Chapter 1

Unconventional Perfusion Flaps

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Abstract

Integumentary defects, either isolated or combined with loss of other tissues, are frequently encountered clinically, and their reconstruction is often vexing and imperfect.

Unconventional perfusion flaps (UPFs) are reconstructive options characterized by being perfused exclusively by veins. They were first introduced in the clinical literature by Vaubel in 1976 and further elaborated experimentally in 1981 by Nakayama. In UPFs at least one of the afferent veins of the flap is anastomosed to a feeding vessel. Usually, this feeding vessel is an artery, and the UPF is called an **arterialized venous flap (AVF)**. If the feeding vessel is a vein, the UPF is called a **venous flap** (VF). The efflux of blood is ensured in most cases by the continuity of one or more of the UPF's veins with neighboring veins.

UPFs present several potential advantages relatively to conventional perfusion flaps, namely: faster and easier dissection; thinness and pliability; minimal morbidity in

the donor zone; and can be harvested from most regions of the body.

Despite all these advantages, UPFs have rarely been mentioned in the clinical literature, probably because some authors report high necrosis rates, particularly in the presence of infection, and because the underlying physiologic mechanisms remain poorly understood.

Notwithstanding, there is considerable evidence to suggest the usefulness of these reconstructive options in integumentary reconstruction, particularly in regions where a thin and pliable covering is desirable. Moreover, UPFs may be useful for bridging nerve defects. However, further studies are needed to certify the efficacy of UPFs in this context.

Unconventional Perfusion Flaps in the Context of Plastic and Reconstructive Surgery

There has ample evidence that from the dawn of times human beings have sustained injuries to all regions of the body [1,2]. In fact, even human ancestors' remains show skeletal evidence of violent blows from as early as the beginning of the Paleolithic period [3]. From these injuries a wide variety of defects presumably resulted, the most well documented being fractures and fractures' complications, such as osteomyelitis [4].

When these injuries did not result in the death of those affected, functional disability and/or deformity resulted. The latter, in turn, devalued individuals both familiarly, socially, and economically, curtailing the potential of the individuals affected. Even today, apart from the obvious consequences of functional impairment, disfigurement has been shown to be associated with low self-esteem, to greatly depreciate one's value in society, and to exert a major toll in one's love life [5-9]. From another perspective, the importance attributed to beauty throughout times has led people from all parts of the world to seek numerous procedures to boost external appearance. The contemporary corollary of this prevailing trend is the hype for aesthetic surgery worldwide [10,11].

As a result of these ancestral worries, tales of body parts transfers between individuals, frequently from different species, are found in many of the most ancient civilizations from all over the globe [12]. More than three millennia ago, local flaps with reconstructive purposes were described in the Edwin Smith papyrus [12]. However, the strategies available to reconstruct faulty or missing parts of the body were limited for a great part of the human history by an insufficient knowledge of physiology [13-15].

It was only in 1628, when William Harvey provided an accurate description of the blood circulation in the human body, that was known that systemic arteries deliver blood rich in oxygen and nutrients to tissues for their maintenance, while systemic veins drain carbon dioxide and metabolic wastes from these tissues back to the right atria of the heart [16]. This knowledge, published for the first time in "*Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*", commonly quoted as "*de Motu Cordis*", truly revolutionized all fields of Medicine. It laid the foundations for understanding tissue transfers, such as grafts and flaps, in what much later become known as Plastic and Reconstructive Surgery [13,17].

In contemporary times, integumentary defects, either isolated or combined with loss of other tissues, such as tendon, bone, vessels and/or nerve, can result from a great deal of situations such as trauma, including burns; tumor extirpation; infection; radiotherapy and/or auto-immune conditions [18]. These defects can thus be rather diverse in nature and clinical implications. However, in most circumstances optimal aesthetical and functional results are difficult to attain. Generally speaking, the following surgical options are available in increasing order of complexity: grafts, local flaps, regional flaps and free flaps [18].

A **graft** is defined as the transference of a tissue or a combination of tissues with no blood supply of their own initially to another place in the body. The potential viable volume and thickness of grafts are therefore limited, as during the first 2 to 3 days after grafting tissues will be forced to survive through a process of "plasmatic imbibition". This process consists in direct exchanges of oxygen, carbon dioxide, water, metabolites and catabolites between the engrafted tissues and the wound bed through direct diffusion [18]. For this process to occur, it is mandatory that the wound bed and neighboring tissues are adequately perfused, until neoangiogenesis provides the graft with a blood supply of its own [19].

There are references to skin grafts being performed as far back as in ancient Indian scrolls more than 2500 years ago [20]. Apart from the anecdotal report of Leonardo Fioravanti replantation of an avulsed nasal tip of a Spanish soldier in 1570 as a skin graft, this technique was all but forgotten until the work of Barionio's work on skin grafts in sheep [21]. This work was published in 1804 with the title "*On grafting in animals*". Notwithstanding, skin grafting only became current clinical practice after the description of pinch skin grafts by Reverdin in 1869 [12]. Ollier and Thiersch further expanded the application of skin grafts by the introduction of partial thickness skin grafts in 1872 and 1886, respectively [22]. The introduction of large full-thickness skin grafts is generally attributed to Wolfe and Krause in 1875 and 1893, respectively [20]. In 1964, Tanner described the mesh skin graft, permitting the expansion of skin grafts up to nine times their original surface. Arguably, this further revolutionized plastic surgery, and in the particular the treatment of burned patients, saving countless lives [23,24]. Building on these milestones, numerous advances were made, leading to contemporary grafting procedures, now encompassing numerous structures besides the skin, such as mucosa, tendon, bone, cartilage, nerve, and fat alone or in multiple combinations [12,25-30].

A **flap** is a composite block of tissues with a blood supply of its own. The flap can be **pedicled** if its original vascular connections are left in place. The flap's pedicle then becomes the pivotal point around each the tissue transfer can be performed. In a **free flap**, the original blood supply is sectioned and subsequently its vessels are microvascularly sutured to vessels in the recipient zone. In large and/or complex tissue defects, free flaps are frequently the only reconstructive option, allowing the replacement of vessels, nerves, tendons, ligaments, bone, cartilage, muscle and/or joints [18,31-35]. Despite the inherent technical difficulties in performing the microvascular anastomoses and the non-negligible risk of pedicle vessel thrombosis, free flaps have become increasingly common in the past decades, with numerous different flaps and variations of these flaps being described [17,36]. Nowadays, free flaps solve otherwise untreatable situations or cases whose prior treatment was clearly insufficient [31-35,37,38].

Most free flaps used in contemporary clinical practice are based on a vascular pedicle composed of, at least, one artery and one vein. These flaps can be considered **conventional flaps (CFs)** In order to obtain arteries of sufficient length and caliber to adequately perform vascular anastomoses at the recipient site, CFs arteries are usually painstakingly dissected below muscular fascias, often demanding a deep, technically challenging and time-consuming dissection. As a corollary, CFs tend to be relatively thick, even after debulking the flap, and the donor site morbidity is not always insignificant. Unfortunately, thick CFs are not always ideal to reconstruct regions where the integument is shallow, such as the head and neck regions, the dorsum of the hand, the foot or the external genitalia. Additionally, the harvesting of a CF demands the sacrifice of significant anatomical structures in the donor zone, as it entails at least the recruitment of a large enough deep artery and eventually of a deep vein, on which the CF is based [39].

In the past two decades, in an effort to minimize these shortcomings of CFs, some surgeons have advocated the resort to **supermicrosurgery** techniques, in which flaps are pedicled on very fine vessels, less than 1 mm in diameter, with resort to special surgical instruments and techniques [40]. Although, supermicrosurgery does preclude the need in many cases of dissecting and sacrificing CP vessels bellow muscular fascia, it has not gained widespread acceptance, as it is technically very demanding, requires special and expensive equipment, flaps' pedicles are often short and difficult to inset, and flaps are, according to many authors, prone to thrombosis, due to the tiny size of flaps' vessels [17,40,41].

Unconventional perfusion flaps (UPFs) are characterized by being perfused solely through their venous system. They were first introduced in the clinical literature in 1976 by Vaubel to reconstruct the dorsum of the hand with a forearm fasciocutaneous flap [42,43]. In 1981, Nakayama *et al*. described a fasciocutaneous UPF in the ventrolateral aspect of the rat's abdomen [44]. In UPFs at least one of the afferent veins of the flap is anastomosed to a feeding vessel at the recipient site. Usually, this feeding vessel is an artery, and the UPF is called an **arterialized venous flap (AVF)**. If the feeding vessel is a vein, the UPF is called a **venous flap (VF)** [43]. In UPFs the efflux of blood is ensured in most cases by the continuity of one or more of the flap's veins with neighboring veins (Figure 1).

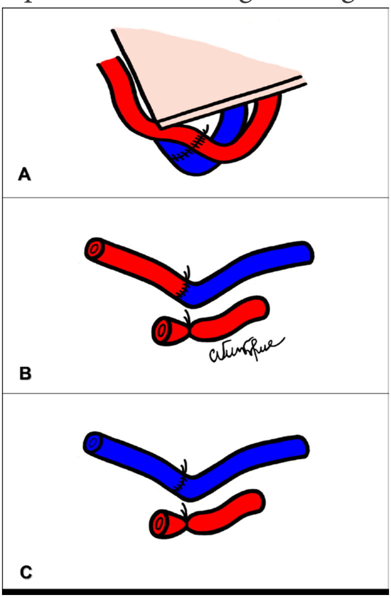

Figure 1: Schematic representation of the basic vascular architecture at the afferent side of the flap of a conventional perfusion flap (A), of a venous arterialized flap (B), and of a venous flap (C). Red vessels represent arteries and blue vessels symbolize veins.

A: In a conventional flap, here exemplified by a conventional free flap, the artery and vein that normally supply the three-dimensional block of tissues that compose the flap are anastomosed to a vein and artery at the reception zone. Blood perfusion through the flap occurs as in the rest of the body.

B: In an arterialized venous flap, the three-dimensional block of tissues that constitute the flap is completely deprived of any arteries and thus become entirely dependent on the venous system for blood flow. At least one of the flap's veins is connected to one recipient site's artery. One or more veins are usually anastomosed to recipient site's veins in order to permit flap outflow (not shown).

C: In venous flaps, the tissues that make up the flap also rely initially completely on perfusion through the venous system. Venous anastomoses are performed at the recipient site at the inflow and outflow regions of the flap (the latter are not shown).

In rare circumstances, the draining vein of the flap is surgically connected to an adjacent artery, usually to satisfy the double purpose of draining the UPFs blood efflux and to reconstruct a missing artery segment. These latter UPFs are called **flow through AVFs** [45,46].

Advantages of Unconventional Perfusion Flaps

Being based solely on the venous system, UPFs can be easily tailored around the superficial venous system. These flaps can include any tissues neighboring veins. Hence, they can include skin, subcutaneous tissue, fascia, nerves, and even bone and/or cartilage in various combinations [43,47]. Consequently, UPFs present several potential advantages relatively to CFs, namely:

- UPFs have a faster and easier dissection, as the superficial venous system is readily observed and accessible above muscle fascia;
- UPFs avoid the need to resorting to ancillary image examinations, making them excellent options when expedite reconstruction is necessary, particularly in trauma cases
- UPFs can be very thin and pliable, being ideal to reconstruct similar regions of the integument;
- UPFs are associated with minimal morbidity in the donor zone, as their dissection does not require going deeper to the muscle fascia;
- UPFs can be harvested from most regions of the body, allowing to choose inconspicuous donor zones where the integument is redundant, such as in the anteromedial aspect of the limbs, in order to facilitate direct closure of the secondary defect [43,48,49].

For all these reasons, there has been some enthusiasm with the use of these flaps in the reconstruction of multiple types of defects, namely in deep burns [50-54], defects of the hands and fingers [49,50,55-60], including congenital or acquired defects of the nail complex [61,62], as well as in the reconstruction of other limb defects [63,64], and in defects resulting from the excision of head and neck tumors [48,65,66].

In the cases of burns to the face and hands, UPFs seem particularly promising, as they allow the reconstruction of aesthetic and functional areas with thin, pliable and homogenous skin. In this way, they reportedly ensure a better functional and aesthetical outcome compared to grafts in these burns [50,53].

Despite all these advantages, UPFs have been reported in relatively few papers, which describe in most cases small series of patients [43,67]. Three main reasons have been proposed to explain this limited use. One is that some authors report high necrosis rates with these flaps, particularly in the presence of infection [43,49]. Another reason is that the physiologic mechanisms that allow UPFs to survive are still poorly understood [48,49,68]. Finally, although a myriad of experimental models of UPFs has been described in various animal species, no one has stood out as ideal. Therefore, overall there is lack of uniformity in the literature on UPFs regarding the best methodologies to improve survival of these flaps [46,69,70].

Physiology of Unconventional Perfusion Flaps

There is no consensus in the literature regarding UPFs' mechanisms of survival, nor on the best vascular patterns for their vascular design and transplantation [46,70,71].

Among the multiple mechanisms proposed to justify the early survival of UPFs, the following are repeatedly mentioned as being the most significant in the short term and are schematically illustrated in Figure 2.

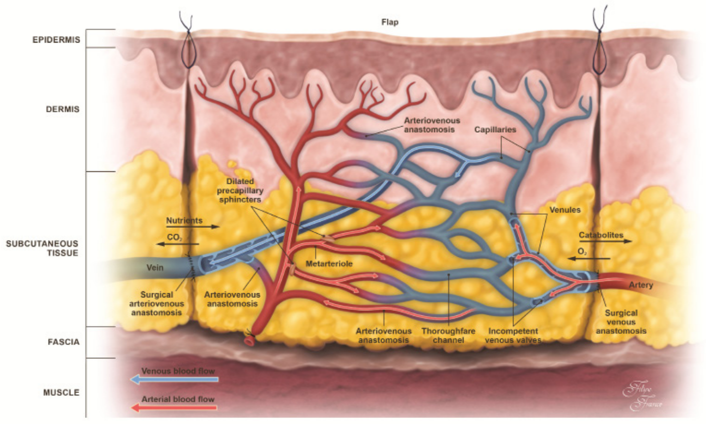

Figure 2: Schematic representation of an unconventional perfusion flap (arterialized venous flap) and its blood supply illustrating the putative physiologic mechanisms that allow its survival during the first 3 to 4 days after flap transfer. Plasmatic imbibition, venous valve incompetency, microvascular arterio-venous shunting, and the Bohr's effect are considered the main mechanisms. Red vessels represent the original arterial system of the flap. Blue vessels represent the original venous system of the flap. Red arrows indicate the direction of arterial blood flow. Blue arrows indicate the direction of venous blood flow. The drawing is not to scale.

- During the first 3 to 4 days, plasmatic imbibition from the wound bed and adjacent margins allows the diffusion of oxygen, water and metabolites from the wound to the flap, as well as the elimination of carbon dioxide and catabolites in the opposite direction [72-78].

- The arterial blood flowing into the venous system renders most venous valves incompetent, allowing antidromic blood perfusion within the flap [48,49].
- The ischemic condition of the UPF promotes the relaxation of the precapillary sphincters and of the thick muscular walls of the arterio-venous anastomoses' permitting antidromical blood flow from the venous component of capillaries and from venules into the arterial component of capillary networks and into arterioles, respectively. From there blood percolates the proximal arterial tree, creating multiple microvascular shunts and functional arterio-venous shunts. For this mechanism to be efficient, a sufficiently extensive venous network must be present [48,49,68,79-83].
- The ischemic and acidic environment of the flap facilitates oxygen uptake from hemoglobin at the precapillary, capillary and postcapillary levels due to the Bohr's effect [73,84-88].

In the long term, the survival of UPFs seems to be mainly dependent on vertical neoangiogenesis from the wound bed into the flap, as well as on horizontal neoangiogenesis from the wound margins into the flap (Figure

3). Neoangiogenesis within the flap itself, increasing flap's collateral circulation, also seems to play a pivotal role [49,70,89,90].

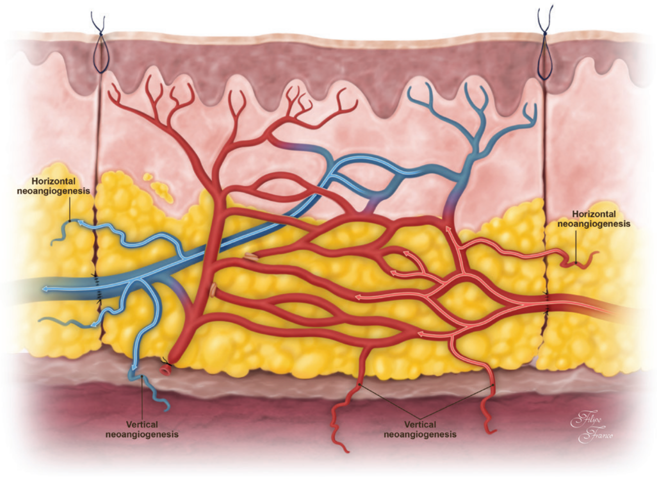

Figure 3: Schematic representation of an unconventional perfusion flap (arterialized venous flap) and its blood supply illustrating the putative physiologic mechanisms that allow its survival after the first 3 to 4 days after flap transfer. Vertical and horizontal neoangiogenesis are considered the prevailing mechanisms. Red vessels represent the arterial system of the flap (original arteries of the flap and the original veins that have suffered a process of arterialization). Blue vessels represent the venous system of the flap. Red arrows indicate the direction of arterial blood flow. Blue arrows indicate the direction of venous blood flow. The drawing is not to scale.

Despite intensive research in the mechanisms explaining the viability of unconventional perfusion, there are several reports of UPFs' high necrosis rates both experimentally and clinically [91-94]. Multiple strategies have been proposed to increase UPFs' viability, namely delay procedures [95-100], pre-arterialization [100-102], surgical expansion [51,75], growth factor application [103,104], arterio-venous shunt restriction (i.e., ligation of large and direct communications between the afferent and efferent sides of the flap, in order to force blood flow into the periphery of the flap) [105] and choice of specific vascular patterns [49,89,102]. Until now, there is no clear evidence of the efficacy of these measures.

Unconventional Perfusion Flaps and Nerve Repair

One of the main limitations in the reconstruction of extensive nerve defects, such as brachial plexus injuries, is the limited number of nerve sources available for nerve repair [106,107]. Moreover, there is growing experimental and clinical evidence that nerve flaps are superior to nerve grafts for bridging long and thick nerve defects [108]. However, currently, nerve grafts are the most commonly used options for bridging nerve defects in the clinical context [109-113].

Nerve flaps, having a blood supply of their own, have been shown experimentally to be more efficient than nerve grafts in promoting the invasion by macrophages, the remotion of myelin fragments in the degenerating nerve fibers, and the survival of Schwann cells [114,115]. Overall, nerve flaps are less prone to central necrosis, fibrosis and histological derangement relatively to nerve grafts, particularly in conditions of local ischemia [116,117]. In fact, nerve grafts are initially entirely dependent on plasmatic imbibition and diffusion from the local medium, until neoangiogenesis occurs. If the local environment is mostly deprived of oxygen and nutrients and/or too far from the inner portion of the graft, nerve graft necrosis and failure of nerve repair will ensue [109,118-121].

These experimental data have been supported by some empirical clinical data. In fact, it has been shown clinically that an adequate blood supply to the proximal and distal nerve stumps is associated with better functional results after peripheral nerve repair [122]. The influence of an adequate blood supply to the zone of peripheral nerve repair is particularly evident in cases of concomitant radiotherapy (as it happens in the context of tumor extirpation and administration of adjuvant therapy), or in areas of marked fibrosis, such as those present after extensive local trauma [111,112,123].

All the data mentioned above refers to "conventional nerve flaps" (CNFs), These can be defined as nerve segments with an arterial and venous blood supply. However, CNFs are seldom used clinically because there are only a few of dispensable nerve segments (i.e., whose extirpation will not result in a significant deficit in the donor zone) that present a blood supply that allows harvesting them as CNFs [120]. The sural nerve, the saphenous nerve, the lateral cutaneous nerve of the thigh, and the sensory branch of the radial nerve to the dorsum of the hand are the most commonly used CNFs, while the ulnar nerve flap has been used in cases of extensive brachial plexus lesions [109,122,124,125].

Another reason that hinders the clinical application of CNFs is that they entail laborious harvesting dissections and technically vexing anastomoses of small sized vessels. Moreover, due to anatomical constraints, CNFs cannot always be raised [126]. To try to surpass these limitations of CNFs, Townsend and Taylor in 1984 proposed concept of "arterialized neurovenous flaps" (**ANVFs**) [127]. These flaps are composed of nerve segments pedicled exclusively on their accompanying veins. When insetted in the recipient zone, at least one of the ANVF's veins is connected to a local artery, whereas at least one of its veins is anastomosed to a recipient site's vein [127]. The use of these flaps greatly expands the choice of nerve flaps for reconstructing peripheral nerve defects. As peripheral nerves and the venous system develop in a synchronous fashion, with multiple levels of molecular cross-talk in their origin, differentiation, and elongation until reaching their target organs, they remain in close anatomical proximity since the end of the fetal period [128]. Consequently, there are numerous places where the superficial venous system is in the vicinity of expendable superficial nerves that thus can be raised as ANVFs [128,129].

However, since their original description, ANVFs use in the clinical context has been reported only rarely and these reports have been limited to case reports and small case series [43]. This may be partly justified by the fact that there are only two papers on the functional, histological and electrophysiological outcome of ANVFs in peripheral nerve repair in the experimental context [130,131]. These studies describe femoral nerve repairs in rats followed during relatively short periods of time. Therefore, further experimental and clinical studies with ANVFs are definitely warranted.

Contemporary Limitations in the Knowledge of Unconventional Perfusion Flaps

As alluded above, there are several significant hiatuses in the knowledge of UPFs, that have been deterring many surgeons to use them in the clinical context. From the authors' perspective, the following are among the most pressing questions to address in this context:

1. Systematically review and analyze the somewhat disperse and often contradictory literature on the experimental and clinical use of UPFs, in order to infer patterns that could maximize the efficacy of these flaps.
2. Establish standardized experimental models of UPFs in order to facilitate comparison of inter-

ventions, and results, as well as to allow surgical training by novices in the field.

3. Thoroughly evaluate the experimental and clinical usefulness of using ANVFs for bridging nerve defects in situations where local perfusion was preserved or compromised.

4. Assess the surgical anatomy of UPFs in different regions of the body, in order to facilitate the choice of particular vascular patterns of UPFs in specific clinical circumstances.

Conclusion

Despite some current limitations in the knowledge of UPFs, there is considerable experimental and clinical evidence to suggest the usefulness of these reconstructive options. Most frequently, these flaps have been used in integumentary reconstruction, particularly in regions where a thin and pliable covering is desirable. In these circumstances, UPFs seem to present several advantages compared to CPFs. Moreover, there is some evidence that UPFs may be useful for bridging nerve defects, especially when local ischemia is present. However, further studies are needed to certify the efficacy of UPFs in this context.

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