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·专家论坛·

同期神经化血管化髂骨瓣修复下颌骨及神经缺损

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【摘要】 颌骨大型缺损的功能性重建是口腔颌面外科临床的重点问题，自体骨移植是主要的方法。然而，自体骨移植后的骨质易吸收，即使通过吻合血管，移植骨的自发性疏松化仍然严重影响牙种植及功能恢复。因此，血管化自体骨移植的疏松化成为颌骨重建的重要并发症之一，尚无预防措施。血供充足的自体骨无法避免自身疏松化的问题提示：血供之外被长期忽略的神经等系统因素可能调控移植骨内环境。笔者基于前期神经微环境调控间充质干细胞的系列研究，通过构建神经化血管化髂骨瓣动物模型及尸体解剖，提出了同期神经支配的血管化髂骨瓣修复下颌骨缺损的新术式。神经化血管化髂骨瓣移植是在髂骨瓣(骨肌皮瓣)植入受区并行血管吻合后，对同时获取的支配髂骨的髂腹股沟神经(传统方法一般忽略并牺牲)与下牙槽神经近心端及颏神经行显微缝合。笔者团队通过开展临床回顾性研究和前瞻性随机对照试验，证实同期神经化血管化髂骨瓣移植的新方法不仅抵御骨质吸收，而且能够恢复唇等周围软组织的感觉，可解决颌骨重建后感觉缺失及疏松化的关键问题，保证了牙种植义齿的成功，并提出“血供+神经”双系统骨移植的新理念。

【关键词】 下颌骨缺损； 下颌骨重建； 游离髂骨瓣； 血管化； 旋髂深动静脉； 髂腹股沟神经； 下颌神经； 颏神经； 神经支配； 骨质疏松症； 感觉
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Simultaneous innervated and vascularized iliac bone flap for reconstructing mandible and nerve defects

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【Abstract】 The functional reconstruction of large maxillofacial defects is a major issue in oral and maxillofacial surgery, and autologous bone transplantation is the main method. However, bone is readily absorbed following an autologous bone transplant. Even with vascular anastomosis, spontaneous osteoporosis of transplanted bone is still serious, which affects dental implantation and functional recovery. Therefore, osteoporosis of the grafted bone has become one of the main complications of jaw reconstruction, and there is no preventive measure. The problem that autologous bone with sufficient blood supply cannot avoid osteoporosis suggests that systemic factors such as nerves, which have been neglected in traditional methods, may regulate the internal environment of the transplanted bone. Based on previous studies on the regulation of mesenchymal stem cells by the neural microenvironment, we initiated a new surgical procedure for innervated and vascularized iliac bone flaps based on animal model and cadaver studies. In the innervated and vascularized iliac bone flap, vascular microanastomosis was performed in conjunction with microneuronal anastomosis between the simultaneously harvested ilioinguinal nerve (which innervates the iliac bone and is usually sacrificed and neglected in the conventional vascularized iliac bone flap) and the inferior alveolar nerve proximally and with the mental

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nerve distally. By conducting clinical retrospective studies and prospective randomized controlled trials, we proved that the novel method of simultaneous innervated iliac bone transplantation can not only prevent bone resorption but also restore the sensation of adjacent soft tissues such as the lip. This may solve the key problems of sensory loss and osteoporosis after mandibular reconstruction, ensure the success of dental implant dentures, and put forward the new concept of "blood supply + innervation" bi-system bone transplantation.
【Key words】 mandible defect; mandibular reconstruction; free iliac bone flap; vascularization; deep circumflex iliac artery and vein; ilioinguinal nerve; mandibular nerve; mental nerve; innervation; osteoporosis; sensation

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因肿瘤、骨髓炎等引起的颌骨大型缺损的功能性重建是口腔颌面外科临床的重点问题。尽管组织工程骨研究不断取得进展，目前自体骨移植仍是重建颌骨大型节段性缺损的首选方法。非血管化的骨移植需实现血运微循环的建立及爬行替代过程，抗感染能力较低，术后吸收非常严重。1979 年，Taylor 首次提出用旋髂深动脉（deep circumflex iliac artery，DCIA）供血的髂骨瓣修复下颌骨缺损[1]，因其取材量充分、外形与下颌骨轮廓相似、供区较为隐蔽等优点，得到广泛应用。经过国内外前辈和同道们数十年的推广和逐步优化，血管化的髂骨瓣或腓骨瓣已被证明抗感染能力强，能显著提高移植成功率[2]，在救治颌骨大型缺损患者中发挥了重要作用。然而，传统的髂骨瓣或腓骨瓣虽然保障了血供，移植骨仍容易发生自发性吸收而影响牙种植体植入，加之下牙槽神经（inferior alveolar nerve，IAN）的节段性缺损会导致术后下唇麻木、流涎、易烫伤等影响生活质量的并发症，使得患者口颌系统的功能康复受到严重影响[3]。例如，Mertens 等[4]通过前瞻性研究发现，经过血管吻合的髂骨瓣移植，术后 17 个月移植骨的吸收率仍高达 12.58%。血管化自体骨移植的疏松化成为颌骨重建的重要并发症之一，尚无预防措施。血供充足的自体骨无法避免疏松化的问题提示：血供之外被长期忽略的神经等系统因素可能调控移植骨内环境。

本文基于国际同行和笔者关于神经影响骨代谢及神经微环境调控骨髓间充质干细胞的研究，以及笔者团队构建的神经化血管化髂骨瓣动物模型与尸体解剖，提出一种同期神经化的血管化髂骨瓣新术式；并通过临床回顾性研究和前瞻性对照试验，证明了这种同期神经化血管化的髂骨瓣能保存下唇感觉并抵御移植骨吸收，较好地解决了颌骨重建后软组织感觉缺失及骨质疏松化的关键问题，有助于提高颌骨重建患者的生活质量。

1　同期神经化血管化的髂骨瓣修复下颌骨及神经缺损的生物学基础

1.1　感觉神经与骨折愈合

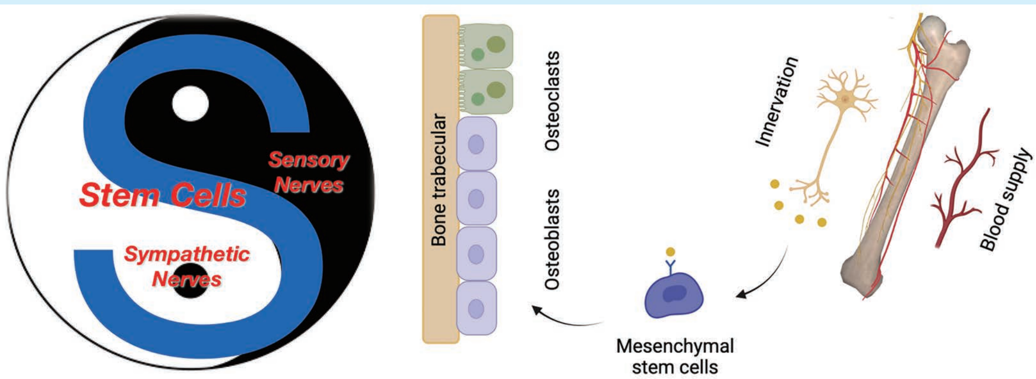
感觉神经与骨代谢、生理改建、骨折愈合等密切相关。大鼠应力骨折模型中，感觉神经纤维再生在骨膜血管化、骨化和矿化等关键节点之前首先出现[5]，提示神经对于骨折愈合的关键作用。感觉神经的损伤则会影响新生成骨的质量、骨小梁的连通性，增强骨吸收、骨脆性。在去感觉神经小鼠（$TrkAAvil^{-/-}$）中，表达降钙素基因相关肽（calcitonin gene related peptide，CGRP）的感觉神经纤维被消除，这些小鼠表现出成骨细胞数量明显降低、骨质流失的特点[6]。从神经生长发育过程来看，神经在骨组织中的生长与骨的矿化过程是平行的。在成熟的骨组织中，尤其是骨膜内，也发现了丰富的感觉神经分布。此外，细小的神经纤维可与哈弗斯系统或骨髓腔中的滋养血管相伴行，大量对疼痛和机械应力敏感的感觉神经纤维支配骨膜和骨小梁[7]，这些发现均表明了神经与骨组织在解剖结构上的密切关系。

1.2　感觉神经与骨稳态

骨稳态是一种矿物质稳态，归功于破骨细胞吸收骨组织与成骨细胞形成新骨间的动态平衡，以利于骨骼系统行使其支持、保护、运动及储存矿

物质等功能[8]。骨髓间充质干细胞(bone marrow mesenchymal stem cells,BMMSCs)是一种具备自我更新能力的非造血干细胞群,能够向成骨、成脂肪和软骨等方向分化[9-10]。BMMSCs保持Hox基因等发育基因的表达。Hox基因编码一种进化保守的转录因子,能够调控骨骼发育模式,在调节长骨的形态和脊椎发育以及骨骼修复中发挥关键作用[11]。炎症因子、激素等微环境会影响BMMSCs的活性及分化方向,这种微环境也被称作“干细胞龛”。微环境的变化常导致BMMSCs的老化,即转为脂肪生成细胞而不是成骨细胞,从而引起骨稳态失衡[12]。而且BMMSCs能够与造血干细胞的分化细胞(T细胞、NK细胞及破骨细胞等)相互作用[13],因此BMMSCs是骨再生及稳态维持的关键细胞。2010年,Méndez-Ferrer等[14]在Nature杂志首次报道神经纤维构成骨髓干细胞龛以来,神经系统调控干细胞的研究受到越来越多的重视。之后,小鼠切牙血管神经束周围被证明存在间充质干细胞(mesenchymal stem cells,MSCs)龛,而且血管神经束通过Shh(Sonic Hedgehog)蛋白调控MSCs的干细胞活力[15]。近年来组织工程研究也发现,神经化也可能促进组织工程骨形成[16]。支配骨的神经纤维通过神经递质发挥对骨内环境及骨细胞的调控[17]。笔者团队通过卵巢切除术构造骨质疏松小鼠模型和体外研究发现:炎性微环境可诱导体内正常的BMMSCs分化低下或凋亡,而且导致BMMSCs诱导破骨细胞凋亡的能力下降[18-19]。然而移植后自体骨BMMSCs的炎性微环境并不显著。因此,笔者进一步研究神经系统在自体骨移植中的作用,并通过临床回顾性研究发现,同期神经化血管化髂骨瓣的新方法能使疏松化明显减少,保证牙种植的成功,该研究论文被*Plast Reconst Surg*列为封面论文[20]。重建神经支配可有效预防移植骨疏松化,这提示缺乏神经支配可能就是导致BMMSCs活力下降的原因之一。

研究发现,信号素3A(semaphorin 3A,Sema3A)通过调节感觉神经来间接调节骨代谢,揭示了感觉神经在骨稳态中的作用,而应用CGRP或Sema3A能够促进骨再生[21-25]。而且笔者团队前期通过大鼠下颌牵张成骨模型发现,感觉神经缺失会导致新生骨体积、骨厚度及骨密度显著降低[26]。局部应用神经生长因子有利于减少牵张成骨过程中神经纤维空泡性变,促进轴突再生[27-28]。此外,神经生长因子还能够提高新生成骨质量[29-30]。人源神经生长因子β修饰的转基因MSCs可以加速牵张成骨过程中下牙槽神经的形态恢复[31]。文献报道及笔者团队前期研究均提示感觉神经在骨再生和改建中发挥重要作用。另一方面,交感神经在骨再生和改建中主要起负向调控作用,即牵张应力能够通过基质细胞衍生因子-1等趋化因子促使局部BMMSCs脱离基于交感神经/内皮细胞的干细胞龛,并迁移到成骨前线[32-34](图1)。



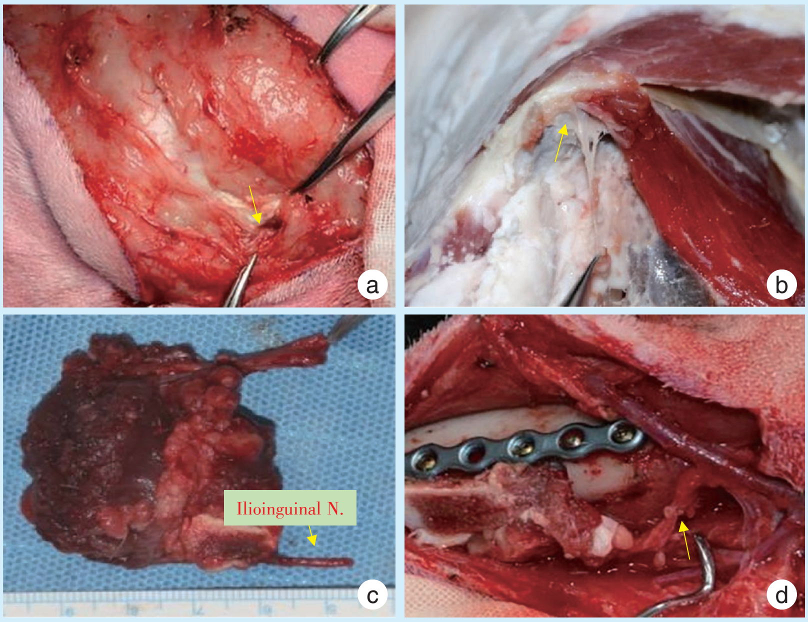
The effects of sensory and sympathetic nerves on BMMSCs are similar to the two poles of Tai Chi, in which sensory nerves can promote the migration of BMMSCs from the vascular wall to the osteogenic front and promote osteogenic differentiation by secreting neurotransmitters. However, sympathetic nerves play a negative regulatory role in bone remodeling, inhibiting the migration and osteogenic differentiation of BMMSCs. BMMSCs: bone marrow mesenchymal stem cells

Figure 1　The nervous system regulates bone metabolism by regulating BMMSCs

图1　神经系统通过调控骨髓间充质干细胞调节骨代谢

2　同期神经化血管化的髂骨瓣修复下颌骨及神经缺损的解剖学基础

笔者团队在神经化旋髂深动脉（DCIA）为供血血管的髂骨瓣（骨肌皮瓣）——简称为神经化DCIA瓣的雄性山羊动物模型中（伦理审批号：SH9H-2019-A334-1），沿着腹股沟韧带解剖以定位DCIA和旋髂深静脉（deep circumflex iliac vein，DCIV），沿腹内斜肌岛两侧解剖分离髂腹股沟神经（ilioinguinal nerve，IlN）约2 cm。自髂前上棘处取出大小约4 cm × 2 cm髂骨，观察骨断面渗血情况，以评估骨瓣血运。离断血管蒂与IlN，至此带IlN的神经化血管化髂骨瓣制备完成。将髂骨瓣置于下颌骨缺损部位，显微吻合血管蒂与受区动静脉，同时吻合IlN与下牙槽神经，重建钛板固定髂骨瓣（图2）。



a&b: incision of the skin and subcutaneous tissue, exposed and dissected IlN (arrows). c: prepared neuralized vasculized iliac bone flap. d: microanastomosis of IlN and IAN (arrow). IlN: ilioinguinal nerve. IAN: inferior alveolar nerve

Figure 2　An animal model of mandibular and inferior alveolar nerve reconstruction with an innervated and vascularized iliac bone flap

图2　神经化血管化髂骨瓣重建下颌骨及下牙槽神经缺损的动物模型

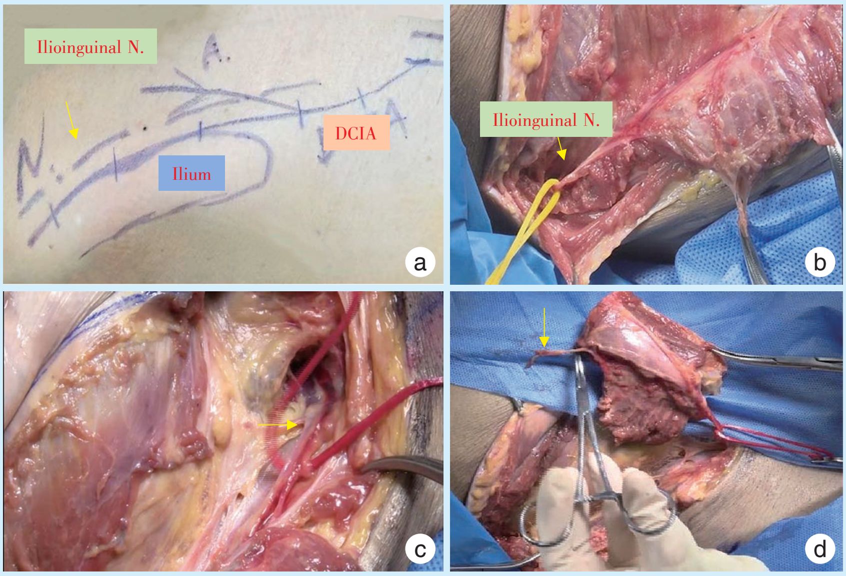
由于人体与山羊解剖的差异，笔者进一步地通过尸体解剖探究神经化血管化髂骨瓣修复下颌骨及下牙槽神经缺损的可行性。于髂前上棘作长约15 cm切口，切开皮肤、皮下、腹外斜肌、腹内斜肌，仔细寻找并解剖DCIA，逆行解剖至髂外动脉，保留其穿支及与髂骨连接。此过程中须仔细分离保护股前外侧皮神经，以避免术后股前外侧区域皮肤麻木。于髂骨内侧分离腹横肌、髂肌，外侧分离臀大肌，IlN在髂嵴上方穿过腹横肌至腹内斜肌深层，在腹股沟韧带中点附近，穿出腹内斜肌。自腹内斜肌两侧解剖分离IlN 3 ~ 5 cm，与腹内斜肌一同切断。切取髂骨肌皮瓣，当截骨完成且骨瓣完全游离后，将DCIA和DCIV从髂外动静脉处分离。至此，带有IlN的神经化血管化髂骨瓣制备完成（图3）。

山羊动物模型及尸体模型的神经化血管化髂骨瓣制备，证实带IlN的神经化血管化髂骨瓣的制备是切实可行的，为神经化DCIA瓣用于临床重建下颌骨及下牙槽神经缺损打下坚实基础。IlN由第一腰神经发出，沿髂骨外侧缘经髂前上棘和髂腹股沟管达外生殖器，包含支配腹内斜肌的运动神经及外生殖器的感觉神经。在进行传统DCIA瓣制备时，因取骨部位常位于髂前上棘，需解剖离断此神经。而神经化DCIA瓣在制备时，仅需沿IlN两端解剖分离3 ~ 5 cm，将原本牺牲掉的神经用于下牙槽神经重建，不会对供区造成额外的损伤。

实际临床应用时，部分病例需行神经骨内解剖以暴露下牙槽神经近心端。近心端与IlN的吻合常在骨瓣固定前进行，以避免骨瓣阻挡视线。而颏神经与IlN的吻合可在骨瓣固定后进行，以减少神经吻合过程中的张力。后续的任何操作都要小心保护血管蒂及神经。值得注意的是，在神经化血管化髂骨瓣应用于临床时，应术中使用神经监护仪确保神经的成功重建[35]。

3　同期神经化血管化的髂骨瓣修复下颌骨及神经缺损的临床应用

笔者前期临床回顾性研究显示，同期神经化

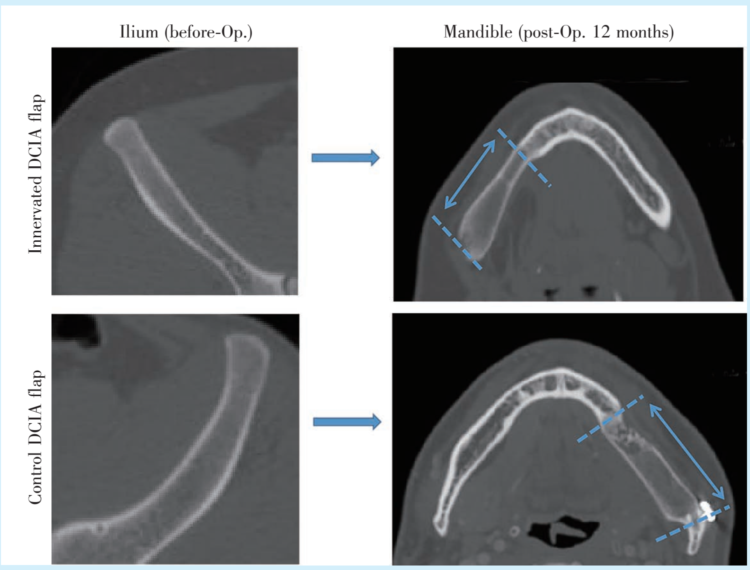


a: design the flap removal scheme and draw lines to mark the iliac crest, DCIA, and IlN. b: trace and dissect the IlN with a length of 3-5 cm from both sides of the internal abdominal oblique muscle. c: find the reverse anatomy of the deep iliac circumflex vessels to the origin. At the distal end, the ascending branch of the deep iliac circumflex vessels (arrow) was found to enter the internal oblique muscle. d: severe the IlN and deep iliac circumflex vessels. The composite tissue flap with one pedicle (deep circumflex iliac vessel), two islands (internal oblique muscle and iliac bone) and one nerve (ilioinguinal nerve) (arrow) was prepared. DCIA: deep circumflex iliac artery. IlN: ilioinguinal nerve. N: nerve

Figure 3　Preparation of an innervated and vascularized iliac bone flap on human cadaver

图3　通过尸体解剖进行神经化血管化髂骨瓣的制备

血管化髂骨瓣移植的新方法能使疏松化明显减少，保证牙种植的成功[20]。为进一步明确神经化血管化髂骨瓣预防骨吸收的效果，笔者团队设计了前瞻性临床试验研究INVITATION（Innervation of Vascularized Iliac Transplant Avoids Resorption in Jaw Bone Reconstruction），并于美国临床试验数据库ClinicalTrials.gov注册（登记号为NCT03889587，注册机构为Shanghai9th）。前瞻性临床试验"邀请"长期被忽视的神经以预防移植的血管化髂骨瓣发生骨吸收，将拟DCIA瓣修复下颌骨缺损患者随机分为传统DCIA瓣组（血管化DCIA瓣）和神经化DCIA瓣组（同期显微吻合IlN及下牙槽神经、颏神经残端的血管化DCIA瓣），探讨神经化血管化髂骨瓣移植预防移植骨术后骨质疏松化的应用效果，所有参与者均知情同意（伦理审批号：SH9H-2018-T95-2）。颌骨重建术后一年行颌面部CT检查发现，常规血管化髂骨瓣发生明显的骨质吸收，而同期行下牙槽神经重建的血管化移植骨骨质与手术前相似（图4），这将有利于患者的种植义齿修复。供区的并发症包括瘢痕、腹股沟及部分外生殖器感觉减退（特别是在男性患者，但一般可在3年内逐步恢复到接近正常），相关运动无受损



One year after the traditional iliac flap transplantation, there was significant resorption of cancellous bone in the transplanted bone, but the innervated and vascularized iliac bone flap was similar to that before the operation (left, iliac crest before harvesting). DCIA: deep circumflex iliac artery. Op: operation

Figure 4　CT examination of bone resorption one year after implantation of the innervated and vascularized iliac bone flap

图4　CT检查神经化血管化髂骨瓣术后1年移植骨吸收

情况。

下牙槽神经是下颌神经的分支，经下颌孔进入下颌管，支配下颌牙齿及牙龈。终末支经颏孔穿出，更名为颏神经，分布在下唇及颏部的皮肤，下牙槽神经的运动支支配下颌舌骨肌和二腹肌前腹。颌骨肿瘤切除、正颌手术、拔牙或外伤常导致下牙槽神经的损伤，患者常出现下唇及颏部麻木感，咬唇、饮水外流等症状。带IIN的髂骨瓣重建颌骨缺损并同期重建下牙槽神经，可有效保存下唇及颏部的感觉，并能有效减少唾液外流[36]。在术后一年测量神经化血管化髂骨瓣修复患者的下唇及颏部感觉电流阈值，手术侧下唇及颏部感觉神经阈值（current perception threshold，CPT）测试评级为3.00，表示非常轻度感觉功能障碍。非手术侧等级为0.00，表示测试无异常（表1），提示IIN可成功重建下牙槽神经并保存下唇及颏部感觉。此外，笔者团队还通过两点辨别觉（two-point discrimination，TPD）检测患者下唇及颏部的触觉。下牙槽神经重建患者手术侧下唇及颏部能分辨的两点间最小距离分别为3.21 mm和10.66 mm，远低于传统DCIA瓣患者的36.16 mm和43.31 mm，表明神经重建后，下唇及颏部皮肤感觉得到保存（图5）。此外，感觉检测的常用方法还有：Vonfrey测试丝[37]、笔触定向识别[38]、针刺痛感知[39]、热刺激[39]、振动刺激以及视觉模拟量表（visual analog scale，VAS）和医学研究委员会量表（Medical Research Council Scale，MRCS）[40]等，能够辅助检测痛觉、冷热觉、触觉、深度感觉等。重建修复下牙槽神经缺损时，国际同类研究往往只关注感觉恢复这项单一指标，未能将感觉神经重建与骨稳态联系起来，因此关于下牙槽神经重建后下颌骨或移植骨质量改变的研究偏少。神经化血管化髂骨瓣修复下颌骨及神经缺损的文献报告见表2。

4　总　结

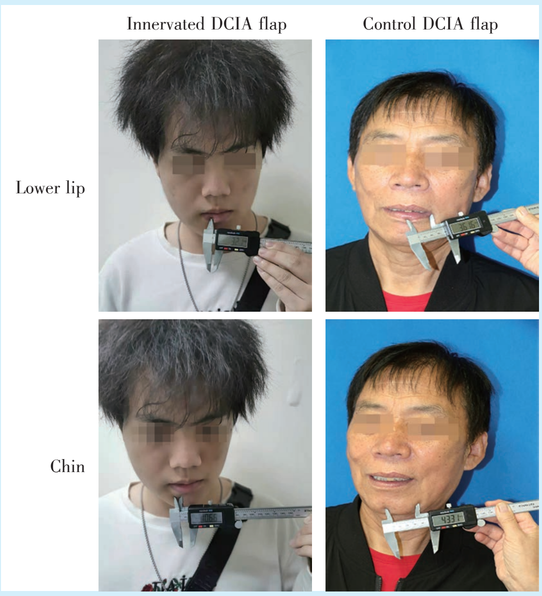
同期神经化血管化的髂骨瓣在修复下颌骨及神经缺损中，既能保存下唇感觉又能预防移植骨的术后吸收，初步解决了颌骨重建后软组织感觉缺失及疏松化的难题，进一步提高了颌骨重建患者的生活质量，回顾性和前瞻性临床研究均表现

表1　神经化血管化髂骨瓣术后1年双侧三叉神经下颌支的电流刺激感觉阈值

Table 1　CPT of the bilateral trigeminal mandibular branches one year after innervated and vascularized iliac bone flap surgery

	2 kHz	250 Hz	5 Hz	Grade
Mandibular nerve	Minimum/Maximum/Mean (40/244/118)	Minimum/Maximum/Mean (4/52/19)	Minimum/Maximum/Mean (1/38/10)	
The operation side (Mean)	85.0	48.0	14.0	3.00
Non-operation side (Mean)	207.0	19.0	7.0	0.00

CPT: current perception threshold



DCIA: deep circumflex iliac artery. TPD: two point discrimination. CPT: current perception threshold

Figure 5　TPD of the lower lip and chin in the innervated DCIA flap group and the control DCIA flap group

图5　神经化DCIA瓣组与传统DCIA瓣组下唇及颏部两点辨别觉检测

表2　神经化血管化髂骨瓣修复下颌骨及神经缺损的文献报告

Table 2　Literature reports on the repair of mandible and nerve defects with innervated and vascularized iliac bone flaps

Year	Number of cases	Bone myocutaneous flap and nerve	The nerve that was anastomosed	Key outcomes	Results/effects	References
2012	12	Fibula flap with sural nerve	Inferior alveolar nerve, mental nerve	Sensation in lower lip and chin	TPD test showed that the mean static TPD of lower lip was 13.7 mm, the mean dynamic TPD was 13.3 mm, the mean static TPD of chin was 13.7 mm, and the mean dynamic TPD of chin was 13.4 mm. There was no control group without inferior alveolar nerve reconstruction	[41]
2015	13	Fibula flap with sural nerve	Inferior alveolar nerve, mental nerve (6 cases) Inferior alveolar nerve (7 cases)	Sensation in lower lip The outflow of saliva	The score of Semmes-Weinstein test was 4.33±1.21 in the inferior alveolar nerve and mental nerve reconstruction group, and 1.43±0.53 in the non-mental nerve reconstruction group (P = 0.000 5) There were significant differences in salivary efflux between the two groups (P = 0.002)	[42]
2016	1	Fibula flap with sural nerve	Inferior alveolar nerve, mental nerve	Sensation in lower lip and chin	Sensory recovery was first noted 5 months after surgery, and the quantitative Semmes-Weinstein test results at 45 months after surgery ranged from 2.83 to 4.08	[43]
2016	66	Rib flap with intercostal nerve	Inferior alveolar nerve, mental nerve	Sensation in lower lip and chin	CPT test showed that the sensory thresholds at 5 Hz, 250 Hz, and 2k Hz in patients undergoing nerve reconstruction were significantly lower than those in the side without nerve reconstruction (P < 0.001)	[44]
2017	10	The iliac crest with the ilioinguinal nerve	Inferior alveolar nerve	Hu value of transplanted bone and initial stability of implant	During the 12-month follow-up, the bone mineral density loss in the innervated group was significantly lower than that in the control group (P < 0.05), and the initial stability of the implant was significantly higher than that in the control group (P < 0.05)	[20]
2022	6	The iliac crest with the ilioinguinal nerve	Inferior alveolar nerve, mental nerve	Sensation in lower lip The outflow of saliva	The results of TPD and CPT in the lower lip of the surgical side 12 months after operation were better than those in the group without nerve reconstruction (P < 0.05). In addition, salivary efflux was significantly reduced after reconstruction of the inferior alveolar nerve in N. ilioinguinal (P < 0.05)	[36]

TPD: two point discrimination. CPT: current perception threshold

出良好的临床疗效。技术操作方面，术中需注意解剖并保护DCIA伴行的IIN神经（传统血管化髂骨瓣中一般忽略并牺牲），分别与下牙槽神经近心端和颏神经断端吻合，使得下唇、颏部皮肤接收外界刺激并将信号传递至中枢，同时接收来自中枢的信号并做出反馈，重构患者的感觉反馈环路。这种神经化血管化髂骨瓣的适应证包括：①年龄18 ~ 65岁患者，性别不限；②下颌骨患良性肿瘤、骨髓炎或术后不需放化疗的恶性肿瘤；③下颌骨节段性缺损5 ~ 12 cm；④全身情况可，无绝经期相关骨质疏松症，血糖可控制于正常范围。禁忌证包括：①恶性肿瘤晚期，需放疗或化疗者（放疗或化疗都能引起骨质疏松和感觉异常，影响效果观察）；②全身情况差，不能耐受骨瓣修复者。然而，应用这种神经化血管化髂骨瓣后，下牙槽神经损伤和修复期间中枢调控机制尚不明确，需要进行深入研究。总之，笔者团队将长此以往被忽视的神经因素"邀请"进骨稳态的临床及基础研究中，希冀能够减少移植骨疏松化并保存下唇感觉，这将有助于提高颌骨重建患者的生活质量。

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