Applying Power Spectral Analysis of Physiologic Signals to Explore Interactions Between Central Neural Regulation and Peripheral Circulation in Plastic Surgical Sciences

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Abstract

Plastic surgery is a specialized branch of surgery treating various kinds of defects without limitations of anatomic boundaries. The foundation of this medical specialty does not rely on fractional techniques derived from divided human body parts, but is an integration of basic and clinical medical sciences, as well as the humanities and social and behavioral sciences. The core is the interactive regulation between various peripheral target organs and central modulation. Power spectral analysis of variability in heart rate, blood pressure, and cutaneous blood flow has been used to explore wound healing in diabetic patients, ischemia and hypoxia, free flap transplantation, and the interaction between central regulation and peripheral circulation. Cardiac neural regulation was found to be generally decreased in diabetic patients with foot complications. Simultaneous management of diabetic neuropathy and problem wound healing would be the key for successful treatment. Sympathetic activity is excited during and after a hypoxic episode. It should be avoided in patients with critical conditions, especially after microvascular reconstructions. Sympathetic denervation and reactive hyperemia are associated with a decreased fractional power contribution in the very low frequency range and an increased high frequency component in power spectral analysis of cutaneous perfusion signals during forearm flap transplantation. Phenylephrine and other α-adrenoceptor agonists are not adequate in reconstructive microsurgery because they reduce flap perfusion, cardiac sympathetic functions, and sympathetic vasomotor activities. In conclusion, the plastic surgical sciences demonstrate the interaction of systemic physiologic function and peripheral perfusion/oxygenation. The autonomic nervous system plays a major regulatory role in this interaction. Power spectral analyses of heart rate, blood pressure, and cutaneous microcirculation are useful in exploring the integration between central neural regulation and peripheral circulation. [Tzu Chi Med J 2010;22(1):1–10]
1. Introduction

Since the humoral concept of disease was proposed by Galen in the 2nd century, there has been debate about treating the disease, parts of the body, and the patient as a whole person. Plastic surgery is a specialized branch of surgery devoted to the treatment of challenging problems involving congenital, accident, disease, and aging etiologies. Because of the special nature of plastic surgery, it is largely concerned with form, as implied in the term plastic. There are neither anatomic boundaries nor specific counterparts of internal medical subdivisions for plastic surgeons. Plastic surgeons are concerned about wound healing, handling of delicate tissues, transplant biology, implant materials, blood supply to the skin and muscles, various kinds of flaps, microvascular reconstruction, repair of peripheral nerves, and tissue expansion (1). They also deal with tumors and trauma to the skin and soft tissue such as vascular malformations, melanomas, carcinomas, sarcomas, and burns. Surgical reconstructions of the head and neck, breast, hand, trunk, genitalia, and lower extremities demand contributions from plastic surgeons who excel in their knowledge, skills, attitude, and practice of the art and science of surgery and who keep the welfare of their patients foremost in their practice. In the broad spectrum of plastic surgery, the general public is most familiar with esthetic surgery, but it accounts for only a minor part of this specialty. Therefore, the foundation of this scientific category does not rely on fractional techniques derived from divided human body parts, but incorporates a solid integration of basic and clinical medical sciences, as well as the humanities, and social and behavioral sciences. Plastic surgeons truly are the managers of patients’ diseases and must consider the interaction of specific involved organs and systemic regulatory modulations (Fig. 1). This article will focus on several typical issues in plastic surgery, namely: wound healing in the diabetic foot (2), ischemia and hypoxia, free flap transplantation (3, 4), and cutaneous microcirculation and the interaction between central regulation and peripheral circulation (5) using power spectral analysis of heart rate, blood pressure, and cutaneous blood flow.

2. Power spectral analysis of physiologic signals

Power spectral analysis was originally used in the field of electroengineering. It was able to detect a damaged gear wheel by analyzing the noise from a running machine. Akselrod et al first reported power spectrum analysis of heart rate fluctuations, providing a quantitative noninvasive means of assessing the functioning of the short-term cardiovascular control systems (6). They showed that sympathetic and parasympathetic nervous activity makes frequency-specific...
contributions to the heart rate power spectrum. Fifteen years later, the European Society of Cardiology and the North American Society of Pacing and Electrophysiology reported important standards of measurement, physiological interpretation and clinical use of heart rate variability analysis in humans (7). In the same year, Yang et al set the experimental cut-off frequency ranges for auto- and cross-spectral analysis of cardiovascular fluctuations in rats (8). This technique was then extended from heart rate to systemic arterial pressure (9), electroencephalographic signals (10), cerebral blood flow velocity (11), cutaneous circulation (12), and perfusion signals from free forearm flaps (3). Definitions of measurements of cardiovascular variability are shown in Table 1.

2.1. Clinical application of heart rate variability

Heart rate variability was first applied in intrauterine fetal monitoring (13), revealing that the first sign of fetal distress is a change in the interbeat interval, so-called pathologic fetal bradycardia. Spontaneous variability in the heart rate is related to some physiologic regulatory mechanisms (14). Researchers demonstrated predications of diabetic autonomic neuropathy using bedside measurements of variability in heart rate and blood pressure (15). It was shown that patients with acute myocardial infarction who presented with a smaller variance of the R-R interval on admission had a lower mortality (16). Patients with cardiac disease who showed higher high-frequency power (HF) in heart rate variability were shown to have a lower risk of sudden death (17). It was demonstrated that individuals with congestive heart failure had a lower HF and higher low-frequency power (LF) to HF ratio (LF/HF) in heart rate variability. We can conclude that parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure (18). Patients with established and borderline hypertension had a lower HF and a higher LF in heart rate variability (19). The Framingham Heart Study also demonstrated that heart rate variability is a useful noninvasive tool to assess cardiac autonomic function. Heart rate variability is reduced in men and women with systemic hypertension. Among normotensive men, lower heart rate variability is associated with a greater risk of developing hypertension (20).

2.2. Clinical application of blood pressure variability

Blood pressure variability also provides indicators for evaluating sympathetic nervous modulation. It has been shown that LF of blood pressure variability (BLF) is significantly increased in spontaneous hypertensive rats (21). This suggests that BLF indicates sympathetic vasomotor regulation (22). On the other hand, the HF of blood pressure variability (BHF) indicates the influence of the respiratory pumping mechanism on the cardiovascular system (23). However, the normalized BHF (BHFn) in anesthetized, positive-pressure ventilated individuals may provide a valid assessment of cardiac sympathetic regulation which is independent of parasympathetic and vascular sympathetic influences (24). The physiological association of cardiovascular variability with autonomic nervous function is summarized in Table 2.

3. Diabetic foot: which is going to be treated? The foot or the diabetic patient?

Foot complications in diabetic patients are challenging for plastic surgeons. It is the leading cause of nontraumatic major limb amputation. Patients often continue to have problems after unilateral major limb amputation. The incidence of contralateral amputation after 5 years is 30–50% (25,26). The mortality rate after major limb amputation is 39–80% in 3 years (27–30). Comorbid cardiac and renal disease associated with autonomic dysfunction contributes to this high mortality rate. The leading cause of diabetic foot is diabetic neuropathy followed by limb ischemia (31,32). Diabetic macroangiopathy such as arterial occlusions in the legs can sometimes be treated with arterial bypass surgery. It appears that strict control of blood sugar is effective in preventing future diabetic neuropathy (33). However, there is no effective treatment for diabetic neuropathy once it is established. To improve patient care and prognosis, plastic surgeons need to find a comprehensive treatment that both enhances diabetic wound healing and restores proper functioning of cardiac neural regulation. Power spectral analysis of heart rate variability is an ideal noninvasive method of measuring autonomic nervous function.

3.1. Simultaneous management of diabetic neuropathy and problem wound healing

A prospective randomized controlled study in patients with diabetic foot problems provided possible resolutions (2). Baseline heart rate variability and transcutaneous oxygen tension (TcPO2) in surgical patients with diabetic foot complications were obtained to verify autonomic neuropathy and local perfusion/oxygenation respectively. It was noted that those who presented with relative hypoxia with a TcPO2 < 40 mmHg in the involved feet had profound
autonomic dysfunction when comparing the heart rate variability parameters with age- and race-matched healthy populations [34]. Adjunct daily hyperbaric oxygen therapy at 2.0 atmospheres absolute for 90 minutes, for 20 treatments, was applied in an experimental group. The local oxygenation increased significantly after hyperbaric oxygen therapy, with a TcPO2 of 27.5±3.1 mmHg in the control group and 53.0±2.6 mmHg in the experimental group (p<0.001).

In frequency-domain analysis of heart rate variability, variance in the R-R, HF and LF significantly increased in the hyperbaric oxygen group, whereas the LF/HF showed a tendency to decrease. Autonomic function of cardiac neural regulation is generally decreased in patients with diabetic foot. Compared with the natural aging process in healthy subjects, there is an early deterioration of autonomic failure in the diabetic population. Applying power spectral analysis of electrocardiac signals demonstrated that hyperbaric oxygen therapy not only increases local oxygenation and perfusion but also potentially increases autonomic nervous functions (LF and variance) with a significant elevation of vagal modulation (HF) and a trend of decreasing sympathetic modulation (LF/HF) in diabetic foot patients.

4. Impact of acute hypoxia on systemic cardiovascular neural regulation

The core competence of plastic surgeons involves knowledge and skills of general reconstructions including blood supply, wound healing, microsurgery, peripheral nerves, tissue expansion, implant material, tissue handling, transplant biology, flaps, and so on (Fig. 1). Plastic surgeons must be concerned with the interaction between various peripheral target organs and central regulatory systems, especially cardiovascular neural regulation. Plastic surgeons are often involved in the care of critically ill patients with conditions such as major burns, necrotizing fasciitis, major trauma, and major reconstructive microsurgeries. Persistent apnea results in profound hypoxia and hemodynamic breakdown in these patients. Intermittent hypoxia, however, is associated with hypertension [35–40]. Sympathetic overactivity is believed to be one of the major pathophysiological mechanisms of hypertension associated with chronic intermittent hypoxia (40). It has been suggested that the overactivity in sympathetic nervous functions after chronic exposure to intermittent hypoxia is associated with accumulation of upregulation of the catecholaminergic and renin-angiotensin systems [35,41], and with down-regulation of nitric oxide synthases [39,42,43]. It is reasonable to suspect that some unexplained thrombotic
failure of microvascular reconstruction might have a connection with sympathetic overactivity. The importance of acute and chronic apneic/hypopneic impacts on either systemic or peripheral cardiovascular regulation can not be overstressed for plastic surgeons when dealing with critically ill patients who have had major reconstructive procedures.

4.1. Hypoxia-induced sympathetic overactivity

A programmable intermittent apnea model in rats together with power spectral analysis of cardiovascular variability was used to determine the neuronal consequences during a single 20-second episode of programmed apnea for elucidating the acute responses to hypoxic apnea (5). This apnea model induced evident hypoxia without significant interference with pH and PaCO₂ (Fig. 2). The influence of consciousness and muscle tone was controlled by closely monitored anesthesia. Ventilatory movements were dissociated from the central respiratory drive by programmed intermittent apnea. Arterial pressure increased in the early apneic phase (0–6 seconds) and returned to the control level in the middle phase (7–12 seconds). Significant hypotension developed in the late apneic phase (13–20 seconds) and deteriorated in

![Graph showing effects of apnea on SAP, Aflow, and ETCP02](image)

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**Fig. 2** — (A) The polygraph illustrates the effects of a 20-second episode of apnea on the systemic arterial pressure (SAP), airway flow (Aflow), and end-tidal partial pressure of CO₂ (ETCP02) in an anesthetized rat. There is no CO₂ accumulation during the apneic period. (B) The polygraph shows the reproducibility of five 20-second episodes of apnea in 12 minutes. The same triphasic SAP responses are induced in each episode.
the reventilatory phase. The interbeat interval increased slightly during the apneic event. The increase in arterial pressure in the early and middle phases was inhibited by a β-adrenoceptor antagonist, propranolol (1.0 mg/kg, intravenous), but was provoked by an α-adrenoceptor antagonist, phentolamine (2.5 mg/kg, intravenous). The decrease in pressure in the late and reventilatory phases was reversed, at least in part, by phentolamine. Power spectral analysis of arterial pressure variability demonstrated significant increases in the LF (sympathetic vasomotor activity) and normalized HF (cardiac sympathetic modulation) after reventilation. The sympathetic nervous system was excited during and after the apneic episode. The β-adrenoceptor function was the first to be involved in the pressor response, followed by an α-adrenoceptor-related depressor response. After reventilation, both β- and α-adrenoceptor functions were further provoked despite sustained hypotension. Although sympathetic activity is excited during and after hypoxic apnea, the immediate pressor effect is related to an inotropic response of cardiac sympathetic regulation whereas the negative chronotropic and subsequent depressor effect may be associated with a failure in the cardiovascular response to the sympathetic excitation. It is recommended that hypoxic episodes be avoided in patients with critical conditions, especially after microvascular reconstruction.

5. **Cutaneous blood flow variability in the forearm**

Forearm cutaneous circulation is under the regulation of complex systemic and local mechanisms. Autonomic neural regulation is promptly interfered with by hypoxic episodes and peripheral skin perfusion is changed (5). Rhythmic sympathetic modulation from the brainstem is involved in cutaneous vasoconstrictor and vasomotor activity (44,45). Laser Doppler flowmetry of the index fingers is coherent with that of blood pressure, heart beat, and muscular sympathetic activity, demonstrating the existence of a common central regulator (46). Autoregulation as a local mechanism, nevertheless, plays an important role in specific threatening situations (47). The forearm has been widely used in basic physiological research as an *in vivo* model to determine peripheral circulatory performance (48–50). It has been demonstrated that the endothelium-dependent vasodilation of forearm vessels is impaired in patients with hypercholesterolemia (51,52). In patients with essential hypertension, this reactive hyperemia of the forearm is also impaired (53). However, treatment with a converting enzyme inhibitor improves this endothelial associated function (54). A radial forearm flap is frequently used to reconstruct challenging defects after ablation of head and neck cancers (55,56). It is a privilege for plastic surgeons to characterize the dynamic properties of regional microcirculation after simultaneous denervation and revascularization in free forearm flap transplantations using spectral power analyses to explore the complex blood flow variability (3,50,57). Reconstructive microsurgeons can interpret the postoperative microcirculatory status to optimize perioperative care and to decide on the proper timing of rescue interventions.

### 5.1. **Power spectral analysis of perfusion signals in forearm flaps**

It has been recognized that lack of an instrument/biological zero is a limitation in laser Doppler perfusion monitoring. Plastic surgeons can determine the background flux signal of forearm cutaneous tissue (6.36±0.78 PU) during the process of free forearm flap transfer (3). Laser Doppler flowmetry revealed that cutaneous microcirculation significantly increases after forearm flap transplantation. The spectral power of the very low, low, and high frequency ranges are significantly increased after transplantation. The major acute impacts are denervation and revascularization. When the flaps are transplanted, the normalized high frequency component (FHF%) increases while the very low frequency component (FVLF%) decreases significantly. It has been reported that cutaneous endothelial activity is manifested in the blood perfusion signal as an oscillation with a repetition time of 1 minute. Acetylcholine (an endothelium-dependent vasodilator) has greater selective effects on the oscillation of 0.009–0.02 Hz than sodium nitroprusside (an endothelium-independent vasodilator) (50). Exercise increases the spectral power of 0.06–0.2 Hz in the perfusion of forearm skin (58). Sympathetic nerve activity influences blood flow oscillation in normal tissues with repetition times of 20–50 seconds (0.02–0.05 Hz) (59). This supports the finding that the significant decrease in the FVLF% (0.003–0.04 Hz) of microcirculation fluctuation after forearm flap transplantation is caused by sympathetic denervation and/or endothelial desensitization. A significant increase in the fractional component of the spectral power at 0.15–0.4 Hz in forearm flap transplantation offers a parameter for verification of reactive hyperemia in human forearm skin. Reactive hyperemia is derived from passive changes in the arteriolar diameter and local chemical changes with insufficient blood supply (60). It has been demonstrated that arterial compliance and the diameter of the radial artery increase during reactive hyperemia (48,61). Power spectral analysis of cutaneous perfusion signals during forearm flap transplantation suggests that the increase in blood flow is derived from a decreased fractional power contribution in the very low frequency range and
an increased FHF%. They are associated with sympathetic denervation and reactive hyperemia respectively.

6. Postoperative blood pressure control and free flap viability

Although research results [55,56,62–65] have optimized surgical outcomes, 10% of transferred flaps need re-exploration because of circulation compromise (66). Hypotension in the postoperative period may cause peripheral vasoconstriction and hypoperfusion of transferred flaps. The hemodynamics of transplanted flaps in elderly surgical patients is threatened by postoperative hypertension and associated sympathetic overshoot. High blood pressure increases the risk of bleeding and hematoma compression on vascular pedicles (67). Hypotension and hypertension both aggravate the damage from reperfusion injuries after free tissue transfer (68). The perfusion and oxygenation of transplanted flaps are actually under the regulation of both central and peripheral mechanisms. Systemic arterial pressure and flap perfusion/oxygenation are interdependent and the homeostasis of both plays a key role in optimizing patient outcome.

6.1. Management of hypotension in microvascular reconstruction

A study using pharmacologic alteration of systemic arterial pressure and simultaneous monitoring of cutaneous microcirculation demonstrated that the regional circulatory environment interacts with the systemic circulation, and their responses are not necessarily parallel (4). When the systemic arterial pressure is elevated by phenylephrine, cutaneous perfusion significantly decreases. Phenylephrine is a common drug used to elevate blood pressure during the perioperative period. It acts on the \( \alpha \)-adrenoceptors and causes vasoconstriction, which in turn elevates systemic arterial pressure. Hypotension can be corrected by phenylephrine, but the transfused flap may still be hypoperfused with profound ischemic reperfusion injury. Power spectral analysis of cutaneous laser Doppler flowmetry found that phenylephrine infusion significantly increases the normalized very low frequency power of the flux spectrum and decreases that of the high frequency interval. Spectral analysis of systemic arterial pressure revealed that phenylephrine significantly reduces cardiac sympathetic functions (BHFn) and sympathetic vasomotor activities (BLF). Infusion of normal saline maintains both the blood pressure and cutaneous perfusion. Intravenous infusion of normal saline does not alter blood pressure variability and the normalized spectral power of the flux spectrum of cutaneous laser Doppler flowmetry. Treatment of hypotension with volume expansion therapy seems better than administration of vasoconstrictors to optimize the perfusion of transferred cutaneous flaps. However, cardiogenic shock should be considered when volume expansion is used for postoperative hypotension in patients with poor cardiac performance. Actually, one study showed that postoperative medical complications related to pulmonary problems and alcohol withdrawal in elderly, debilitated patients were statistically far more important than microsurgical complications in negatively affecting the outcomes and true costs of microsurgical reconstruction (69). It is obvious that well-monitored volume status and controlled speed of volume expansion play crucial roles in postoperative care. Dopamine and dobutamine should be used with caution because these drugs do not increase flap flow equally relative to total cardiac output (70). If vasoactive agents are needed in patients with microvascular reconstruction, dobutamine seems more advantageous than dopamine (71–73).

6.2. Management of hypertension in microvascular reconstruction

High blood pressure can cause oozing from the surgical bed and hematoma formation, which in turn induce free radical and cytokine production (67,68). Anastomoses of vascular pedicles are more likely to leak when the blood pressure is too high. Sympathetic overactivity due to wound pain and postoperative hypertension may further elicit vasoconstriction and compromise flap perfusion and oxygenation. Phentolamine, an \( \alpha \)-adrenoceptor antagonist, is able to reduce blood pressure effectively. Unfortunately, cutaneous perfusion is decreased significantly as well (4). Although intravenous infusion of phentolamine does not have significant effects on the normalized spectral power of the flux spectrum of cutaneous laser Doppler flowmetry, sympathetic vasomotor activities are reduced significantly. It is interesting that cutaneous perfusion is maintained when the systemic arterial blood pressure is reduced by intravenous infusion of sodium nitroprusside. Sodium nitroprusside is a nitric oxide donor and known to be an endothelium-independent vasodilator. Intravenous infusion of this drug does not affect the normalized spectral power of the flux spectrum of cutaneous laser Doppler flowmetry. Administration of sodium nitroprusside significantly reduces cardiac sympathetic functions (BHFn) and there is a trend of increasing vascular sympathetic modulation (BLF). It is suspected that nitric oxide donors are superior to \( \alpha \)-adrenoceptor antagonists in preserving cutaneous flap perfusion when treating postoperative hypertension (4). It is better to use a nitric oxide donor than an \( \alpha \)-adrenoceptor blocker to
7. Conclusion

The basis of medical education is to teach students the skills of self-learning and how to think. Plastic surgery is an important member of the medical family. Professor Joseph E. Murray, a plastic surgeon at Brigham and Women’s Hospital in Boston, won the Nobel Prize in physiology and medicine in 1990 for his work in kidney transplantation. The achievement was made through observation, thinking, practice, reflection, assessment, and metacognition. The plastic surgeon should not behave like a technician who deals only with the defects but does not care for the whole patient. When a plastic surgeon treats patients with diabetic foot, it is important to assess the severity of all diabetic complications, including angiopathy and neuropathy. Diabetic foot problems represent systemic disease with presentation in the foot. Focusing on the gangrenous foot and neglecting autonomic neuropathy may lead to a disastrous outcome in the perioperative period, with failure to regain proper perfusion and oxygenation in problem wounds. The same care is needed for patients who have microvascular reconstruction after wide excision of oral cancer. Proper evaluation of comorbid disease and meticulous perioperative care are as important as the surgical procedure itself. Misjudgment in systemic blood pressure management may cause inadequate perfusion and oxygenation of the transferred flaps. Plastic surgery is a specific branch of surgery with no limitation of anatomic boundaries. The common connection for each region treated by a plastic surgeon is the regulatory mechanisms between central autonomic modulation and peripheral perfusion and oxygenation. Plastic surgeons have an important role to play in the translation of basic research into clinical practice because they are concerned with not only the details of microstructures, but also with the context of perfusion/oxygenation and its central neural regulation.

In conclusion, plastic surgery is a good scientific category to demonstrate the interaction of systemic physiologic function and peripheral perfusion/oxygenation. The autonomic nervous system plays a major regulatory role in this interaction. Power spectral analyses of heart rate, blood pressure, and cutaneous microcirculation are useful in exploring the integration between central neural regulation and peripheral circulation.

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