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Effect of computed tomographic venography on donor selection in submandibular gland transplantation in patients with severe dry eye

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Background: A reliable anterior facial vein (AFV, donor vein) is cardinal for the success of submandibular gland (SMG) transplantation. This study determined the impact of computed tomographic (CT) venography in identifying AFV variations for SMG transplantation.

Methods: CT venography was performed in consecutive patients with severe dry eye prior to SMG transplantation in order to identify disadvantageous AFV variations for vascular anastomosis, namely, AFVs that did not drain the SMG and those that did not match the superficial temporal vein (STV, recipient vein; AFV:STV caliber ratio, ≥3). The CT results were compared with the intraoperative findings for the diagnostic accuracy.

Results: Forty-two donors were included. Compared with the intraoperative findings, the CT results accurately identified AFV–STV caliber mismatches ($P = 1.00$; sensitivity and specificity, 100%). In the identification of AFVs not draining the SMG, CT showed 94.7% sensitivity and 100% specificity ($P = 0.25$). According to the CT findings, 10 contralateral SMGs with AFVs (23.8%), instead of ipsilateral donors, were selected for transplantations (conventionally ipsilateral donor was the first choice). The surgical success rate was 95.2% (40/42).

Conclusion: CT venography is valuable in determining disadvantageous AFV variations for anastomosis and choosing a reliable donor for SMG transplantation.

1. Introduction

Dry eye syndrome, or keratoconjunctivitis sicca (KCS), is a relatively common disease of the tear fluid and ocular surfaces and results in discomfort, visual disturbances, tear-film instability, and possible damage to the ocular surfaces (Lemp et al., 2007). Conventional therapeutic options for dry eye include artificial tear substitutes, ciclosporin eye drops, and occlusion of tear drainage. These treatments largely provide symptomatic relief and give satisfactory results in mild dry eye, but are insufficient in severe dry eye (Geerling et al., 1998). Autologous microvascular submandibular gland (SMG) transplantation enables the permanent autologous substitution of tears by secretions from the transplanted and revascularized SMG. This procedure, which was recommended by the International Dry Eye Workshop for patients with end-stage dry eye disease (Pflugfelder et al., 2007), has been proved to be effective in eligible patients and offers a good prognosis (Schroder et al., 2003; Yu et al., 2004; Paniello, 2007; Jacobsen et al., 2008; Geerling et al., 2008; Yu et al., 2009; Borrelli et al., 2010; Qin et al., 2013; Yu et al., 2013).

During the transplantation, the SMG, Wharton duct, and facial artery and vein are harvested and transplanted to the temporal region. The facial artery and anterior facial vein (AFV) are

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anastomosed with the superficial temporal artery and superficial temporal vein (STV), respectively, and the Wharton duct is implanted and reopened into the upper conjunctival fornix (Geerling et al., 1998; Sieg et al., 2000; Yu et al., 2004). This procedure enables secretions from the transplanted SMG to serve as "tears". Reconstruction of the blood circulation is crucial for the survival of the donor SMG. In some patients, however, the AFV has no branch into the SMG, i.e., it does not drain the SMG (Li et al., 2007). Occasionally, the AFV is too big to be anastomosed with the STV. In such cases, drainage failure of the donor gland may occur after transplantation and lead to failure of the surgery, or the surgeon may choose to abandon the transplantation or harvest the contralateral SMG. Hence, preoperative evaluation of the AFV anatomy is valuable in choosing a favorable donor gland with a reliable AFV. Multidetector computed tomography (CT) has been proven to be useful in the preoperative evaluation of the anatomy of potential donor portal and hepatic veins in liver transplantation (Kamel et al., 2001). In the present study, we aimed to determine the feasibility and value of multidetector CT venography in the depiction of AFV anatomy and the identification of important disadvantageous AFV variations for vascular anastomosis, including AFVs that did not drain the SMG and AFVs that did not match the STV in terms of vascular caliber.

2. Materials and methods

2.1. Patient population and ethics statement

This prospective cohort study enrolled consecutive patients with severe dry eye who were referred to us for SMG transplantation between October 2010 and October 2015. All transplantations were performed at Peking University School of Stomatology by the same surgical team. The study was approved by the Ethics Committee for Human Experiments of Peking University Health Science Center and was conducted in accordance with the Declaration of Helsinki guidelines for human research. All patients provided informed consent prior to participation in the study.

2.2. CT protocol

Spiral CT scans were obtained using an 8-detector scanner (BrightSpeed, GE Healthcare, Milwaukee, Wisconsin, USA). With the patients in a supine position, plain and intravenously enhanced CT scans were obtained. For the enhanced CT scans, 2.0 ml/kg of a contrast medium (Iopamidol 370 mg/ml, Bracco Sine, Italy) was injected through the antecubital vein at a rate of 3 ml/s using an autoinjector. CT attenuations of the internal jugular veins at the level of hyoid bone were monitored after the initiation of injection. Scanning was begun immediately after the CT attenuations of both internal jugular veins reached 100 HU. Scans were obtained from the level of the clavicle to the calvaria. The following scanning and reconstruction parameters were used for the multidetector CT venogram acquisition: automatic exposure control; current, 200–380 mA; voltage, 120–140 kV; collimation, 1.25 mm $\times$ 8; pitch, 1.375; reconstruction slice thickness, 1.25 mm; and reconstruction increment, 1.25 mm.

2.3. Image interpretation

Axial images were reformatted with a standard algorithm, and post-processing was conducted using commercially available software (OsiriX MD 1.3; Pixmeo, Geneva, Switzerland). Multiplanar two-dimensional (2D) reformation images were generated using maximum intensity projection (MIP) techniques. Three-dimensional (3D) models of the vascular structures were visualized using volume rendering.

On axial images, vascular enhancement was quantitatively evaluated using the attenuation values of the AFV at the level of the hyoid bone and of the STV at the level of the zygomatic arch. The mean attenuation values for each vein were measured using regions of interest (ROIs). Observers placed ROIs on the vessels and manually drew an elliptic ROI within the inner edge of each vessel. The attenuation values of the vein on the enhancement scan (H1) and the plain scan (h1) were recorded. The formula $\Delta H = H1 - h1$ was used to assess vascular enhancement.

In 3D models, the location and course of the AFV and STV were identified. The AFV caliber was measured at the level of the hyoid bone, and the STV caliber was measured immediately after its frontal and parietal branches united or at the superior border of the zygomatic arch when there was only one branch. The results were calculated to a minimum value of 0.5 mm. The anatomic relationship between the AFV and the SMG was assessed in both the 3D models and 2D images. When there were visible branches of the AFV going into the SMG parenchyma, it was determined that the AFV collected the venous drainage of the SMG. Otherwise, the AFV was considered to not drain the SMG.

Each SMG was evaluated for two possible disadvantageous anatomic variations: AFV not draining the SMG and AFV-to-STV caliber ratio $\geq$3. A surgical plan was devised according to the CT findings. For the recipient eye, the ipsilateral SMG with a draining AFV was the first choice of donor. If preoperative CT showed any disadvantageous AFV variations, the contralateral SMG would be evaluated as the potential donor. When both SMGs showed disadvantageous variations, the ipsilateral SMG was selected as the donor, and the accompanying vein of the facial artery was used as the donor vein.

2.4. Surgical procedure

SMG transplantation was performed as described previously (Yu et al., 2004). In brief, the SMG, including the facial artery and AFV, was dissected in the submandibular triangle. The calibers of the AFV and STV were measured using vernier calipers. When the distal ends of the vessels were cut off and ligated, and the proximal parts of the facial artery and AFV were the only connections between the SMG and the body, the AFV was transected and bleeding from the AFV indicated that it collected the venous drainage from the gland. After the gland and the vessels had been totally released, heparinized saline was irrigated into the facial artery. Seepage of this solution from the AFV confirmed that it collected the venous drainage from the gland.

Afterwards, the free submandibular gland was transferred to the temporal region, and the facial artery and AFV (or the accompanying veins of the facial artery) were anastomosed with the superficial temporal artery and STV. Wharton's duct was passed through a tunnel prepared subcutaneously to the upper lateral conjunctival fornix by blunt dissection. As the last procedure of the transplantation, the mucosal cuff around the orifice of Wharton's duct was sutured with the palpebral conjunctiva to form an opening in the upper lateral conjunctival fold.

Secretion from the transplanted SMG into the eye after operation indicated functioning of the gland and success of the transplantation. Further more, scintigraphy with ^{99m}Tc-pertechnetate examination was performed for every patient on the 10th postoperative day. Uptake of the ^{99m}Tc-pertechnetate in the temporal region indicated the transplanted gland was viable. And ^{99m}Tc-pertechnetate drained into the orbit through Wharton's duct implied the duct was unobstructed (Yu et al., 2004).

2.5. Statistical analysis

Proportions were used for categorical data. Mean ± standard deviation or median (interquartile range) was used for continuous data. The associations between continuous variables were analyzed using the Student *t*-test (symmetric distribution) or Mann–Whitney test (asymmetric distribution). Diagnostic accuracy was used to compare the CT results and the intraoperative findings (sensitivity, specificity, and predictive value). All analyses were conducted using SPSS 13.0 (SPSS Inc., Chicago, Illinois, USA), and $P < 0.05$ (two-tailed) was considered statistically significant.

3. Results

Forty-two SMG transplantation operations were performed for 39 patients (3 patients underwent bilateral transplantation). There were 23 women and 16 men with a mean age of 27 years (range, 20–42 years). The most common etiology was Stevens–Johnson syndrome (30 patients), followed by acute conjunctivitis (6 patients); in 3 patients, the etiology was unclear. The average disease duration was 9 years (range, 3–18 years).

CT examination was performed in all patients, and the CT data from 78 SMGs were interpreted. On CT images, the AFV and STV showed complete opacification in all patients. The mean ΔH was 189.78 ± 58.42 HU for the AFV and 162.37 ± 28.58 HU for the STV, indicating that both veins achieved very good vascular enhancement (Park et al., 2013). In the 3D models, the 3D courses, vascular shapes, and borders of the AFV and STV, and even their tertiary-order branches, were well visualized (Fig. 1).

According to the CT data, the potential donors for the 42 recipient eyes included 24 ipsilateral SMGs with satisfactory AFVs (Fig. 2), 10 contralateral SMGs that were better suited for AFV anastomosis than the ipsilateral glands, and 8 ipsilateral SMGs whose hosts had bilateral AFV variations that were disadvantageous for anastomosis (Fig. 3). The CT results and intraoperative findings were compared in all 42 patients. The average vessel caliber did not differ between the CT and intraoperative measurements for the AFV (3.11 ± 1.39 mm vs. 2.99 ± 1.33 mm, $P = 0.270$) or for the STV (1.83 ± 0.53 mm vs. 1.71 ± 0.59 mm, $P = 0.119$). Furthermore, no significant differences were observed between the CT data and the intraoperative findings in terms of the AFV:STV caliber ratio and identification of AFVs draining the SMG (Table 1). With the intraoperative findings as the gold standard, the preoperative CT data were shown to have 100% sensitivity, specificity, positive predictive value, and negative predictive value in determining the match between AFV and STV calibers (Fig. 3). In determining whether the AFV drained the SMG, preoperative CT was found to have 100% sensitivity, 94.7% specificity, 66.7% positive predictive value, and 100% negative predictive value (Figs. 2 and 3).

In 2 cases, both of them showed bilateral disadvantageous AFV variations on preoperative CT: the CT results had incorrectly shown that the AFV did not drain the SMG, i.e., false positive result. In one of them the ipsilateral SMG was transplanted with the AFV as the donor vein, while in the other case the accompanying vein of the facial artery had to be used as the drainage vein because this case also had AFV–STV caliber mismatch on preoperative CT, which was confirmed during operation.

For the remaining 6 SMGs shown to have bilateral disadvantageous AFV variations on CT, the accompanying vein of the facial artery was used as the drainage vein. For all of the 34 SMGs (24 ipsilateral glands and 10 contralateral glands) shown to have adequate AFVs on CT, AFVs were confirmed to be reliable during operation and were used as the donor veins. Among patients in whom the AFV was used, the surgical success rate was 97.1% (34/35). The rate in patients with the accompanying vein of the facial artery as the donor vein was 85.7% (6/7).

All patients were followed up for more than 6 months (range 6–72 months, average 47 months). In patients with successful transplantation, the secretory function of the viable transplanted SMGs remained stable. The lubricant effect of the saliva effectively alleviated the dry eye symptoms. The ocular surface structures improved, and the patients could reduce and eventually stop using artificial tears (Fig. 4). In the two patients in whom the surgery was unsuccessful, the failure was caused by venous thrombosis; they were left in situ without further treatment. The total surgical success rate of the 42 transplantations was 95.2%. In two cases ranula were found and treated successfully with sublingual gland removal. No other severe complications were founded.

4. Discussion

The venous blood of the SMG is drained mainly into the AFV, the accompanying vein of the facial artery, and the hilum vein of the SMG. Compared with the other two veins, the AFV is bigger and longer with a thicker vessel wall, which makes its anastomosis easier and more reliable. Therefore, the AFV is the first choice of donor vein in SMG transplantation, with the STV as the recipient vein (Yu et al., 2004). The AFV and STV are both commonly used veins in head-and-neck microsurgical anastomoses. However, the reported revascularization success rate of SMG transplantation is only around 86% (Paniello, 2007; Borrelli et al., 2010), which is much lower than the success rate of free flap reconstruction of defects in the head-and-neck region in most centers (around 95%). Most cases of failure of SMG transplantation are caused by failure of venous drainage and are highly related to AFV variations (Yu et al., 2004; Paniello, 2007). Hence, the preoperative determination of any disadvantageous AFV variations for anastomosis is valuable for choosing a reliable donor vein in SMG transplantation.

In a cadaver study, Li et al. found that in 6.7% of cases, the AFV had no branch into the SMG (Li et al., 2007). In such cases, the AFV was not the drainage vein of the SMG and could not be used during SMG transplantation. In the present study, 6 (14.3%) patients had no AFV branch into the SMG on CT images, and in 2 patients, the lack of

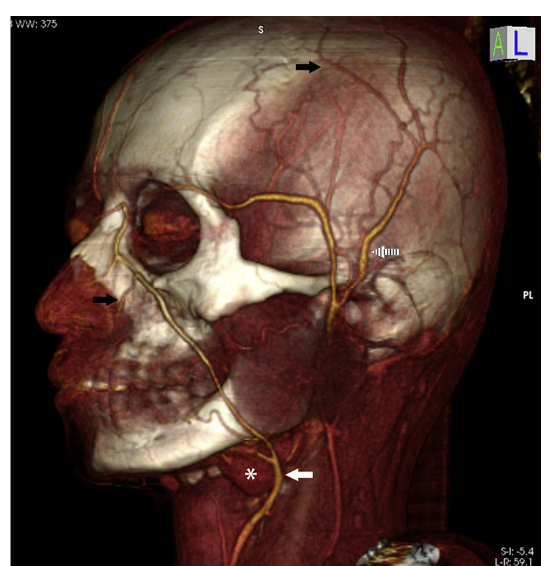

Fig. 1. The submandibular gland (*), anterior facial vein (white arrow), superficial temporal vein (white arrow with dashes), and their venous branches (black arrows) are all clearly illustrated on a volume-rendered three-dimensional image.

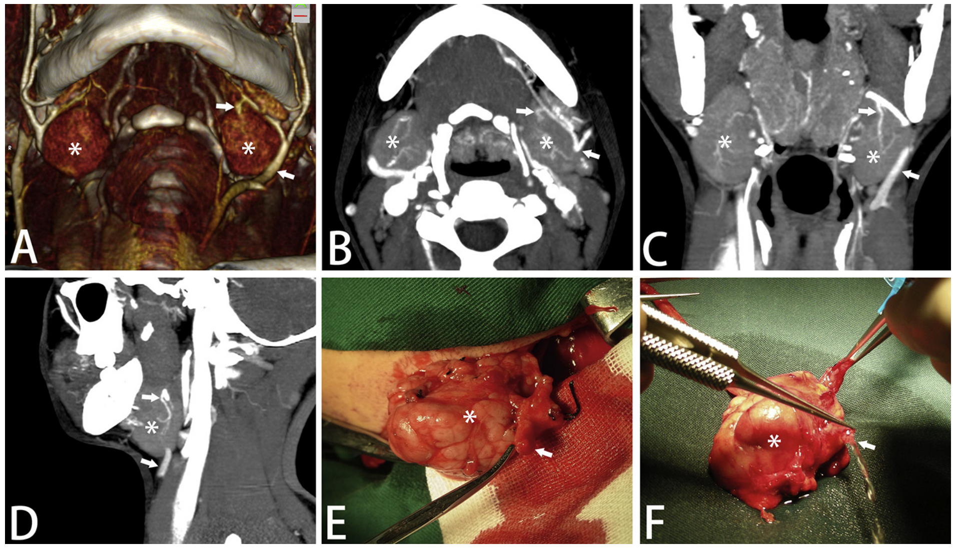

Fig. 2. A patient with a good ipsilateral donor submandibular gland (SMG) and anterior facial vein (AFV). The left AFV has a definite branch (arrow) into the SMG (*) in the 3D model (A), the axial maximum intensity projection (MIP) view (5 mm, B), the coronal MIP view (5 mm, C), and the sagittal MIP view (5 mm, D). No draining AFV branch can be found for the right SMG. The preoperative findings are confirmed during operation. There is bleeding (E) and seepage of heparinized saline solution (F) from the AFV (white arrows).

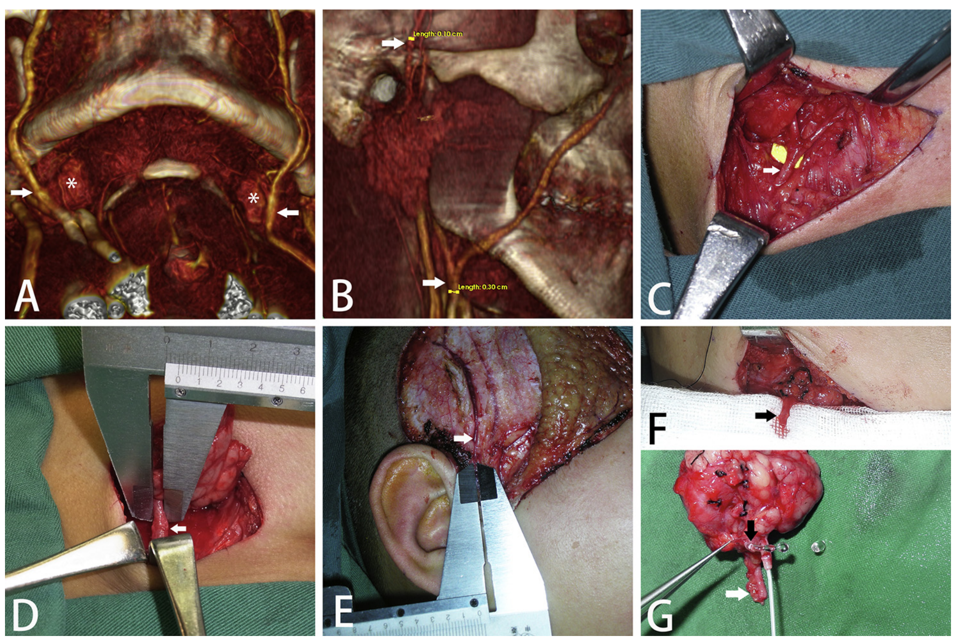

Fig. 3. A patient with bilateral disadvantageous anterior facial vein (AFV) variations for anastomosis. No AFV branch (white arrows) can be found entering the submandibular glands (SMGs; *) on preoperative computed tomography (CT; A). This finding is confirmed during the operation. The AFV (white arrow) is totally separated from the SMG (C). There is no bleeding (black arrow; F) or seepage of heparinized saline solution (white arrow; G) from the AFV. The heparinized saline solution flows from the accompanying vein of the facial artery (black arrow) (G). Both AFVs are too big to match the superficial temporal vein (STV). This finding is confirmed during operation. The calibers of the AFV and STV measured on preoperative CT (B) are validated during the operation (D, E).

Table 1
Comparison of the CT data with the intraoperative findings.

			Intraoperative findings		*P* value
			Positive	Negative	
CT data	AFV–STV caliber mismatch	Positive	4	0	1.00
		Negative	0	38	
	AFV not draining the SMG	Positive	4	2	0.25
		Negative	0	36	

AFV, anterior facial vein; STV, superficial temporal vein; SMG, submandibular gland; CT, computed tomography.

an AFV draining the SMG on CT images was confirmed to be a false-positive result during intraoperative examination. This false-positive result might be attributable to fine branches that are difficult to depict on CT images. In 36 cases, the AFV had a branch into the SMG on preoperative CT, and all of these AFVs were confirmed to be the drainage veins of the SMGs during operation. Thus, if the AFV is found to have any branch into the SMG on preoperative CT, the AFV can be reliably considered to be the drainage vein for the SMG.

The AFV caliber in the submandibular region was much larger than the STV caliber in some cases (Shima et al., 1998; Park et al.,

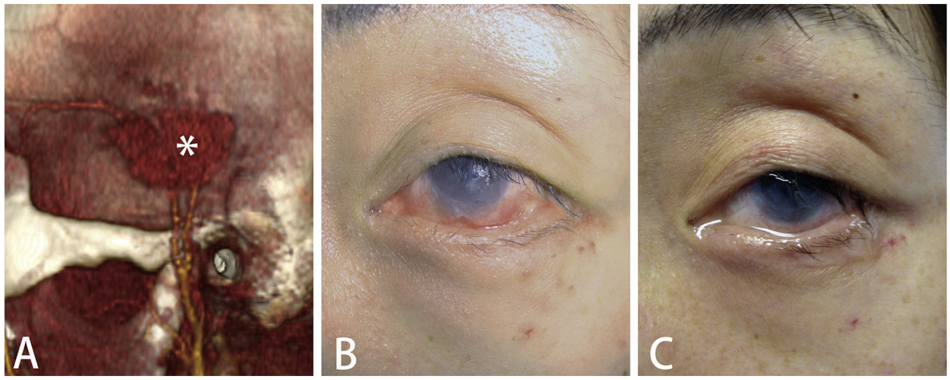

Fig. 4. A case of successful transplantation. The transplanted submandibular gland (*) and vessels are clearly illustrated (A). Compared with the preoperative state (B), secretions from the transplanted submandibular gland have provided lubrication to the ocular surface structures of the treated eye, and the ocular surface shows great improvement after the operation (C).

1999; Yano et al., 2014), indicating an AFV–STV caliber mismatch (AFV:STV caliber ratio $\geq$ 3:1). CT measurements of vascular calibers are not very accurate. However, for our purposes, the ratio of the calibers of the two vessels rather than the exact caliber of each vessel was more important. Therefore, in the present study, we measured vascular calibers only to the nearest 0.5 mm. At this degree of accuracy, the preoperative CT measurements showed no significant differences from the intraoperative measurements. Thus, CT venography was capable of predicting which of the two SMGs had an AFV that better matched the recipient STV.

The AFV and STV showed complete opacification on both 2D and 3D images in the venous phase of preoperative CT. For detecting AFV branches, 2D images are more reliable, as some small branches might be overlooked on 3D images or be covered by the SMG parenchyma and AFV. In contrast, for measuring vascular calibers, 3D images are preferred, as 2D images not perpendicular to the vessel would give rise to predictable measurement errors because the vessel might cross the 2D section at an acute angle, leading to an apparent magnification of its caliber.

In our study, the total surgical success rate of the 42 transplantations was 95.2%, which is much higher than that reported in the literature (Geerling et al., 1998; Paniello, 2007; Borrelli et al., 2010) and that in our previous study (87.7%) without preoperative CT examination (Yu et al., 2004). Our team had previously performed 163 SMG transplantations before this study of CT venography, and generally, the ipsilateral SMGs were chosen as the donor glands for surgical facilitation. Because some AFVs did not drain the SMG or did not match the recipient STV, the accompanying vein of the facial artery (49 cases) or the hilum vein (4 cases) had to be used as the donor vein in 32.5% of cases. Moreover, in 8.7% of cases, the surgeons even had to switch to the contralateral SMG, or use the venous bypass technique to anastomose the AFV to the cervical vein, which greatly increased the surgical trauma. In the present study, no preoperatively selected gland had to be abandoned for the contralateral gland intraoperatively, and the bypass technique was not required in any patient. The accompanying vein of the facial artery was used as the donor vein in only 16.7% of cases. Thus, preoperative CT was valuable in choosing a better donor gland with a reliable AFV from the two candidate SMGs. This might be one of the reasons for the relatively high surgical success rate of the present study.

5. Conclusion

In conclusion, the results of the 42 SMG transplantations performed in this study indicate that CT venography permitted detailed preoperative examination of the AFV and STV anatomy and was able to satisfactorily identify AFV variations that were disadvantageous for vascular anastomosis. Thus, CT venography should be an essential part of the preoperative evaluation of potential donors for SMG transplantation.

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Authors' contributions

Conception and design of the work: Jia-Zeng Su, Guang-Yan Yu.

Acquisition, analysis and interpretation of data: Jia-Zeng Su, Hong-Kui Yu, Zhi-Peng Sun, Xiao-Jing Liu, Zhi-Gang Cai, Lan Lv, Guang-Yan Yu.

Drafting the article: Jia-Zeng Su, Guang-Yan Yu.

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Conflict of interest

The authors declare no conflict of interest.

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