Breast reinnervation—the next frontier in autologous breast reconstruction: a review of early results

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Abstract: Breast cancer continues to be one of the most common cancers among women with an increasing rate of treatment and prophylactic mastectomies. Breast reconstruction has a well-established positive impact on the psychosocial well-being of women recovering from breast cancer. Surgeons have made substantial advances in breast reconstruction techniques and autologous breast reconstruction has become a popular choice for women seeking a more natural appearance to the breast. However, a lack of sensation remains a challenge and is a source of patient dissatisfaction. Neurotization of breast flaps using donor intercostal nerves in the abdominal flap to recipient intercostal nerves in the chest has been shown to improve recovery of sensation to the reconstructed breast and increase patient satisfaction through earlier recovery of sensation, increased sensitivity to pressure, and even increased erogenous sensation. The authors report the current understanding of re-innervation in autologous breast reconstruction and their preferred technique as well as early results using nerve allograft. A retrospective chart review of 49 autologous free flaps (29 neurotized and 20 non-neurotized) on 26 patients was performed. Recovery of sensation to 9 previously described areas of the flap and mastectomy skin were measured with Semmes Weinstein monofilaments post operatively at 3, 6, and 12 months in order to determine incidence of recovered sensation, area of recovered sensation, and quality of recovered sensation.

Keywords: Breast reconstruction; flap innervation; resensation

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Introduction

Breast cancer has been one of the foremost cancer diagnoses and leading causes of cancer mortality among women for decades, resulting in more than 40,000 deaths annually (1). Nearly 13% of women will be diagnosed with breast cancer during their lifetime (2). Fortunately, continued advances in medical and surgical oncological practices have improved 5-year average survival rates to 90.0%, allowing for greater focus on minimizing the morbidities associated with breast cancer (3).

As rates of prophylactic mastectomies increase across the United States, including contralateral prophylactic mastectomies, increased attention has been given to refining reconstructive techniques to improve both aesthetic and functional outcomes, with surgeons exploring new methods by which to address areas of discontent and improve patient

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reported outcomes (4-11). The lack of sensation after breast reconstruction is one such arena.

While improvements have been made to the aesthetic form of the reconstructed breast, studies show that a major cause of patient dissatisfaction after breast reconstruction is the unnatural decreased sensation of the reconstructed breast (12-14). Autologous breast reconstruction has been shown to fare better than implant-based reconstruction in this regard, and sensibility of free flap breast reconstruction has been shown to improve patient rated quality of life (4,13,15-21). Studies from the 1980s were able to demonstrate that spontaneous recovery of sensation from both the skin margins and the deep surface of the flap is possible in autologous breast reconstruction (12,19,22-24). However, this recovered sensation is quite limited, and there have been documented injuries including thermal injuries sustained by patients who do not regain protective sensation and the ability to respond to nocuous stimuli to the breast (25-28). Surgical repair of the affected nerves has been shown to increase not only the quality and quantity of recovered sensation, but also the likelihood of recovery of erogenous sensation to the remaining breast tissue (22,25,29-31).

Nerves can be repaired through direct coaptation or with the use of a conduit or graft, which serve as a scaffold to guide nerve regeneration and growth (32). In autologous breast reconstruction, a tension free coaptation of donor nerves within the flap to recipient intercostal nerves within the chest can be limited by the availability of adequate length and quality of the cutaneous nerves at both sites requiring increased surgical dissection of the nerves within the rectus abdominis muscle in order to obtain greater length of the donor nerve within the flap. This extensive dissection can weaken and injure the remaining muscle (22,31). To mitigate abdominal wall morbidity caused by harvesting increasing lengths of flap donor nerve, nerve allografts are used to provide the length necessary for coapting the donor and recipient nerves with little to no tension (31-33). The use of nerve allografts over autografts is supported by reduced donor site morbidity, as allografts are readily available, and show comparable clinical outcomes. The authors describe a surgical technique for using an interpositional nerve allograft as a method of breast innervation in autologous breast reconstruction using abdominal free tissue transfer and share their early results using nerve allograft.

Methods

A retrospective chart review of patients undergoing post mastectomy autologous breast reconstruction by the senior author (MDC) was conducted. Females greater than 18 years of age who had undergone post mastectomy autologous breast reconstruction within the previous 18 months and were able to provide informed consent were included in the study. Demographic information, mastectomy and reconstructive surgical details, and post-operative sensory outcomes were recorded. Sixty-seven autologous free flaps were performed on 52 enrolled patients between 2017 and 2019. Forty flaps underwent neurotization using nerve allograft while twenty-seven flaps were not neurotized and thus serve as controls. Neurotizations were performed to the third or fourth intercostal nerve by coaptation to the flap donor nerve with the allograft assisted with a nerve connector consisting of porcine submucosal extracellular matrix. Recovery of sensation to nine previously described areas of the flap and mastectomy skin were measured with Semmes Weinstein monofilaments post operatively at 3, 6, and 12 months in order to determine incidence of recovered sensation, area of recovered sensation, and quality of recovered sensation (*Figure 1*).

Surgical technique

During the standard elevation of the abdominal flap and identification of the major skin perforators from the deep inferior epigastric artery, thoracic intercostal nerves are also identified at the T10, T11, and T12 levels (*Figure 2*). To ensure that only the sensory component of the nerve is utilized and that the motor branches to the rectus muscle are maintained, the donor nerve is taken at the level of the anterior abdominal fascia. Once the nerve has pierced the fascia the composition is purely sensory, whereas the nerve is mixed and comprised of both sensory and motor components below the level of the fascia (22,31). After the donor intercostal nerve on the abdominal flap is identified, a recipient nerve in the breast cavity must also be identified. The recipient nerves are the anterior cutaneous branches of the third or fourth intercostal nerves or the anterior branches of the lateral cutaneous branches of the third or fourth intercostal nerves encountered along the medial or lateral aspect of the breast cavity after mastectomy,

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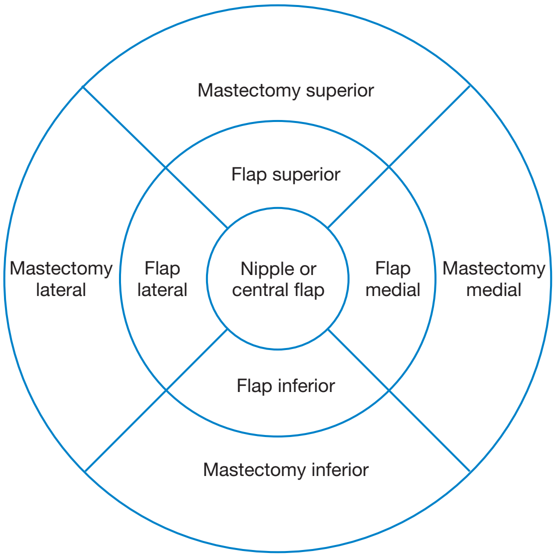

Figure 1 Nine areas for sensory testing of the reconstructed breast.

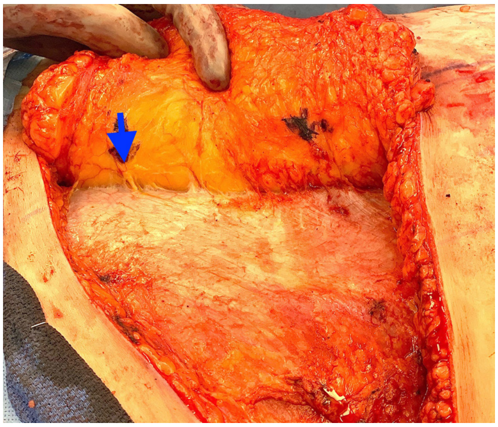

Figure 2 During the abdominal flap elevation, donor intercostal nerves are encountered and marked. Blue arrow demarcates potential T12 donor nerve.

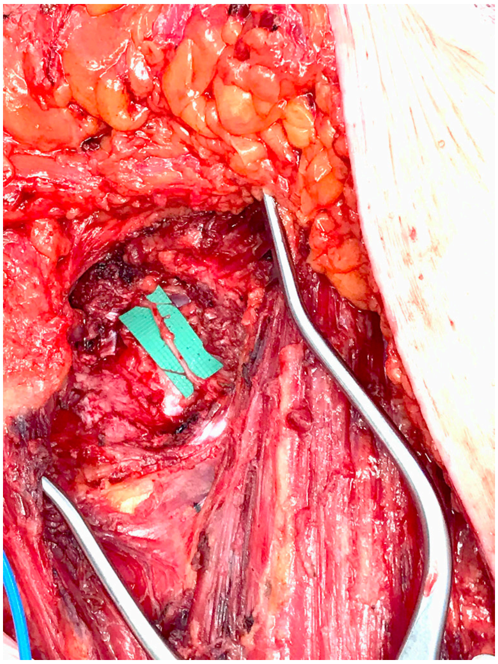

Figure 3 The anterior cutaneous branch of the intercostal nerve in the medial chest can be found during recipient vessel dissection and is visualized crossing perpendicular superficial to the internal mammary vessels. The green background separates the cutaneous nerve from the internal mammary vessels lying beneath.

respectively. The anterior cutaneous branch of the intercostal nerve is easily encountered along the medial aspect of the breast cavity during rib harvest as it travels consistently along the inferior border of the rib external to the perichondrium and crosses over the internal mammary artery and vein (*Figure 3*). The surgeon can further dissect out this nerve laterally along the rib to obtain additional length for coaptation. The anterior branch of the lateral cutaneous branch of the intercostal nerve is often found along the lateral border of the pectoralis major muscle and can be further dissected into the muscle for additional length (*Figure 4*) (31). When possible, the anterior cutaneous branch of the lateral fourth intercostal nerve is selected given its significant contribution in providing sensation to the nipple areolae complex in the native breast, however selection of the recipient nerve is ultimately based on ease of dissection, identification, and proximity to the donor nerve within the abdominal flap after anticipated flap inset to ensure a tension-free coaptation. Collaboration with breast surgeons to identify and dissect the nerves from the breast specimen at the time of mastectomy may further facilitate and expedite neurotization.

Once the donor and recipient nerves have been prepared, there is often an expected gap which may be overcome by placement of an interpositional nerve allograft with sufficient length to span the anticipated gap. To minimize ischemia time, the nerve allograft is coapted to the donor nerve within the abdominal flap *in situ* prior to transfer and vascular anastomosis (*Figure 5*). The nerve and allograft are coapted by with two handsewn epineural interrupted sutures using 9-0 nylon under Loupe magnification

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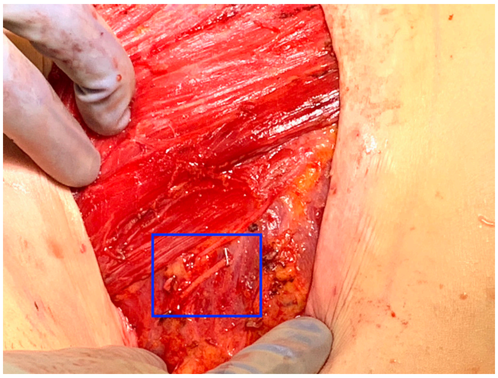

Figure 4 Anterior branches of the lateral cutaneous branch of the 4th intercostal nerve is found along the lateral border of the pectoralis major muscle (blue box).

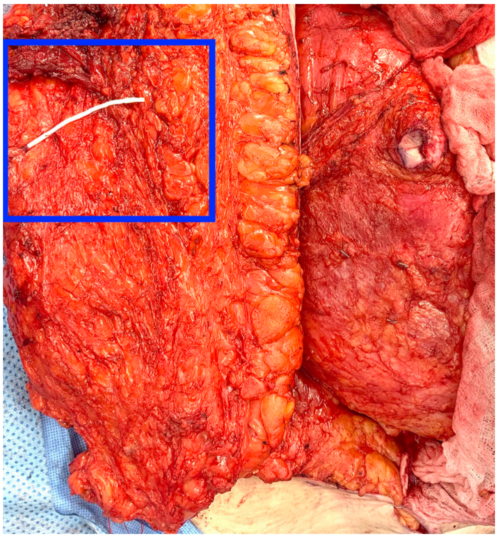

Figure 5 The nerve allograft may be coapted to the donor nerve within the abdominal flap prior to transfer to minimize ischemia time. Flap is reflected caudally after isolation on pedicle where the nerve allograft is connected prior to ischemia of the flap (blue box).

(*Figure 6*). The authors utilize a nerve connector made from porcine submucosa to facilitate the nerve repair, as several studies have shown that connectors can improve directed nerve regeneration across the coaptation site (*Figure 7*) (30-32,34). Following vascular anastomosis, the recipient intercostal nerve is then coapted to the nerve allograft, which is coapted to the donor nerve within the abdominal flap. If the anterior intercostal nerve branch in the medial breast cavity is selected as the recipient nerve then the coaptation is performed within the same operative field as

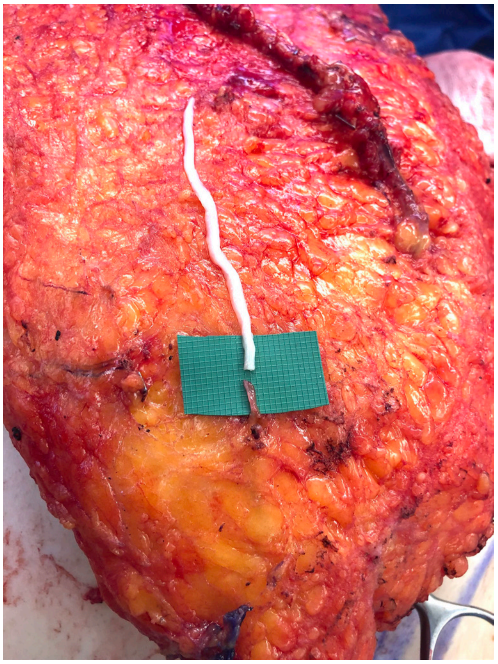

Figure 6 Operative set up for coaptation of the abdominal donor cutaneous nerve to the nerve allograft.

the vascular anastomosis (*Figure 8*). If the lateral cutaneous intercostal nerve in the lateral breast cavity is selected as a recipient nerve, then the coaptation may be performed by reflecting the flap medially with the use of a surgical assistant. The coaptation is again assisted with the nerve connector and the flap is then inset, taking care to avoid tension on the repair. As with any new surgical technique there is a learning curve to performing neurotization, but with familiarity, this procedure may be completed within minutes.

Results and discussion

Forty-nine flaps (29 neurotized and 20 non-neurotized flaps) had greater than 6 months follow up. Initial results demonstrated a higher incidence of recovered sensation and a greater area of recovered sensation in neurotized flaps, however this difference narrowed toward the 12 month follow up. After 12 months, 93% of the neurotized flaps showed evidence of recovered sensation compared with only 87% of non-neurotized flaps. The average number or areas with recovered sensation in neurotized and non-neurotized flaps had sensation recovery to an average of 2 of the 9 previously described areas of the flap and

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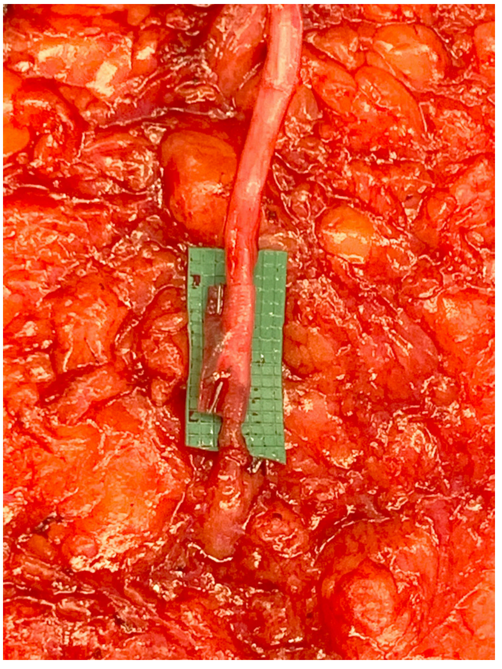

Figure 7 Nerve coaptation assisted with nerve connector.

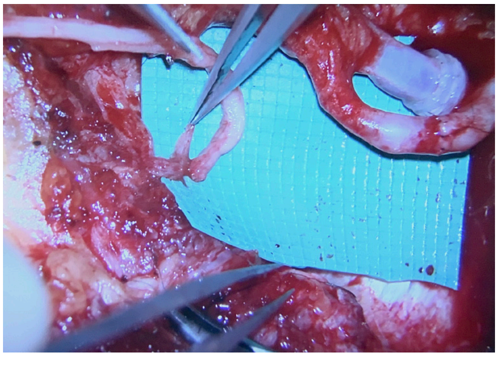

Figure 8 Nerve coaptation of allograft to anterior cutaneous branch in the medial chest may be carried out in same operative field following completion of the vascular anastamosis.

mastectomy skin. There was a slight difference in the return of protective sensation and sensation density as evidenced by the Semmes-Weinstein monofilament test of between the neurotized and non-neurotized flaps, however, this difference was not clinically significant (5.18 and 5.43 g respectively).

Several studies have shown that sensation after autologous breast reconstruction is improved after neurotization, with return of sensation occurring at an accelerated rate and with greater quality and in greater quantity (12-13,22,30,35). Blondeel was one of the earliest to demonstrate improved sensory recovery outcomes after pure sensory coaptation. He studied 121 breasts comprised of 56 nonoperated breasts, 24 neurotized DIEP flaps, 13 non-neurotized DIEP flaps, and 28 non-neurotized TRAM flaps and evaluated quality of recovered sensation using Semmes–Weinstein monofilaments to measure detection of pressure and metal probes to ascertain hot and cold recognition, as well as through sensory evoked potentials. Results showed that 75% of neurotized DIEP flaps regained protective sensation and this sensation was present in all five segments of the breast, compared with 31% of non-neurotized DIEP flaps and 18% of non-neurotized TRAM flaps. The neurotized flaps also demonstrated greater return of erogenous sensation compared with the non-neurotized groups and recovered sensation at lower pressure thresholds (22). More recently, a retrospective study by Speigel showed that of 57 DIEP flaps (9 non-neurotized controls, 48 neurotized flaps of which 33 neurotizations were performed with a 4-cm conduit and 15 neurotizations were performed by direct coaptation), neurotization with nerve conduit achieved recovery of sensation at significantly lower pressure thresholds as compared with flaps neurotized by direct coaptation (30). This finding is noteworthy as conduits are often touted as being most beneficial for noncritical gaps of less than 1 cm (32,36). Improved sensory recovery with the use of a conduit may be related to the manner in which conduits help to take tension off of the coaptation and realign nerve ends, especially in the case of size mismatch. Conduits also decrease the incidence of collateral sprouting, permit an environment rich in neurotrophic factors, and protect the coaptation from scar (37). Several additional studies have reproduced similar results and have also demonstrated improvement in recovered in sensation after neurotization in autologous breast reconstruction, strongly suggesting that the sensory recovery of neurotized flaps occurs sooner with improved innervation density that gradually improves over time and has a greater chance of approaching normal sensation compared to a non-innervated flap (*Table 1*) (35,37-44).

Neurotization has been shown not only to improve sensory recovery after autologous breast reconstruction, but to also improve patient rated satisfaction scores. A randomized, prospective study by Temple employed three different assessment tools (the Medical Outcomes Study, the Body Image after Breast Cancer Questionnaire, and the Functional Assessment of Cancer Therapy–Breast quality-of-life instrument) to survey patients about satisfaction in

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Table 1 Studies comparing outcomes of neurotized and non-neurotized abdominal flaps in autologous breast reconstruction

Study	Type of reconstruction	Total number of pts	Number of pts in each group	Number of breasts or flaps in each group	Mean time to follow up in months [range]	Neurotization			Sensory evaluation			Results
						Donor nerve	Recipient nerve	Technique	Areas tested	Pressure testing	Other testing	
Blondeel (1999), (22)	Unoperated; DIEP–; DIEP+; TRAM–	104	43; 12; 23; 26	56; 13; 24; 28	19.6 [12–38]; 21.4 [13–40]; 19.9 [12–39]	T10, T11, or T12	LCB 4th ICN	Direct end to end	Flap skin Native Skin NAC	SWM	Temp, Vib, SEP	DIEP+ flaps had lower pressure thresholds, greater area recovered sensation, higher incidence of erogenous sensation
Speigel (2013), (30)	DIEP–; DIEP+; DIEP+ with NC	35		9; 15; 33	111 [23–309]	T11 or T12	ACB 3rd ICN	Direct end to end	Flap skin Native Skin NAC	PSSD		DIEP+ with NC had lower pressure thresholds than both DIEP+ and and DIEP-
Slezak (1992), (38)	Unoperated; pTRAM –; pTRAM+	23	10; 10; 3	–; –; 6	53 [24–84]	T10, T11, or T12	LCB 4th ICN	Direct end to end	Flap Skin NAC	SWM	2 pd, Vib	pTRAM+ recovered vibratory sensation earlier
Doncatto (1997), (39)	pTRAM–; pTRAM+	54	27; 27		>8	T11	LCB 4th, 5th, 6th, or 7th ICN	Direct end to side		finger	Temp, Pain	More pTRAM+ had return of superficial sensation
Yano (1998), (40)	pTRAM–; pTRAM+	31	16; 15	16; 15	24 [11–41]; 14 [4–24];	T11 or T12	ACB or LCB or 3rd, 4th, or 5th ICN	Direct end to end	Flap skin Native Skin NAC	SWM	Temp, Pain	TRAM+ had earlier recovery of sensation to touch, pain, and temperature
Yap (2005), (41)	TRAM–; TRAM+	14	7; 7	7; 7	40 [31–46]; 39 [35–46]	Single thoraco-abdominal nerve	LCB 4th or 5th ICN	Direct end to end	Flap skin Native Skin NAC	SWM	Temp	TRAM+ had earlier recovery of sensation, lower pressure thresholds, and better recovery of sensation to temperature
Temple (2006), (42)	TRAM–; TRAM+	27	15; 12	19; 18	16; 15	T10	ACB 4th ICN		Flap skin NAC	SWM	2 pd, Temp	TRAM+ had lower pressure thresholds, better recovery of sensation to temperature, and a more uniform recovery of sensation throughout the flap
Puonti (2011), (43)	TRAM–; TRAM+	40	20; 20	20; 20	54 [27–77]; 32 [23–43];	T10, T11, or T12	Thoraco-dorsal, ICN, or intercosto-brachial nerve	Direct end to end or direct end to side	Flap skin NAC	SWM	Temp, Vib, Pain	TRAM+ had improved total sensory scores
Mori (2011), (44)	pTRAM or pVRAM–; pTRAM or pVRAM+	33	18; 15	18; 15	[12–57]; [12–19]	T10 or T11	LCB of 4th ICN	Direct end to end	Flap skin Native Skin NAC	SWM	Temp, Pain	Conventional mastectomy with neurotized flap had lower pressure thresholds and better recovery of sensation to pain

DIEP, deep inferior epigastric artery perforator flap; TRAM, transverse rectus abdominis myocutaneous flap; VRAM, vertical rectus abdominis myocutaneous flap; p, pedicled; +, with neurotization; –, without neurotization; NC, nerve conduit. Neurotization; T, thoracic intercostal nerve; ICN, intercostal nerve; LCB, lateral cutaneous branch; ACB, anterior cutaneous branch. Sensory evaluation; NAC, nipple areolar complex; SWM, Semmes-Weinstein monofilament; PSSD, pressure specified sensory device; Temp, temperature; Vib, vibration; SEP, sensory evoked potentials; 2 pd, 2-point discrimination.

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various health related domains following neurotized and non-neurotized TRAM flap breast reconstruction. With the use of the Medical Outcomes Study, patients with neurotized flaps scored higher in six of eight domains, including physical function, physical role, body pain, general health, social function, and emotional role. Similarly, innervated flaps outperformed noninnervated flaps in 4 of the 5 domains within the Body Image after Breast Cancer Questionnaire, including vulnerability, body stigma, limitations, and arm concerns, and outperformed in all 5 of the domains within the Functional Assessment of Cancer Therapy–Breast quality-of-life instrument, which include physical well-being, social well-being, emotional well-being, and functional well-being (13).

Though there is evidence to support that neurotization enhances recovery of sensation, results remain heterogenous and there is little consensus in regards to the optimal technique. Peripheral nerve studies in the upper extremity have shown that repair with nerve allograft results in greater meaningful functional outcomes than repairs with nerve conduits, as defined by at least an M3 or S3 recovery on the Medical Research Council Classification scale, and that outcomes are comparable to repairs with nerve autograft that at shorter lengths, though there is evidence to support their use up to 7 cm (32). There is a paucity of literature surrounding the use of allografts in autologous breast reconstruction, though the anatomical basis for their potential benefit in maximizing sensory recovery is well established (31).

Advancements in microsurgical technique have increased interest and investigation of flap neurotization. Anatomical constraints limiting direct coaptation have led to a variety of techniques to overcome these barriers including long intramuscular dissection of native abdominal intercostal nerves for additional length, use of nerve autograft, and use of nerve allograft (22,29-30). Increased length of donor nerve required for flap neurotization via direct coaptation can be acquired by retrograde dissection through the rectus abdominis fascia and rectus abdominis muscle. This additional dissection, however, increases the risk of motor denervation of the rectus abdominis muscle contributing to abdominal wall donor site morbidity (32-33). Furthermore, the use of the mixed sensory-motor nerves that lie posterior the fascia, as opposed to the use of a purely sensory nerve as is the case once the nerve penetrates the abdominal fascia, introduces multiple blind ends from the severed muscular branches which dilutes the potential directed axonal regeneration and leads to suboptimal sensation recovery (31). Limiting donor nerve dissection and harvest from its exit point from the abdominal wall fascia ensures full potential for sensory regeneration and minimizes the amount of muscular denervation at the expense of nerve length and is the anatomical basis for supporting the use of nerve allografts. The use of nerve allograft compensates for the resulting shorter length of nerve and mimics the revascularization and remodeling that would occur with the use of a nerve autograft but without the morbidities associated with autograft harvesting (32).

Conclusions

Flap neurotization is a microsurgical technique that requires minimal additional operative time and improves both functional outcomes and patient satisfaction following autologous breast reconstruction by enhancing the sensibility of the reconstructed breast. Use of a readily available nerve allograft greatly expands the number of patients who may be able to undergo flap neurotization and benefit from this technique by bridging the anatomical limits from the distance between the recipient to donor nerve. Also, use of nerve allograft decreases the morbidity of secondary sensory loss in those with donor autografts with similar sensory outcomes. Further studies are required to better characterize the role of allograft in augmenting the functional and psychosocial outcomes in autologous breast reconstruction.

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Footnote

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to declare.

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