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ARTICLE

Effects of arterial blood supply and venous return on multi-territory perforator flap survival

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ABSTRACT
This study aimed to design arterial ischemic and venous congested areas on the same multi-territory perforator flap, assessing the effects of arterial blood supply and venous return on flap survival. Totally 68 rats were randomly divided into the experimental (Exp) and control (Con) groups. In the Exp group, flaps were based on left superficial epigastric artery and right superficial epigastric vein. In the Con group, flaps were based on the left superficial epigastric artery and vein. Immediate postoperative ink-gelatin angiography, epidermal metabolite levels detection, tissue edema measurement, survival rate evaluation in half of the flaps and average microvessel density assessment were performed. Blood in the Exp group flowed through most angiosomes, but only flowed around pedicled vessels in the Con group; metabolite levels of left halves in the Con and Exp groups were comparable with those of right halves. Angiosomes with high water contents occurred in the Exp group. Survival rates of left halves in the Con and Exp groups were higher than those of right halves, and more microvessels were found in the left ventral areas of both groups compared with the right ventral area in the Exp group. These findings revealed that on the same multi-territory perforator flap, arterial blood supply, affected by venous return, is a prerequisite for flap survival.

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KEYWORDS
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Introduction

Multi-territory perforator flaps are extensively used to repair large skin defects following trauma, burns or cancer resection [1,2]. However, blood flow in the distal part of the multi-territory perforator flap is unstable. Arterial ischemia or venous congestion is the most serious complication in the distal part of multi-territory perforator flap. Choke vessel is the reduced-caliber anastomotic vessel between the two adjacent angiosomes of the multi-territory perforator flap . When resistance of choke vessels is high, arterial blood supply or venous return is difficult to get through choke vessels, resulting in arterial ischemia or venous congestion of the distal part of the multi-territory perforator flap [3,4].

In order to stabilize blood flow in the distal part of the flap, arteries or veins are added, but their effects remain controversial [5–7]. In cases with insufficient information about whether the distal part of the flap has deficient arterial function or blocked venous return, blindly increasing arteries or veins cannot increase flap survival.

To investigate the effects of arterial blood supply and venous return on flap survival, Matsumoto et al. designed models for arterial ischemic and venous congested flaps to assess the causes of distal necrosis [8]. However, the pedicled artery or vein of the above flap models was completely blocked, and arterial blood supply or venous return was fully lost. In addition, multiple scholars designed models for partial arterial ischemia and venous congestion by limiting partial blood flow [9,10]. However, clinical arterial ischemia or venous congestion is often caused by high choke vessel resistance, with the pedicled artery or vein of the multi-territory perforator flap not damaged, having the complete ability of arterial blood supply and venous return [11–13].

In this study, the artery and vein of the flap were separated, and the left superficial epigastric artery and right superficial epigastric vein were retained, aiming at designing arterial ischemic and venous congested areas on the same multi-territory perforator flap by using the high resistance of the choke vessel between the bilateral superficial epigastric angiosomes, and assessing the effects of arterial blood supply and venous return on flap survival.

Material and methods

Animals and surgical procedure

This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and approved by the Institutional Animal Care and Use Committee of Wenzhou Medical University (Wenzhou, Zhejiang province, China). Here, 68 Male 2-month old Sprague Dawley rats (body weight, 240 ± 10 g) were purchased from Laboratory Animal Centre of Wenzhou Medical University (License No. SCXK [ZJ] 2015-0001), and divided into two groups ($n = 34$ per group). Rats were randomly assigned to the control (Con) and experimental (Exp) groups. The animals were anesthetized by intraperitoneal injection of pentobarbital sodium (50 mg/kg; Boyun Biotech, Shanghai, China) [14], and the trunk was shaved and disinfected. The shape of the flap from the lower abdomen to the back (1 cm to the dorsal midline at each

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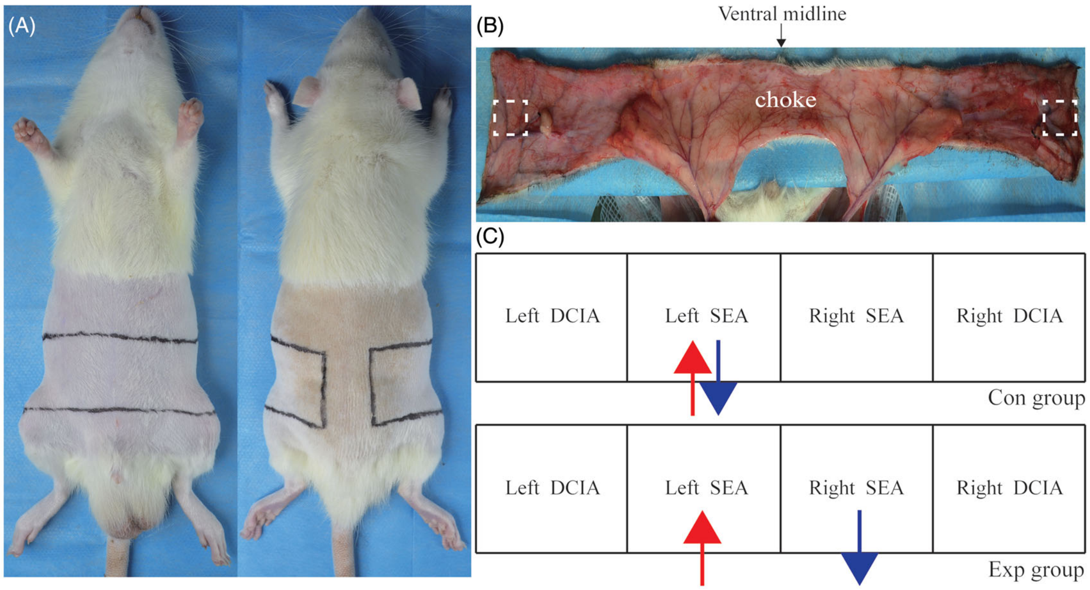

Figure 1. Flap shape and grouping. A, the flap expanded from the lower abdomen to the back (1 cm to the dorsal midline at each side); B, the flap contained the bilateral superficial epigastric (SEA) and bilateral deep circumflex iliac (DCIA) angiosomes, with the choke vessel between the bilateral SEAs, the white boxes of the left and right halves of the flap indicate the sites of specimen harvested for Epidermal metabolite levels detection; C, the flap in the Con group was based on the left superficial epigastric artery (red arrow) and drained to the accompanied left superficial epigastric vein (blue arrow), whereas that of the Exp group was based on the left superficial epigastric artery (red arrow) and drained to the right superficial epigastric vein (blue arrow).

side) was outlined according to the anatomy of ventral and dorsal vessels and the hypogastric nourished flap [3,15]. The flap was approximately 3 cm × 14 cm in size, and included four angiosomes as follows: bilateral superficial epigastric angiosomes (SEAs) and bilateral deep circumflex iliac angiosomes (DCIAs). The rat flap was divided into the left and right halves by the ventral midline. In the Con group, the flap was based on the left superficial epigastric artery and drained to the accompanied left superficial epigastric vein. In the Exp group, the flap was based on the left superficial epigastric artery and drained to the right superficial epigastric vein (Figure 1). The flap containing the skin and superficial fascia was fully dissected from the underling soft tissue, and arteries and veins were ablated or preserved according to grouping. After careful hemostasis, the flap was restored into the orthotopic site with interrupted 4/0 nylon sutures (Pudong Jinhuan Medical Products, Shanghai, China). The rats were maintained postoperatively in individual cages and provided standard laboratory rat chow and water containing penicillin.

Immediate postoperative ink-gelatin flap angiography

Immediately after operation, 5 rats in each group were randomly selected to receive heparin sodium salt (0.3 ml/100g; Boyun Biotech, Shanghai, China). After 5 min, ink-gelatin (Haiwen (Group) Co. Ltd., Shanghai Ink Factory, Shanghai, China) was injected into the left femoral artery through a 22-G silicone rubber catheter (Pudong Jinhuan Medical Products, Shanghai, China) until drainage to the preserved vein. Then, the vascular side of the flap was photographed with a digital camera (Nikon, Japan).

Epidermal metabolite levels detection

6 h after operation, 5 rats per group were randomly selected for the detection of the epidermal metabolite levels of lactate and glucose. The flap samples ($1 \times 1\ cm^2$) from the left and right halves of the flap in the Con and Exp groups as shown in Figure 1(B) were harvested and then immediately frozen in liquid nitrogen and grinded into 10% tissue homogenate. The total protein content of the tissue lysate samples was determined using the Bradford assay [16]. The contents of lactate and glucose were determined by colorimetric assay kits (Nanjing Jiancheng Bioengineering Institute, Jiangsu, China) based on the following equation: content of lactate or glucose (mmol/gprot) = [(OD of the sample tube - OD of blank tube)/(OD of standard tube-OD of blank tube)] × concentration of standard sample/total protein content [17].

Tissue edema measurement

Tissue edema was reflected by water content. The day after operation, 8 rats per group were randomly selected, and flap tissues from the bilateral deep circumflex iliac angiosomes and superficial epigastric angiosomes were weighed and then dehydrated in a convection oven at 65 °C [18]. All samples were weighed daily until the weights remained constant for 2 subsequent days. Water content (%) was determined by the following formula:

$$\text{Water content }(\%) = (\text{wet weight} - \text{dry weight}) \times 100/\text{wet weight}.$$

Survival rate evaluation of one-half of the flap

At 14 days after operation, 8 rats per group were randomly selected, and flaps were photographed with a digital camera (D5100, Nikon, Japan). The images were analyzed with the Image-Pro Plus 6.0 software (Media Cybernetics Inc., Rockville, MD, USA). Survival of left or right half area relative to the corresponding total area of the flap was considered the survival rate of the half of the flap, which was computed by dividing the number of pixels constituting the left/right half survival area by the number of pixels representing the total area of the left/right half of the flap [15].

Average microvessel density (aMVD)

At 14 days after operation, 8 rats per group were randomly selected, and skin tissue samples from left and right ventral flap areas (about 2 cm to the ventral midline; skin tissue samples from the right ventral area in the Con group were not harvested because of necrosis) sized 1 cm × 0.2 cm were harvested, fixed with 4% paraformaldehyde, and embedded in paraffin. Then, 4-μm slices were stained with hematoxylin and eosin (H&E; Solarbio, Beijing, China). The aMVD was assessed as previously described by Weidner et al. [19]. First, tissue samples were screened at low magnification (100×) to identify three hot spots of typical angiogenesis. Within these hot spots, aMVD was assessed at high magnification (200×). All analyses were performed by two investigators in a blinded manner. Counts were compared, and any discrepancy was resolved by a third investigator. Consensus was used for aMVD analysis.

Statistical analysis

Data are mean ± standard error (SE). The SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. One-way analysis of variance (ANOVA) followed by the Tukey's test was used to compare multiple groups. $p < 0.05$ was considered statistically significant.

Results

Redistribution of blood flow in the flap immediately after operation

In order to assess the redistribution of blood flow in the flap immediately after operation, rats were sacrificed for ink-gelatin flap angiography. As shown in Figure 2, the blood mostly flowed through the left superficial epigastric and left deep circumflex iliac angiosomes, and flowed less through the right superficial epigastric angiosome *via* the ventral choke vessel to complete blood supply and drainage in the Exp group. Meanwhile, the blood only flowed through the left superficial epigastric angiosome and part of left deep circumflex iliac angiosome in the Con group.

Epidermal metabolite levels 6 h after operation

As shown in Figure 3, lactate contents of the left halves of the flap in the Con (5.49 ± 0.48 mmol/gprot) and Exp (5.07 ± 0.38 mmol/gprot) groups were lower than those of the right halves in the Con (10.16 ± 0.88 mmol/gprot) and Exp (8.03 ± 0.46 mmol/gprot, $p < 0.05$) groups, and glucose contents of the left halves of the flap in the Con (4.39 ± 0.30 mmol/gprot) and Exp (4.96 ± 0.38 mmol/gprot) groups were significantly higher than those of the right halves in the Con (2.60 ± 0.15 mmol/gprot) and Exp (2.76 ± 0.21 mmol/gprot, $p < 0.01$) groups, and lactate/glucose (L/G) of the left halves of the flap in the Con (1.28 ± 0.16) and Exp (1.05 ± 0.10) groups were significantly lower than those of the right halves in the Con (3.94 ± 0.34) and Exp (3.00 ± 0.32, $p < 0.01$) groups.

The exp group shows tissue edema

In order to assess tissue edema in the four angiosomes the day after operation between the two groups, water contents were measured. As shown in Figure 4, the areas with highest water contents were the left deep circumflex iliac and left superficial epigastric angiosomes in the Exp group, followed by the right

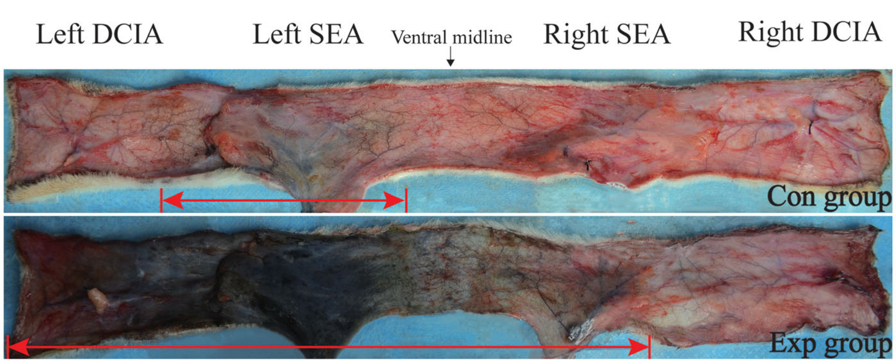

Figure 2. Immediate postoperative ink-gelatin flap angiography. Red arrow area, ink-gelatin perfusion area ($n = 5$); DCIA: deep circumflex iliac angiosome; SEA: superficial epigastric angiosome.

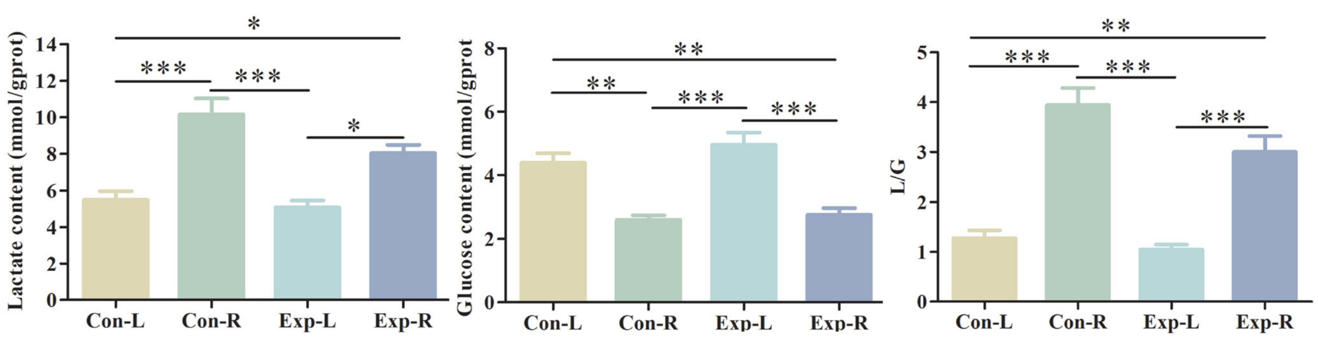

Figure 3. Epidermal metabolite levels 6 h after operation ($n = 5$). Lactate contents and L/G of the left halves of the flap were lower than those of the right halves (*$p < 0.05$), and glucose contents of the left halves of the flap were significantly higher than those of the right halves (*$p < 0.01$).

superficial epigastric angiosome area in the Exp group; the remaining five areas showed similar values.

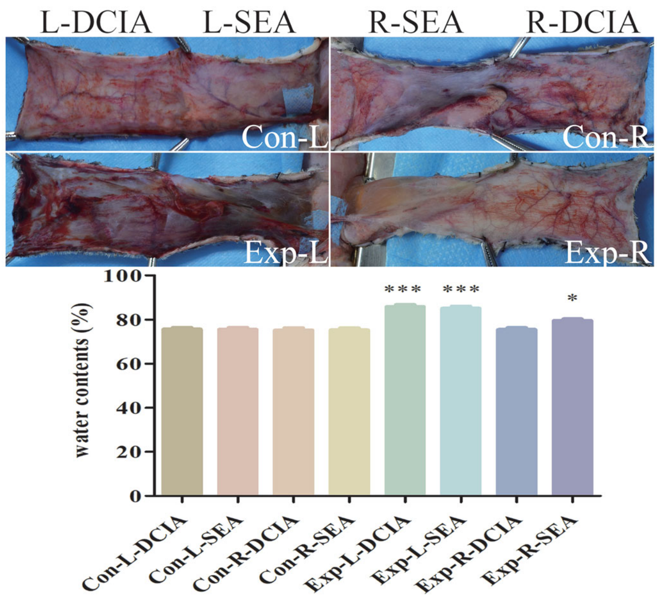

Figure 4. Tissue edema the day after operation ($n = 8$). Con-L and Con-R, left and right halves of the flap in the Con group, respectively; Exp-L and Exp-R, left and right halves of the flap in the Exp group, respectively. L-DCIA: left deep circumflex iliac angiosome area; L-SEA: left superficial epigastric angiosome area; R-SEA: right superficial epigastric angiosome area; R-DCIA: right deep circumflex iliac angiosome area. Exp-L-DCIA and Exp-L-SEA had the highest water contents (***$p < 0.001$), followed by Exp-R-SEA (*$p < 0.05$).

Flap survival of one-half of the flap in both groups

In order to visually compare the survival of different halves between the two groups, images were acquired and recorded at 1, 3, 7, 11 and 14 days after operation. As shown in Figure 5, significant edema was observed on the left half of the flap in the Exp group the day after operation, which continued until 3 days after operation; meanwhile, no edema was observed in the Con group. Necrotic areas in the Exp and Con groups mainly occurred on the right halves of the flap, and the necrotic process was faster in the Con group compared with the Exp group. Indeed, there was obvious necrosis in the right abdomen in the Con group at 3 days post-operation, which was not the case for the Exp group. Next, survival rates of the left and right halves of the flap were assessed at 14 days after operation (survival rate was not stable until 14 days post-operation). The survival rates of the left halves of the flap in the Con (94.1 ± 2.7%) and Exp (94.6 ± 2.7%) groups were higher than those of the right halves in the Con (23.8 ± 2.5%) and Exp (28.1 ± 0.8%, $p < 0.001$) groups.

Angiogenesis levels reflected by aMVD

Angiogenesis was compared among flap halves by assessing aMVD. At 14 days after operation, more microvessels were found in the left ventral flap area in the Con (24.5 ± 1.4, $p < 0.05$) and Exp (26.9 ± 1.3, $p < 0.001$) groups compared with those of the right ventral flap area in the Exp group (18.7 ± 1.1) (skin tissue samples from the right ventral area in the Con group were not harvested because of necrosis).

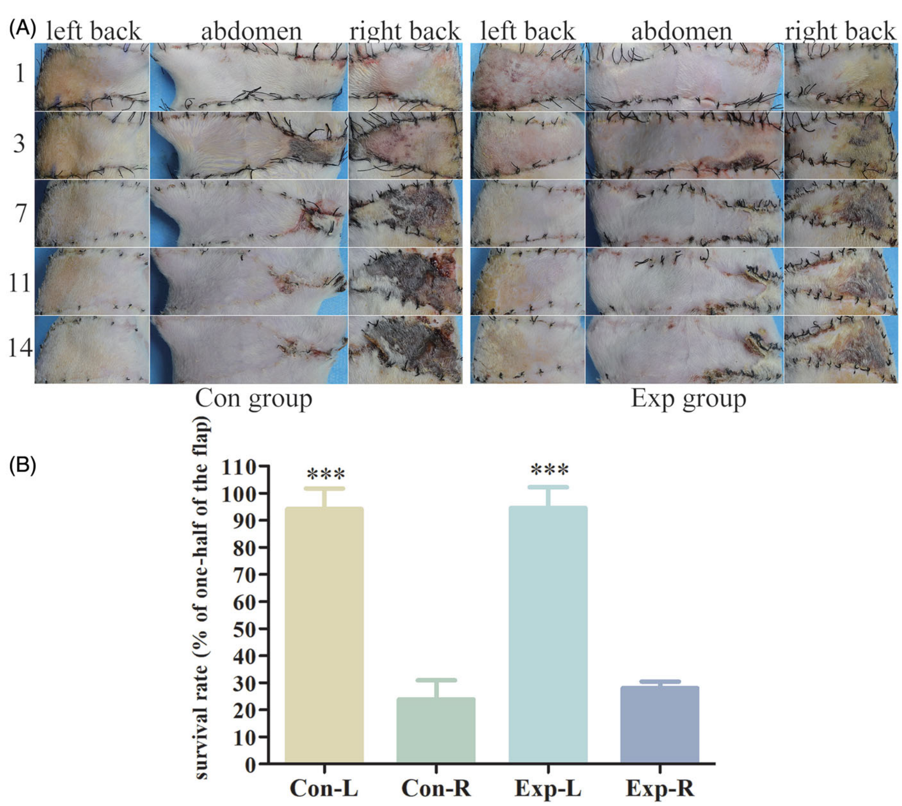

Figure 5. Flap survival ($n = 8$). A, gross appearance of flaps in both groups at 1, 3, 7, 11 and 14 days after operation. B, survival rates of the left and right halves of the flap in the Con and Exp groups at 14 days after operation; the survival rates of the left halves of the flap in the Con and Exp groups were higher than those of the right halves (***$p < 0.001$).

Discussion

The perforator flap was initially reported by Koshima et al.. Since then, multi-territory perforator flaps have been widely used. However, necrosis often occurs in the distal part of the multi-territory perforator flap. Whether arterial ischemia or venous congestion, as a key factor, may lead to distal necrosis of the flap remains controversial. Matsumoto et al. [8] designed models for arterial ischemic and venous congested flaps by ligating the pedicled artery and vein, respectively, blocking arterial blood supply and venous return, respectively, and suggested that insufficient venous return is more likely to result in distal necrosis of the flap than insufficient arterial blood supply. However, the venous flap nourished by the vein could partially survive [20], with a survival mechanism totally different from that of the arterial flap nourished by the artery. In addition, the above-mentioned flap models with artery and vein totally blocked, respectively, are not appropriate for assessing flaps with insufficient arterial blood supply or venous return. Henrich et al. [9] only ligated the central artery or vein to induce partial arterial ischemia or venous congestion, and suggested that insufficient venous return is more detrimental to early flap survival than insufficient arterial blood supply. However, Tsuzuki et al. [10] supported the opposite view that insufficient venous return is less important for flap necrosis than insufficient arterial blood supply. Although the above-mentioned flaps had arterial blood supply or venous return, they differ from arterial ischemic or venous congested flaps caused by the high resistance of choke vessels whose arterial blood supply and venous return could be increased by compensatory angiogenesis. This study successfully designed arterial ischemic and venous congested flap models by using the high resistance of choke vessels within the flaps, and found that arterial blood supply was a prerequisite for flap survival, while venous return affected arterial blood supply in the multi-territory perforator flap.

The choke vessel is a bridge connecting two adjacent angiosomes and also a barrier to the exchange of blood flow between adjacent angiosomes. Excessive arterial resistance of the choke vessel could lead to insufficient arterial blood supply in the flap, while excessive venous resistance could result in venous return obstruction [21–23]. In the Con group, the flap was based on the left superficial epigastric artery and vein; the arterial and venous resistance of choke vessels of the left half was smaller than that of the right half, as the choke vessels that arterial perfusion and venous return of the left half of the flap passed through were less than those of the right half, resulting in relatively sufficient blood supply and venous return in the left half of the flap, while the right half shows insufficiency. In the Exp group, the flap was based on the left superficial epigastric artery and drained to the right superficial epigastric vein; the arterial resistance of choke vessels of the left half was smaller than that of venous resistance, as the choke vessels that arterial perfusion passed through were less than those of venous return, and arterial blood supply was relatively sufficient, whereas venous return was relatively insufficient, which led to venous congestion in the left half; similarly, the arterial resistance of choke vessels of the right half was higher than that of venous resistance, as the choke vessels that arterial perfusion passed through were more than those of venous return, and arterial blood supply was relatively insufficient, while venous return was relatively sufficient, which resulted in arterial ischemia of the right half. Therefore, the left half of the Exp group was a model for venous congested flap, and the right half for arterial ischemic flap.

Immediate postoperative ink-gelatin flap angiography showed that the arterial blood supply and venous return of the left half of the flap were relatively higher in the Con group compared with the right half, and the accompanying vein of the pedicled artery reduced arterial blood supply to the distal part of the flap. However, in the Exp group, there was ink-gelatin perfusion in the left half of the flap and blood vessels were swollen, indicating that arterial blood supply in the left half was relatively sufficient, whereas venous return was relatively insufficient. Besides, there was no ink-gelatin perfusion in most of the right half, and only the venous area had ink-gelatin return, indicating that arterial blood supply in the right half was relatively insufficient, while venous return was relatively sufficient. The above-mentioned findings further suggested that the developed models for venous congested and arterial ischemic flaps were successful, with the vein position affecting arterial blood supply.

When flaps suffer from ischemia and hypoxia, the lactate content will increase and the glucose content will decrease significantly with a much higher L/G [17,24]. In the present study, the differences in lactate and glucose levels among halves indicated that the ischemia and hypoxia of the left halves of the flap in the Con and Exp groups were lower than that of the right halves.

The day after operation, in the Exp group, the left half of the flap (i.e. venous congestion area) showed severe edema, while the right half (i.e. arterial ischemic area) only had mild edema in the anatomic territory of the pedicled vein, and no edema was found beyond the anatomic territory. Previous studies showed that venous congestion could cause flap edema [12,25]; however, this study revealed that both venous congestion and arterial ischemia could cause edema of the flap; venous congested edema was caused by congestion as arterial perfusion was greater than venous return, which was more severe and lasted longer, while arterial ischemic edema was caused by venous reflux as arterial perfusion was insufficient and the internal venous pressure of the flap was higher than that of the artery; consequently, edema was only limited to around the pedicled vein and mild, and lasted for a short period of time, as the venous pressure was not remarkable. Therefore, venous congested edema and arterial ischemic edema could be distinguished according to their locations. In the multi-territory perforator flap with distinct advantage of the artery or vein, edema confined to the anatomic territory where the vein is relatively dominant represents arterial ischemic edema; otherwise, it is venous congested edema. However, in the Con group, edema did not occur due to similar arterial and venous resistance of choke vessels. The reason might be that there was no obvious advantage of the artery over the vein and vice versa, with a reasonable dynamic balance between the artery and vein in the left half of the flap; meanwhile, arterial perfusion and venous return were both insufficient in the right half of the flap, which was in a state of low arterial perfusion and low venous return.

Figure 5 shows that the survival rate of the venous congested flap in the Exp group was notably higher than that of the arterial ischemic flap as well as the flap with relatively insufficient arterial perfusion and venous return in the Con group. No significant difference was found compared with the flap in the Con group with relatively sufficient arterial perfusion and venous return (Figure 6). Additionally, the survival rate of the arterial ischemic flap was slightly higher than that of the flap with relatively insufficient arterial perfusion and venous return; however, there was no statistical significance. The above-mentioned findings indicated that arterial perfusion plays a decisive role in the survival of flap under certain conditions. In conditions with relatively sufficient arterial perfusion, increased venous return could improve the postoperative edema of the flap, while there was no significance on the survival of flap with postoperative edema, which could be

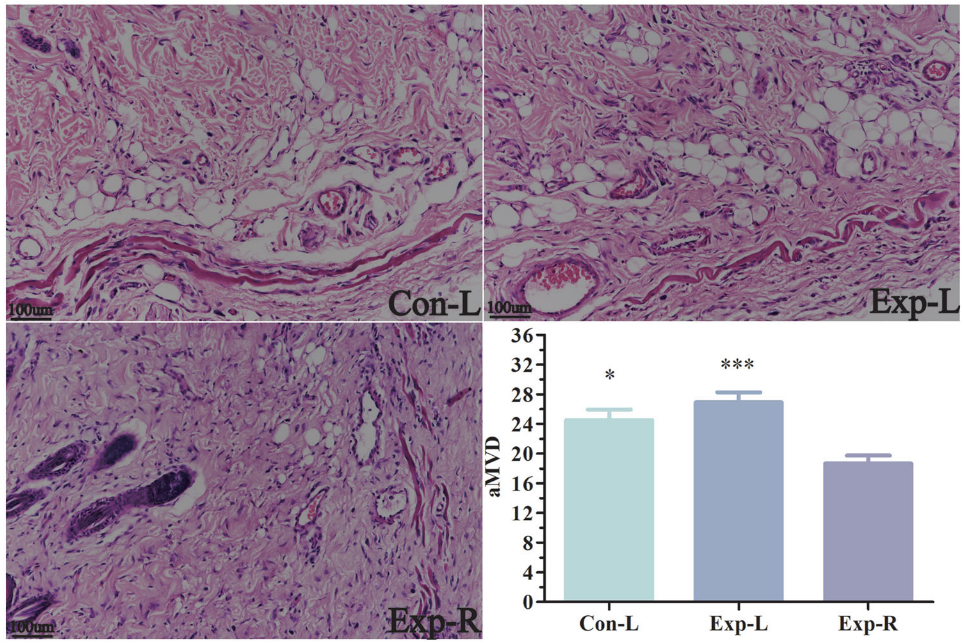

Figure 6. H&E staining for aMVD assessment at 14 days after operation ($n = 8$). Con-L, left ventral flap area in the Con group (skin tissue samples from the right ventral area of the Con group were not harvested because of necrosis); Exp-L and Exp-R, left and right ventral flap areas in the Exp group, respectively. More microvessels were found in Con-L ($^*p < 0.05$) and Exp-L ($^{**}p < 0.001$) compared with Exp-R. Scale bar = 100 μm.

spontaneously resolved. In conditions with relatively insufficient arterial perfusion, increased venous return might slow down the process of flap necrosis, and would not promote flap survival, while causing venous reflux, which does not promote flap survival. Hence, it can be suggested that arterial blood supply should be seriously taken into account in flap design, rather than blindly increasing the number of veins to avoid flap congestion, resulting in prolonged and difficult operation.

The phenomenon of angiogenesis was identified by the aMVD [24,26]. H&E at 14 days after operation showed that aMVD in the venous congested flap was higher than that of the arterial ischemic flap, while there was no significant difference compared with the flap with relatively sufficient arterial perfusion and venous return. This suggested that arterial perfusion promotes angiogenesis of microvessels; however, venous return had no effect on angiogenesis of microvessels.

Arterial supercharging and venous superdrainage are widely used to promote the distal survival of multi-territory perforator flaps, although their effects are controversial. Arterial supercharging promotes flap survival by increasing arterial blood supply [3,27], indicating that arterial blood supply is essential for the survival of the flap, corroborating the present study. Whether venous superdrainage associated flap survival [28,29] is related to increased arterial blood supply is not fully understood. When the flap is transplanted, the vein is easily damaged due to its thin wall, resulting in blocked venous return, which does not promote flap survival, and the added vein of venous superdrainage could replace the damaged vein to promote venous return. Meanwhile, the vein at the distal part of the flap could guide arterial blood supply to this part, leading to improved arterial blood supply at the distal part of the flap, and increased survival of the flap [4,24]. Therefore, the essence of venous superdrainage is still to improve arterial blood supply; however, this effect was achieved by changing the venous position. Therefore, arterial and venous problems should be treated differently during flap transplantation. The artery mainly increases blood supply; if arterial blood supply could not be increased, the guiding role of venous return could be used to solve the arterial blood supply problem; the vein mainly guarantees that venous return is unobstructed. In summary, arterial blood supply determines the survival of the flap, and venous return affects arterial blood supply, which in turn determines flap survival. However, the specific associations of arterial blood supply and venous return with flap survival area should be further studied.

Conclusion

On the same multi-territory perforator flap, arterial blood supply is a prerequisite for flap survival, and is affected by venous return. This suggested that during the process of designing flaps in clinic, a relatively appropriate main artery should be found according to the size of flaps required by the recipient areas, and veins should be designed according to the main artery; eventually, it should be assessed whether or not additional arteries should be added.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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