) selection for 4D analysis. 4D = 4-dimensional.

which blood flow passed through the IVC was selected to calculate the flow rate and 4-pixel averaged peak velocity (Fig. 3).

2.3. Definition of variables

The main outcome variable was blood flow velocity, which was assessed before and 90 days after treatment. The blood flow velocity was defined as the "Th-plane peak velocity," which is the velocity at the pixel of the maximum peak velocity in a cross-sectional curve. Th-plane peak velocity and the mean velocity of the surrounding 4 pixels were defined as the Th-plane average velocity. The demographic characteristics of the participants, including sex, age, height, weight, family history, history of surgery, and history of pregnancy, were assessed.

2.4. Statistical analysis

In general, the continuous variables are presented as means and standard deviations. The categorical variables are presented as the number of participants (N) and frequencies (%). A paired *t* test or Wilcoxon signed-rank exact test was conducted to evaluate differences in blood flow velocity before and after treatment in each group. All statistical analysis was performed using the statistical software R, version 4.1.0, and a $P < .05$ was considered statistically significant.

This study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB No. 04-2018-020), and written consent was obtained from all participants before their enrollment.

3. Results

Table 1 presents the demographic characteristics of the study participants. The mean age of the participants was 56.83 years, and there were more women (15 participants; 65.22%) than men (8 participants; 34.78%). Though the demographic characteristics between stocking treatment group and stocking + GSPE treatment group were compared, there was no statistically significant difference.

The Th-Plane peak velocity was increased by 2.48 ± 5.05 cm/s in the stocking treatment group after treatment ($P = .16$). In the stocking + GSPE treatment group, the Th-Plane peak velocity was increased by 4.85 ± 5.57 cm/s ($P < .001$). The Th-Plane average velocity was increased by 1.26 ± 3.17 cm/s in the stocking treatment group after treatment ($P = .24$). In the stocking + GSPE treatment group, the Th-Plane average velocity was increased by 1.92 ± 2.52 cm/s ($P < .01$). Intragroup comparison

Table 1

Demographic characteristics of the study participants.

	All	Stocking treatment group	Stocking + Entelon® treatment group	*P* value*
n	23	10	13	
Sex				
Men	8 (34.78)	2 (20.00)	6 (46.15)	.682**
Women	15 (65.22)	8 (80.00)	7(53.85)	
Age	56.83 ± 9.26	56.20 ± 10.69	57.31 ± 8.42	.783†
Height (cm)	164.68 ± 7.44	163.39 ± 6.84	165.68 ± 8.00	.478†
Weight (kg)	71.37 ± 12.49	67.97 ± 11.20	73.99 ± 13.22	.251‡
Family history (yes)	7 (30.43)	2 (20.00)	5 (38.46)	.405**
History of surgery (yes)	2 (8.70)	1 (10.00)	1 (7.69)	1.000**
History of pregnancy (yes)	15 (65.22)	8 (80.00)	7 (53.85)	.379**

*Stocking treatment group versus Stocking + Entelon® treatment group.
**Fisher's Exact test.
†Independent *t* test.
‡Mann–Whitney *U* test.

Table 2

Comparison of the average blood flow velocity before and after treatment in each group.

	Treatment group	Before treatment	After treatment	Change rate	*P* value*
Th-plane peak velocity	Stocking treatment group (n = 10)	18.77 ± 5.27	21.26 ± 5.45	2.48 ± 5.05	.16
	Stocking + Entelon® treatment group (n = 13)	16.86 ± 3.62	21.71 ± 6.65	4.85 ± 5.57	<.001
Th-plane average velocity	Stocking treatment group (n = 10)	13.20 ± 4.87	14.46 ± 4.51	1.26 ± 3.17	.24
	Stocking + Entelon® treatment group (n = 13)	11.17 ± 2.26	13.09 ± 2.97	1.92 ± 2.52	<0.01

*Paired *t*-test or Wilcoxon signed rank exact test.

of blood flow velocity before and after treatment showed that blood flood velocity was significantly increased in the stocking + GSPE treatment group after intervention (Table 2).

4. Discussion

This study compared differences in blood flow velocity before and after treatment in patients exhibiting CVI who received stocking treatment with those who received adjunct treatment with GSPE. The Th-plane peak and average velocities were compared before and after treatment in each group. In the stocking treatment group, the Th-Plane peak and average velocities increased following treatment; however, the increase was not significant. In the stocking + GSPE treatment group, the Th-Plane peak and average velocities increased following treatment, and these changes were statistically significant.

The main pathophysiology of CVI is an increase in the venous pressure in the lower extremities. The main causes of increased venous pressure include venous valve insufficiency, outflow venous obstruction, and insufficient muscle contractility.[22] Venoactive drugs mainly used in CVI treatment include Flavonoids (gamma-micronized benzopyrons), Alpha-benzopyrons, Saponins, Other plant extracts, and Synthetic products.[23] The main mechanisms of action of venoactive drugs derived from natural synthetic extracts are increased tension of the venous wall and reduced edema and pain.[24] Previous studies have reported the efficacy of various therapeutic agents,[25–27] and CVD treatment guidelines also recommend venoactive drug therapy for patients with C0s-C6 of the clinical etiologic anatomic pathophysiological (CEAP) classification.[23,28,29] Among them, GSPE is a type of flavonoids (gamma-micronized benzopyrons), which is recommended as Grade C in 2005 and 2008 guidelines for the management of CVDs of the lower limbs according to the action of reducing capillarity permeability and free radical scavengers.[23] In a previous study, GSPE demonstrated an improvement in CVI symptoms,[30] and it has also shown to improve symptoms of edema by reducing capillar permeability.[31,32] In our study, blood flow velocity significantly increased after treatment with GSPE.

In clinical practice, 4D flow MRI is used to visualize patterns of large and hepatic artery blood flow.[12,13] This study attempted to objectively evaluate CVI using 4D flow MRI and quantitatively measure blood flow velocity at an accurate location in the blood vessels, which is not possible using conventional 2D MRI. The flow rate was calculated by multiplying the cross-sectional area of the blood vessel by the blood flow velocity. However, the cross-sectional shape and size of the IVC before and after treatment are not identical in some patients. A previous study reported that IVC diameter reflects changes related to intrathoracic, abdominal, and central venous pressure.[33] Therefore, in this study, the Th-plane peak velocity, which shows the highest blood flow velocity within the diameter without being affected by the cross-sectional value, was used instead of the flow rate. In addition, the Th-plane average velocity, which can reduce the variation in measurements while reflecting more pixels, was also calculated (Fig. 4). As a result, the blood flow velocity significantly increased after treatment in the GSPE-treated group.

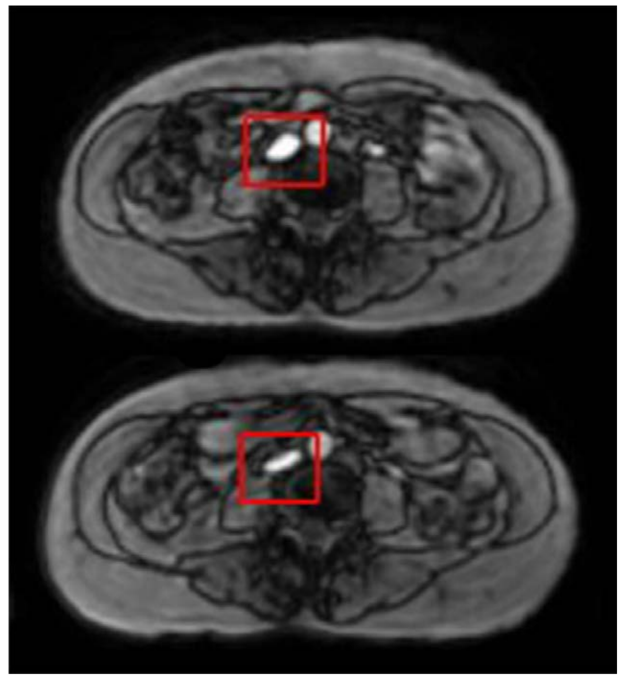

Figure 4. Differences in cross-sectional shapes and sizes of Inferior Vena Cava (top: before treatment; bottom: after treatment).

This study has limitations. First, the sample size of the participants in this study was rather small, which may have affected the reliability of the results. However, this is an inevitable limitation of pilot studies. Although the difference in the change in blood flow velocity between the 2 groups was large, there was no statistically significant difference observed in this study. This could be attributed to the small number of participants. However, the novelty of the current study lies in the evaluation of the increase in blood flow velocity as an improvement in venous function using 4D flow MRI in patients with CVI, who are typically diagnosed using inaccurate ultrasound. A second limitation is that there is no direct evidence that GSPE improves blood flow. However, it can be inferred that GSPE can indirectly improve blood flow and contribute to improving symptoms in patients with CVI, as studies have shown improvements in lymph circulation, volume, and symptoms of lymphedema.[34]

5. Conclusion

This is the first study to quantitatively evaluate the increase in blood flow velocity using 4D flow MRI in patients with CVI. In the stocking + GSPE group, the blood flow velocity of the participants significantly increased after treatment, suggesting that GSPE can improve venous function in patients with CVI. Therefore, a larger-scale follow-up study of venous function in patients with CVI using 4D flow MRI is necessary to confirm our initial findings.

Author contributions

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Writing – original draft: Hyuk Jae Jung, Ki Seok Choo.
Writing – review & editing: Hyuk Jae Jung, Ki Seok Choo.

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