Saphenous Vein Valves Assessment Utilizing Upright CT. -Potentially Improve the Graft Assessment for Bypass Surgery-

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Abstract

The saphenous veins (SV) are frequently employed as bypass grafts. The SV graft failure is predominantly seen at the valve site. Avoiding valves during vein harvest would help reduce graft failure. We endeavored to detect SV valves, tributaries, and vessel size employing upright CT for the raw cadaver venous samples and in healthy volunteers.

Five cadaver legs were scanned. The anatomical analysis showed 3.0 (IQR: 2.0-3.0) valves and 13.50 (IQR: 10.00-16.25) tributaries. The upright CT completely detected, compared to 2.0 (IQR: 1.5-2.5, p=0.06) valves and 9.5 (IQR: 7.5-13.0, p=0.13) tributaries by supine CT.

From a total 190 volunteers, 138 (men:75, women:63) were included. The number of valves from the SF junction to 35 cm were significantly higher in upright CT than in supine CT bilaterally [upright vs. supine, Right: 4 (IQR: 3-5) vs. 2 (IQR:1-2), p<0.0001, Left: 4 (IQR: 3-5) vs. 2 (IQR: 1-2), p <0.0001]. The number of tributaries and vessel area was also higher for upright compared with supine CT.

Upright CT enable detection of SV valves, tributaries, and vessel size non-invasively. Although not tested here, it is expected that upright CT might potentially improve the graft assessment for bypass surgery.

Introduction

For decades, the saphenous vein (SV) has served as the most reliable bypass conduits for coronary and peripheral artery revascularization. Over 250,000 coronary artery bypass grafts and over 80,000 lower extremity vein grafts are performed annually in the United States alone [1]. The average rate of CABG has been reported to be 44 per 100,000 individuals [2], and almost 80% of bypass grafts include saphenous veins (SV) [2,3]. However, the SV graft failure during the follow-up is not uncommon [3,4] wherein most stenotic lesions are focal and often occur either at the valve sites or anastomotic regions [5-7]. Therefore, it has been proposed that not including the venous samples with valve sites may reduce the SV graft failure.

The valves of venous systems with venous muscle pumps allow the blood to return to the heart against gravity, and generally demonstrate expansion at the valve site during upright position [8]. We have developed an upright CT (Figure.1 A, B) to negate the postural effect of gravity and render the clinical imaging as close to physiology as possible [9-11]. Employing the upright CT, we aimed to detect SV valves, tributaries and venous area compared with standard supine CT imaging.

Materials And Methods

Cadaver study. Cadaveric specimens were obtained from the Willed Body Program (Department of Anatomy, Keio University School of Medicine) and were investigated in accordance with institutional regulations. Lower extremities, with no scars and no signs of vascular disease, were obtained from raw cadavers. Lower extremities were disarticulated at the hip joint and the external iliac artery, external iliac vein and the surrounding soft tissue remained attached to the specimens. The distal position of saphenous vein was cannulated with 22-Gauze catheter at above ankle level and phosphate buffered saline (PBS) with 10% polyethylene glycol [12] was infused during the scan to reproduce the venous reflex. The CT images were acquired as *ex-vivo* imaging of the disarticulated leg. Thereafter, the leg specimens were fixed in formaldehyde and the saphenous vein was dissected and made a long single incision along the venous path from the cannulation point to the saphenous-femoral junction (SF junction) (Supplemental Figure.1). The SV valves and tributaries positions were anatomically identified as the reference standard for CT images.

Volunteer study. The volunteer prospective study was approved by the institutional review board (Keio University Independent Ethics Committee) (Clinical Trail number: UMIN000026586), and written informed consent was obtained from all participants. Healthy volunteers were recruited from a volunteer recruitment company from July 2017 to March 2019; volunteers of over 30 years of age were requested so that they could understand the purpose of the study. Individuals with a history of hypertension, dyslipidemia, diabetes, smoking, or those who had previously undergone cardiac surgery or were currently receiving treatment were excluded.

Image acquisition. A conventional 320-detector row CT (Aquilion ONE, Canon Medical Systems Corporation, Otawara, Japan) was prospectively performed for all volunteers in the supine position. In addition, and upright CT (prototype TSX-401R, Canon Medical Systems Corporation, Otawara, Japan) [9] was performed in standing position immediately after the conventional procedure. The upright and conventional supine CT scanners were next to each other, and the two examinations were consecutively performed. The upright CT system is characterized by up-and-down movements of a transverse 320 row-detector gantry (isotropic 0.5 mm in detector size), with a bore size of 780 mm, a gantry rotation speed of 0.275s, maximum vertical speed of 100 mm/s, and a 1200 view at optimal performance. Scanning was performed at 100kVp and a gantry rotation speed of 0.5s in the helical scan mode (80-row detector), with a noise index of 24 and helical pitch of 0.8 for the body trunk from the level of superior margin of the external acoustic meatus to the lowest position of the upright CT (37 cm height).

For cadaver study, cadaver legs were placed in plastic moulds and scanned whole samples in both supine and upright CT scanners. The plastic box containing the sample was fixed on a pedestal (42 cm height) and tube current for scanning was set as approximately 600mA to compensate the noise from the fixtures.

Image reconstruction was performed using Adaptive Iterative Dose Reduction 3D (Canon Medical Systems Corporation, Otawara, Japan), which could reduce the radiation dose.

Image analysis. CT images were transferred to an off-line workstation (SYNAPSE VINCENT, FujiFilm, Tokyo, Japan) and multiplanar reconstruction (MPR) images were developed from the SF junction of saphenous vein both for cadaveric images and clinical images. The position and number of valves were counted visually. Simultaneously, the vessel area in cross-sectional images was measured to calculate dilation ratio (vessel area at valve /vessel area at reference segments). The reference segments were set at the average of the vessel area of proximal and distal position of the valves. The dilation ratio was derived in the cadaveric study and applied for the volunteer study to study the valves. The number of tributaries were counted visually. The vessel area was measured of the cross-section image on the 15cm from the SF junction were measured. For cadaveric study, two observers analyzed the data with consensus reading. For volunteer study, all measurements were performed in a blinded and randomized manner.

Statistical analysis. Intra-observer and inter-observer variability for the assessment of valves, tributaries, and cross section measurements were examined using Bland-Altman analysis and Pearson's correlation. Data were presented as median (interquartile range [IQR]; i.e., 25th to 75th percentile, or Q1, Q3). Continuous data were compared using Wilcoxon rank sum test between the 2 groups. The Spearman Rank Correction coefficient test was used for the assessment of linear correlation of 2 parameters. A 2-sided $p < 0.05$ was considered statistically significant. All analyses were performed using SAS software, version 9.4. (SAS Institute Inc., Cary, North Carolina).

Results

Cadaver study. Five legs were dismembered from cadavers (age range,78-93 years, mean 88.4±6.0 years, 4 left and 1 right leg, 4 female and 1 male). On visual assessment 3.0 (IQR 2.0-3.0) valves and 13.50 (IQR 10.00-16.25) tributaries were observed in SV (Figure. 1 C-E).

The upright CT images accurately identified the valves and tributaries; the identification was difficult by the conventional supine CT. The upright CT image showed 3.0 (IQR 2.0-3.0) valves and 13.50 (IQR 10.00-16.25) tributaries, while supine CT image showed 2.0 (IQR 1.5-2.5, p= 0.06) valves and 9.5 (IQR 7.5- 13.0, p= 0.13) tributaries; given a small sample size the difference however was not statistically significant. The expansive venous diameter at the valve site (referred to as dilation ratio) in the upright CT images was 1.56 (IQR 1.44-1.83, range 1.20-4.24), and the minimum dilation ratio of "1.20" was used to confirm the valve site in the volunteer images.

Volunteer study. Of 190 volunteers, 38 who received the scan with 120KV were excluded; another 14 volunteers were excluded where complete CT data from the SF junction to 35 cm could not be obtained due to the short stature. We report the CT characteristics of SV from 138 volunteers (men 75, women 63) who completed the study (Table.1).

Firstly, 40 CT leg images from 10 consecutive volunteers, both sides and both supine and upright positions, were analyzed by two observers; high intra-/inter- observer agreement was noted (Supplemental Figure 2, 3 and 4). The upright images allowed identification of the valves and tributaries (Figure. 2). It was difficult to characterize valves and tributaries in supine CT images similar to cadaveric study.

The number of valves were significantly higher in upright CT than in supine CT on both sides [upright right side: 4 (IQR: 3-5) vs. supine right side: 2 (IQR: 1-2), $p< 0.0001$, upright left side: 4 (IQR: 3-5) vs. supine left side: 2 (IQR: 1-2), $p< 0.0001$] (Figure.3A and B). The dilation ratio at the valve site was 1.85 (IQR 1.57-2.25). The frequency of valve distribution was maximum between 0 to 5 cm from the SF junction, followed by 5 to 10 cm from the SF junction (Figure.3C).

The number of tributaries was also higher in the upright CT compared with the supine CT [upright right: 12 (IQR: 10-15) vs. supine right:11 (IQR: 9-13), $p< 0.0001$; upright left: 12 (IQR: 9-14) vs. supine left:11 (IQR: 9-13), $p< 0.0001$] (Figure.4A).

The area of cross section image at 15 cm from the SF junction was larger in the upright CT [upright right side: 14 (IQR: 11-17) mm^2 vs. supine right: 12 (IQR: 9-16) mm^2, $p< 0.0001$; upright left: 14 (IQR: 11-18) mm^2 vs. supine left:12 (IQR: 9-15) mm^2, $p< 0.0001$] (Figure.4B).

Discussion

This study showed that the SV valves were clearly visualized in the standing position utilizing upright CT both in cadaveric legs and *in-vivo* study of healthy volunteers. In the cadaver study, SV valves and tributaries identified by upright CT were confirmed by anatomical analysis. The minimum dilation ratio of "1.20" was found to be the cut-off point to define the level of the valve to confirm the valve site in the *in-vivo* study. In the volunteer study, upright CT detected larger number of valves and tributaries and larger size of vessel area comparison with supine CT. We propose that upright CT could have an advantage for SV characterization prior to bypass surgeries.

The SV grafts have surgeries for long due to their easy availability, they are more resistant to iatrogenic injury, less susceptible to vasospasm [13] and provide longer length compared with other kind of grafts. The SV grafts have been most used for non-LAD coronary territories worldwide. It has major disadvantage of high graft failure rate [2,3]; approximately 40-50% grafts occlude at 10 years after the CABG surgery, of which 10-25% are occluded within first year post-operatively [4,14,15]. In comparison, the occlusion rate of other grafts is lower, for instance the radial artery shows 17-37% failure rate [14,16]. One of the several causes of SV failure is the endothelium dysfunction during the harvest and new harvesting techniques including bridge, no-touch, endoscopic resection help reduce the dysfunction and the graft failure. The other underlying cause has been reported as the presence of venous vales. Although the mechanisms of primary stenosis of coronary artery bypass graft and peripheral artery bypass graft have been suggested to be different, they share thrombosis as the basis of luminal loss [17]. In SV grafts, valve sites frequently gather clots [18], which cause valve dysfunction, scarring and develop post-thrombotic syndrome [17]; the response of local smooth muscle cells to injury is found to be accelerated *in-vitro*[19]. The clinical studies have confirmed that the valve sites frequently cause stenotic lesions when SV graft reoperations are performed [5-7,20-22]. We assumed that knowing SV valve position and avoiding the valve sites during harvesting may offer another approach to reduce the SV graft failure.

To identify the best portion of the SV as a conduit for bypass surgery, the number and position of valves in SV were reviewed. A Brazilian study characterized 60 veins from 30 adult cadavers and reported that the average number of the valves from the medial epicondyle of the femur to the saphenous hiatus were 4.77 and 4.87 on the left and right side, respectively [23]. Similarly a Japanese study of 26 SV from 20 adult cadavers found 111 valves (average: 4.27) between the SF junction and the upper patellar margin compared to 63 (average: 2.42) valves between the upper patellar margin and the medial malleolus [24]; they also reported that the valves most valves were observed within 10 cm from the SF junction and between 35-45 cm from the SF junction. Because we identified 4 (IQR: 3-5) valves from between 0 cm to 35 cm from the SF junction and the distribution of valves was mainly observed between 0 to 10 cm, the results of our volunteer study were comparable with these autopsy studies; however, the data beyond 35 cm from the SF junction was not available in this study. Therefore, the upright CT demonstrated an accurate characterization of SV valves not easily possible by the conventional computed tomography.

Another merit of the upright CT was the noninvasive identification of tributaries and vessel area. Vessel size is an important factor to predict graft failure and a luminal diameter of over 2.0 mm is preferable for SV graft patency and longevity [3,14,25]. New harvesting techniques less touch SV may reduce the damage compared with conventional open harvesting technique, however; it is difficult to evaluate the valve sites and the vessel size in the whole SV. In addition, it is important to be able to ligate all side tributaries [26]. The upright CT allowed to locate valves, identify tributaries and accurately define vessel size noninvasively and should assist the strategy for harvesting.

Recently upright (or weight-bearing) CT [27] and MRI [28] have been proposed to evaluate the effect of gravity. However, the previous upright CT was equipped with a cone beam CT and scan range was limited. The upright MRI has lower spatial resolution compared with CT [29]. Compared to these machines, the upright CT used in the current study carries a wide-scan range with quick motion and high spatial resolution, similar to a high-end supine CT at standing position. It has an ability to evaluate blood distribution of whole body [9], and may contribute to the development of the *Phlebology,* which has room for the development compared with the *Arteriology.*

Limitations of the study. Although a novel attempt, this study has several limitations. First, since the upright CT is a prototype machine, this is a single center study. Second, the protocol of this study was designed to obtain body-trunk images and the scan range of this prototype machine could not detect beyond 37 cm height, not allowing the images of entire saphenous vein. However, we could acquire the whole SV with pedestal with 42 cm height, which we utilized for the evaluation of ankles [30]. Third, the valve insertion sites were identified by defining venous (expansive) dilation ratio compared to the lumen and a cut-off point of 1.20 was based on the anatomic observation in the cadaveric limb. An application of workstation is being developed to enable detecting the valve automatically in future clinical studies. Fourth, we could not identify the valve leaflet directly, because the upright CT scans were performed without contrast medium and the limit of the spatial resolution of CT is 0.4 to 0.6 mm. The invasive OCT with 15 micro-meter spatial resolution [29] have allowed to recognize the culprit valve lesions after CABG

[31]. However, it is difficult to identify the valves of SV in supine CT even with contrast materials. Thus, this approach will be practically useful to detect valves positions.

Conclusions

Upright CT enables detection of SV valve sites, tributaries, and vessel size noninvasively. It may potentially assist the strategies for SV harvesting to improve patency of bypass-grafts.

Declarations

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Author contributions

T.N. made contribution to the conception and design of the study, acquisition, analysis and interpretation of cadaver study data and volunteer study data, and drafting the article. Mi.Y., Y.Yo., made contribution to the acquisition of cadaver study data and volunteer study data, and revising the manuscript critically for important intellectual content. Y.Ya. and K.N. made contribution to the acquisition of volunteer study data and revising the manuscript critically for important intellectual content. N.I., Ma.Y. H.S. and J.N. made contribution to revising the manuscript. M.J. made contribution to the conception and design of the study and revising the manuscript.

Conflict of Interest

This study was supported by Japan Society for the Promotion of Science (JSPS KAKENHI: grant number JP17H04266), Uehara Memorial Foundation, and Canon Medical Systems (Otawara, Japan). Masahiro Jinzaki has received a grant from Canon Medical Systems. Canon Medical Systems has loaned the upright computed tomography machine to Keio University. However, Canon Medical Systems is not involved in the design and conduct of the study; in the collection, analysis, and interpretation of the data; and in the preparation, review, or approval of the manuscript. All other authors have no relationships with industry or other entities.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

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