Skin perfusion pressure as a predictor of ischemic wound healing potential (Review)

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Abstract. Skin perfusion pressure (SPP) is the blood pressure that is the requisite for the restoration of microcirculatory or capillary flow following controlled occlusion and subsequent flow return. The purpose of the current review was to evaluate the value of SPP for the prediction of wound healing in patients with limb ischemia. Articles published up to January 31, 2017 were searched in the PubMed database and Chinese database CNKI, using the keywords of 'skin perfusion pressure', 'limb ischemia' and 'wound healing'. Articles were obtained and reviewed to analyze the predictive value of SPP with regard to the healing potential of ischemia wounds on limbs. Three different types of techniques are currently used for the measurement of SPP, namely radioisotope clearance, photoplethysmography and laser Doppler, with laser Doppler as the most widely applied technique, due to its noninvasiveness and ease of operability. SPP may effectively assess wound healing potential in ischemic limbs with high sensitivity and specificity; however, its optimum cut-off point remains uncertain. Compared with other noninvasive microcirculatory assessment tools including ankle-brachial index, toe blood pressure and transcutaneous oxygen pressure, SPP has its advantages including that it is not affected by vascular calcification, anatomical structure or patient condition. In conclusion, SPP may be used as an index to accurately predict wound healing in patients with limb ischemia. However, it is difficult to determine the optimum cut-off of SPP due to the limitations of current data. Further study is necessary to confirm the optimum cut-off value of SPP in predicting wound healing potential.

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Contents

1. Introduction

In general, wounds heal rapidly in an ideal local environment. However, the process of healing is affected by various factors, including wound type, which encompasses diabetes ulcers, pressure ulcers, radiation injuries and peripheral vascular diseases. Limb ischemia decreases perfusion and oxygenation to skin cells in the distal extremities, leading to cell death and ulceration (1). Patients with ischemic ulcers often suffer from at-rest pain and may develop gangrene (1). Previous studies have demonstrated that negative pressure wound therapy may accelerate wound healing by promoting blood perfusion (2,3). However, revascularization to restore perfusion is critical for the treatment and prevention of ischemic ulcers in different clinical guidelines (4,5).

It is a challenge for clinicians to predict the wound healing potential of ischemic limbs, and to assess the necessity of amputation, particularly in patients with diabetes, whose ankle artery pressure may be artificially elevated due to arterial calcification (6). Skin perfusion pressure (SPP) is a noninvasive technique of assessing tissue viability (7). Previous studies have demonstrated that SPP is useful in the prediction of wound healing in limb ischemia (8,9); however, key points of its clinical application require further investigation. The present article is a review of the role of SPP in predicting wound healing in patients with limb ischemia. A comparison with other noninvasive techniques assessing peripheral circulation is also provided.

2. Literature search

Articles published up to January 31, 2017 were searched in the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) and Chinese database CNKI (http://www.cnki.net/), using the keywords of 'skin perfusion pressure', 'limb ischemia' and 'wound healing', to identify relevant studies reported in the English or Chinese language. All articles reporting the treatment of patients with limb ischemia in which SPP was measured were reviewed. Major information and findings in this area were summarized.

3. Measurement of SPP

The measurement of SPP was first introduced in the 1960s (10,11). There are currently three different techniques for SPP measurement, namely radioisotope clearance, photoplethysmography and laser Doppler, the principles of which are the same (6). In brief, SPP is measured by gradually decreasing the inflation cuff pressure and observing the washout of the isotope, the reappearance of pulsatile flux or the movement of red blood cells at the site of measurement (6). The minimal external counter pressure on the underlying skin exerted by the pressure cuff is defined as the SPP, above which skin blood flow ceases (6).

Radioisotope clearance was the earliest technique for detecting SPP, which used to be considered as the 'gold standard' for measuring SPP, and a reliable method for predicting amputation and ischemic ulcer healing (12-14). However, this method was not widely used due to the complexity of the measurement process and the need for injection of radionuclides. In 1987, Castronuovo *et al* (15) reported a novel noninvasive technique for measuring SPP, which could be performed in minutes using a laser Doppler probe. There was a high correlation of measurement accuracy for SPP when the radioisotopic and laser Doppler methods were compared (16). Photoplethysmography determination has also been used to measure SPP (17,18). However, in a study performed by Malvezzi *et al* (16), the results were not consistent with those of the previous studies (17,18) reporting the successful determination of SPP using photoplethysmography.

Laser Doppler is fast, effective and easy-to-operate, and is the most widely used method of measuring SPP (19). In recent years, the majority of research on SPP has been conducted using laser Doppler (7). In addition to its use in the diagnosis of critical limb ischemia (CLI) (20), in evaluating the severity of ischemia (21-24), in the selection of the amputation plane (25), and in predicting wound healing, SPP is also used to evaluate the therapeutic efficacy of arterial revascularization surgery (26,27), endovascular therapy (28), and medicines used for the treatment of peripheral artery disease (PAD) and CLI (29,30). In a previous study, Watanabe *et al* (31) revised the laser Doppler technology, and SPP was measured using a thermostatic heating probe. It was demonstrated that this was useful for improving the detectability of SPP in ischemic limbs, and that an increase in SPP following heating may be a potential predictor of limb ischemia.

4. Predictive value of SPP in wound healing during limb ischemia

Numerous studies have demonstrated that SPP may effectively predict the wound healing potential of ischemic limbs (6,8-9,25), but the optimum cut-off values of SPP for predictive accuracy remain to be determined.

In a previous meta-analysis by our group (19), relevant studies were searched with the following inclusion criteria: i) Randomized controlled trials, two-arm prospective studies or retrospective studies; ii) patients with limb ischemia; iii) SPP was measured; and iv) studies reporting quantitative outcome data on sensitivity and specificity of SPP. There were 5 studies that met the inclusion criteria, of which 3 examined a cut-off of 30 mmHg and 2 examined a cut-off of 40 mmHg, as described previously (19). This meta-analysis indicated that SPP is an index with sufficient sensitivity and specificity for the prediction of wound healing in patients with limb ischemia.

The earliest study included in the meta-analysis was published in 1995 and examined patients treated with above- and below-knee amputations (25). The results of this study demonstrated that SPP ≥30 mmHg predicted complete healing in 90% of cases, while SPP <30 mmHg predicted the failure of healing in 75% of cases. Also analyzed was a study by Castronuovo *et al* (20) in 1997, which studied 61 limbs with non-healing foot ulcers, and determined that the sensitivity of SPP <30 mmHg as a diagnostic test of CLI was 85%, while its specificity was 73%; the overall diagnostic accuracy of the diagnostic criterion of SPP <30 mmHg for critical limb ischemia was 79.3%. Also reported previously (19) was the study by Yamada *et al* (6) in 2008, which examined 403 limbs with arteriosclerosis obliterans in 211 patients, half of whom had diabetes or were treated with dialysis. Receiver operating characteristic (ROC) curve analysis suggested that an SPP of 40 mmHg had a sensitivity of 72% and specificity of 88% for the prediction of wound healing. Subsequent to this, Urabe *et al* (32) measured SPP in 62 limbs of 53 patients, and a value of 40 mmHg was adopted for clinical decision-making. All the patients were treated with conservative therapy, and outcomes at 1 month were categorized as 'improved' or 'no change or worse', while the fate of wounds was determined as 'healed' or 'not healed'. The SPP ≥40 mmHg examined in the study had a sensitivity of 75.0% and specificity of 82.6% in predicting the 1-month outcomes. Furthermore, logistic regression analysis revealed that SPP ≥40 mmHg was an independent predictor of improved outcome with an accuracy of 80.6% and an odds ratio of 14.2 (95% confidence interval: 3.6-55.8; $P<0.0001$). The criterion of SPP ≥40 mmHg to predict the fate of wounds had a sensitivity of 61.1%, a specificity of 79.5% and an accuracy of 74.2% (19,32). The most recently published study of the meta-analysis was reported by Utsunomiya *et al* (9) in 2014, in which 123 limbs in 113 patients who had undergone successful balloon angioplasty with or without stenting were examined. ROC analysis indicated that the optimal SPP cut-off for predicting wound healing was 30 mmHg, with a sensitivity of 81.4% and a specificity of 69.2%. Notably, the results confirmed that SPP was an independent predictor of wound healing and suggested that the probability of wound healing with SPP values >30, >40 and >50 mmHg were 69.8, 86.3 and 94.5%, respectively (9).

Other studies were noted in our previous meta-analysis (19), despite not meeting the inclusion criteria, that also examined the predictive value of SPP in wound healing. For instance, Watanabe *et al* (33) retrospectively examined 19 lower limbs in 18 patients who had undergone arterial reconstruction for CLI, and identified that an SPP ≥30 mmHg was a requisite for wound healing. Also noteworthy is a previous prospective, single center comparative study, in which SPPs in 100 patients with chronic extremity wounds were examined, which also suggested that SPP with a value ≥30 mmHg was a useful positive independent predictor of wound healing potential (8). Furthermore, Tsuji *et al* (34) retrospectively examined 47 patients with 69 ischemic limbs with foot ulcers or gangrene, and observed that SPP measurement was useful for predicting wound healing in the presence of CLI; the results indicated that SPP ≥35 mmHg was a requisite for wound healing, while SPP <35 mmHg indicated that a peripheral arterial reconstruction was necessary prior to debridement. As we highlighted previously (19), Okamoto *et al* (28) performed an analysis of patients who were treated with endovascular therapy due to critical limb ischemia based on the data of the OLIVE registry, and the results indicated that postprocedural SPP was significantly correlated with 1-year amputation-free survival, modified major adverse limb events and wound healing.

It is difficult to determine the optimum cut-off of SPP in the prediction of wound healing in CLI patients due to the limitations of current literature. Firstly, few studies measured the cut-off of SPP, and inconsistencies exist among these (19). Secondly, the numbers of patients in the studies were relatively small and the treatment of patients varied among debridement/conservative management, amputation and endovascular treatment (19). Further studies with larger samples are necessary to confirm the findings.

5. Comparison of SPP with other noninvasive methods for assessing peripheral circulation

Ankle-brachial index (ABI) is the most commonly used and internationally recognized method for evaluation of peripheral circulation. However, it may fail to accurately indicate the severity of peripheral ischemia if the underlying vessels are calcified in patients with long-standing diabetes, renal failure or other disorders resulting in vascular calcification, or if there is an extensive distal arterial lesion below the ankle (6,35). In these instances, ABI values are falsely elevated as calcification in the arterial wall makes the artery noncompressible (36). In a consensus document (1), ABI was recommended to confirm the diagnosis of leg ulcers, being assigned the highest level for evidence and the highest level for recommendation in the Strength of Recommendation Taxonomy (37). Recommended thresholds for ABI were the following: Values ≥0.9 and ≤1.3 are in the normal range; values <0.9 are consistent with the presence of arterial disease; values ≤0.5 are consistent with significant peripheral arterial disease; and values ≥1.3 in those with diabetes should be followed by Duplex ultrasound imaging of the leg arteries to exclude artifactual high values (1). Diabetes is a major risk factor for a high (>1.40) ABI (38). Patients with high ABI should be considered as PAD-equivalent, as there is a high prevalence of occlusive PAD in such cases (38). Castronuovo *et al* (20) noted in their study that ABI was not predictive of the demand for reconstruction or major amputation, or the outcome of conservative local therapy. For patients with incompressible tibial arteries, an alternative is to measure toe blood pressure (TBP), which rarely gives false positive results in incompressible legs (6,39). TBP provides an accurate measurement of distal limb systolic pressures in vessels that do not typically become non-compressible (35). TBP is tested by placing a small cuff around the base of the toe with a digital flow sensor beyond the cuff (40,41). However, it requires a noninvasive vascular laboratory testing with standard environmental conditions, expertise and equipment necessary to make the measurement (35). Additionally, it may be impossible to measure TBP while there are inflammatory lesions, ulceration or tissue defects on the toes. SPP measured in the foot correlates well with TBP and may be substituted for TBP when TBP cannot be measured (42).

Measurement of transcutaneous oxygen pressure ($TcPO_2$) is another method to determine the severity of lower-limb ischemia. $TcPO_2$ is measured using skin surface sensors at 43-45˚C. It has been reported to be accurate in noncompressible artery patients and in diabetes patients (43,44). Additionally, a $TcPO_2$ level below a cut-off of 20 or 30 mmHg was an independent predictor of complications during chronic wound healing (45). In a meta-analysis by Nishio *et al* (46), $TcPO_2$ values of 20 and 30 mmHg were considered appropriate cut-off values for deciding the level of limb amputation and predicting wound healing following amputation, respectively. However, the results of $TcPO_2$ may be unreliable as they can be influenced by various physiological, methodological and technical factors, including room temperature, patient status prior to examination, smoking and caffeine intake, and local skin integrity (6). The prospective single center comparative study by Lo *et al* (8) evaluated $TcPO_2$ and SPP test results in 100 patients with chronic extremity wounds and identified that SPP alone more successfully predicted wound outcome in 87% of the cohort, compared with $TcPO_2$ with a rate of 64% ($P<0.0002$). Furthermore, SPP had a higher sensitivity in the prediction of wound healing compared with that of $TcPO_2$ (90 vs. 66%; $P<0.0001$) (8). Thus, it is recommended that SPP should be continuously applied and investigated in wound assessment protocols and other microperfusion assessments as a reliable and objective measurement tool (8). Okamoto *et al* (47) compared the four noninvasive methods with results of multidetector-row computed tomography in patients with occlusive PAD, and the sensitivity and specificity of each method was calculated via ROC analysis. The results suggested that SPP was the most useful tool for detecting PAD with an accuracy of 84.9%. However, as previously established, wound healing prediction depends on the set cut-off value and endpoint. Since there was no equivalent standard for the cut-off settings of different methods in these studies, the comparisons between the results were questionable.

6. Conclusions

In conclusion, laser Doppler is the most widely used method for the determination of SPP. Overall the advantages of SPP measurement include noninvasiveness, high reproducibility and independence from the influence of vascular calcification compared with other indices for peripheral circulation assessment. Furthermore, SPP is an accurate predictor of wound healing potential in patients with limb ischemia, but the optimum cut-off value is controversial at present. Further studies are required to clarify several key issues in the clinical application of SPP, including a reliable cut-off value.

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Availability of data and materials

The datasets reviewed in the current report are available from the corresponding author on reasonable request.

Authors' contributions

CH and GC were responsible for study design. XP, PW and JKH performed data collection and analysis. XP and PW were responsible for manuscript writing. GC, CH and JKH were responsible for revision of the manuscript. XP checked the integrity of the manuscript throughout.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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