

## Evaluation of Skin Perfusion Pressure to Assess Refractory Foot Ulcers

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## Objective

The number of patients with foot gangrene caused by critical ischaemia and severe infection is increasing significantly in developed countries. The measurement of perilesional skin blood flow by skin perfusion pressure (SPP) is useful to select the appropriate treatment of gangrenous lesions, in that it is not affected by calcifications of blood vessels. However, the prognosis of a foot ulcer may also be affected by the level of blood sugar and infections. This study aimed to validate the use of SPP in cases of foot gangrene and ulcers in patients with and without diabetes mellitus (DM) and infection.

## Method

Clinical symptoms, ankle-brachial pressure index (ABPI) and SPP were assessed to evaluate the condition of each foot ulcer. Every foot ulcer was treated as independent, even if a participant had multiple ulcers. All ulcers for which we measured SPP were subject to the analysis. All ulcers were purely ischaemic in nature and were exclusively located on the foot or toes.

## Results

Data were collected from 117 foot ulcers on 91 toes and feet from 65 patients. Almost all SPP values in healed cases were  $> 27$  mmHg. There were three patients whose ulcers failed to heal by conservative treatments were complicated with severe infection. However, no effect of DM on the relationship between SPP values and prognosis was observed. Logistic regression analysis of all ulcers except for the 5 cases complicated with infection revealed that those with 30 mmHg or lower SPP values are likely to heal by conservative treatment with 23% or lower probability, whereas any ulcer with more than 50 mmHg SPP value and without severe infection may heal without the need for further operations with 80% or higher probability.

## Conclusion

The combination of SPP and careful evaluation of infection may be a good parameter to decide the appropriate treatment for ischaemic skin ulcers, regardless of the complication of DM.

In developed countries, the number of patients who are treated by leg amputation due to a refractory foot ulcer is increasing along with the increase of critical limb ischaemia and diabetes mellitus (DM).<sup>1</sup> Various factors, such as blood flow, neuropathy, metabolism, and infection are known to make foot ulcers intractable, either independently or through interactions with each other. However, the precise relationships between these factors and the probability of ulcer healing remain unclear. Moreover, the involvement of these factors makes it difficult to find adequate sites of amputation for ulcers that cannot be expected to heal by conservative treatments.

Ankle-brachial pressure index (ABPI), which evaluates the blood flow at the proximal side of an ankle, is widely used as means for non-invasive leg blood flow inspection.<sup>2</sup> However, it does not correctly evaluate blood flow in toes and vessels with leg calcification and oedema, which often complicate diabetic foot ulcers (DFUs). This is because calcified vessels are hard, and therefore apparent ABPI values tend to be higher than real value of blood flow. In contrast, skin perfusion pressure (SPP) reflects the blood flow of superficial skin microcirculation. It can be measured at the nearest skin surface of the foot ulcers regardless of its location. Moreover, oedema or

calcification have less effect on the SPP value, as the vessels targeted by SPP are capillary vessels in upper dermis, where none or almost no calcification is seen. Thus, the measurement of SPP has a large advantage over conventional evaluation methods for blood flow in ischaemic limbs.<sup>3</sup> However, the prognosis of foot ulcers is also largely affected by complications, such as DM and infections,<sup>3-8</sup> and no clinical evidence is available regarding the relation of SPP value to the prognosis of foot ulcers along with such complications. We here analysed the relationship between SPP values and prognosis in the presence or absence of DM and infections, to help appropriate decision-making for leg amputation or for conservative treatment of ischaemic foot ulcers.

## Methods

### Evaluation of foot ulcer

Clinical symptoms, ABPI and SPP were assessed to evaluate the condition of the foot ulcers. The values of SPP were measured by six qualified dermatologists with a laser Doppler scanner LD 2000 or PAD 3000 (Vasamedics, St. Paul, Minnesota, US) at the proximal margin of the ulcer in

viable tissue,<sup>3</sup> after patients were placed in the supine position and rested for about 5 minutes. The patients were not constrained in behaviour before this resting period. Room temperature was kept at  $24\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$  through the study. This study was approved by the Ethics Committee of the Hiroshima University (E-218-2, 18 November 2016).

Every foot ulcer was treated as independent, even if a participant had multiple ulcers. All ulcers for which we measured SPP were subject to the analysis. They were developed on ischaemic vascular conditions with or without infectious disease, and/or DM. All ulcers were purely ischaemic in nature and were exclusively located on the foot or toes. Ulcers developed in patients with connective tissue disease, blue toe syndrome and malignant tumour were excluded. The cases of unclear information on outcome were excluded. There was no other criteria for exclusion.

#### Data analysis

Taking into account a few outliers in the data set, we employed non-parametric test for the analysis. The Mann-Whitney U test was used to compare two groups (healed and non-healed). The Steel-Dwass test was used

to evaluate four groups (healed with DM, healed without DM, non-healed with DM and non-healed without DM). Logistic regression analysis was performed to calculate the probability of ulcer healing for a given SPP based on the measurements of 62 patients with 112 ulcers on 86 toes and feet, excluding 5 ulcers on 5 toes and feet of 3 patients with severe infections. A receiver operating characteristic (ROC) curve was drawn to calculate the cut-off value for ulcer healing.<sup>9</sup> On the revascularisation patients, preoperative and postoperative (bypass surgery and bone marrow mesenchymal stem cell transplantation (BMT)) SPP values were compared using the Wilcoxon signed-rank test. All calculations were performed by JMP Pro 12 (SAS Institute Japan, Tokyo).

## Results

A total of 117 foot ulcers on 91 toes and feet of 65 patients, who visited Hiroshima University Hospital from 2005 to 2007 due to foot gangrene and ulcer with or without DM and infection for the evaluation of blood circulation insufficiency, were studied retrospectively.

The procedures of revascularisation treatments were bypass surgery in 13



cases, percutaneous transluminal angioplasty (PTA) in 2 cases, and BMT in 14 cases. Both pre and postoperative SPP measurements were performed for 11 sites in 8 patients who received bypass surgery and/or PTA, and for 10 sites of 8 cases treated with BMT. The postoperative SPP measurements were conducted between 3 and 14 days after the bypass surgery and/or PTA and between 3 and 10 months after BMT, respectively. The age of patients was from 24 to 90 years old (mean age  $\pm$  standard deviation (SD):  $64.3 \pm 16.6$ ). A total of 40 patients suffered from DM with 55 affected toes. The age of patients with diabetes was from 43 to 90 years old (average  $\pm$  SD:  $69.8 \pm 10.9$ ). The average  $\pm$  SD of glycated haemoglobin (HbA1c) in the patients with diabetes was  $7.47 \pm 1.81\%$ .

#### Relationship between SPP value and ulcer healing

A significant difference in SPP value was observed between the healed group and the non-healed group. The SPP values in healed cases were  $> 27$  mmHg except one case (Fig 1). In both groups, no significant difference of SPP was observed between patients with DM and those without (Fig 1). In the non-healed group, three cases showed exceptionally high values of SPP. These

patients suffered from severe infections and were treated with an antimicrobial agent, and were all under tight glycemic control. No difference of HbA1c values between the healed group and the non-healed group was observed (Fig 2).

#### The effect of vascular reconstruction therapy on SPP

We examined the effect of operations on SPP values and its relation to ulcer prognosis. The SPP values significantly increased in all patients who received bypass operations. The SPP values in patients who received BMT also increased except for 3 ulcers out of 10 (Fig 3). Nevertheless, 2 of them with < 28 mmHg postoperative SPP did not heal. All ulcers with > 40 mmHg SPP values healed (Fig 3).

#### Logistic regression analysis

We calculated the probability of healing on the basis of given SPP values, excluding those of three cases with severe infections, using logistic regression analysis. The probability curve obtained by this analysis suggests that the probabilities of an ulcer healing at 30 mmHg and 50 mmHg are 23% and 80%,

respectively (Fig 4).

In order to select the optimal cut-off values, a ROC curve was obtained by calculating the sensitivity and specificity at every possible cut-off point, and by plotting sensitivity against 1-specificity. The ROC curve analysis of SPP value revealed that the cut-off value to indicate foot ulcer healing is 31-43 mmHg (Fig 5).

## Discussion

Patients with diabetes account for a majority of nontraumatic leg amputation.<sup>10,11</sup> The risk of lower limb gangrene in patients with diabetes is between 10 and 15 times higher than that those without.<sup>12,13</sup> However, the parameters of diabetic conditions do not necessarily reflect the prognosis of foot ulcer and indicate the necessity of amputation.

The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II)<sup>2</sup> recommends ABPI as a method of screening peripheral blood flow disorders. However, in peripheral arterial diseases with diabetes, it is necessary to take into account the characteristics of impaired vascular conditions due to diabetes. In general, the degree of

blood vessel calcification and that of peripheral limb ischemia are more severe in patients suffering from foot ulcers with diabetes than those without. In the case of severe blood vessel calcification, the apparent ABPI values measured by presently available devices tend to be higher than the values of real blood flow. Moreover, ABPI does not reveal blood flow precisely around ulcers or in the area of interest located in more peripheral zones than the ankle where the blood pressure is measured for ABPI. In contrast, SPP is neither affected by vascular calcification nor by DM itself.<sup>3</sup> Moreover, SPP can be measured at any point where a 7x3 mm sensor is attached with a manchette (cuff). Thus, blood flow of patients with diabetes may be precisely evaluated regardless of their vascular calcification and a location in the foot.

On the other hand, laser Doppler scanner for the measurement of SPP captures microcirculatory perfusion at 1–1.5mm under the skin surface. Therefore, SPP reflects superficial, but not deep blood flow. Thus, it is also important to assess deep blood flow insufficiency, poor metabolism, deep muscular and subcutaneous infections, pressure load and neuropathy as well. In fact, ulcers in 3 cases of DM complicated with severe infections did not heal in spite of high values of SPP. Nevertheless, our study suggested that DM

itself is not directly related to the prognosis of foot ulcers.

By measuring SPP, we can determine the site of leg amputation and monitor the blood flow of pre and post revascularisation surgery. Castronuovo et al. reported that ulcers in limbs < 30 mmHg local SPP values cannot heal by minor amputation or conservative management.<sup>3</sup> Miyajima et al. reported 45 mmHg as a cut-off value of SPP for amputation in the treatment of the foot ulcers accompanying ischaemia with DM.<sup>14</sup> Low values of SPP may be raised by revascularization treatments, such as bypass surgery, percutaneous transluminal angioplasty and/or BMT. However, they are invasive and represent a substantial burden for patients. Therefore, precise and comprehensive parameters to assist the decision of treatment of foot ulcers are in high demand. The sensitivity and the specificity of a cut-off value of 31 mmHg for refractory foot ulcer to heal was 88% and 74%, if they are not complicated with serious infection. These calculations suggest that foot ulcers < 31 mmHg SPP values may heal only at low ratio and are recommended to be surgically treated. When a cut-off value was set to 43 mmHg, the sensitivity and the specificity were 67% and 94%. It is suggested that surgeries for revascularisation should aim for an increase of SPP value to 43

mmHg or higher.

In our study, all ulcers with 27 mmHg or lower SPP failed to heal by conservative treatments except one case. Castronuovo et al.<sup>3</sup> reported that ulcers of certain patients had healed in spite of 10–20 mmHg SPP. This difference may be due to a difference of follow-up periods with conservative treatments. We performed major amputations and revascularisation surgeries for several patients regardless of SPP. In medical practice, it may be more important for patients to consider an aggressive but rapid treatment, such as amputation, so as to return to their daily lives earlier than would be the case for long conservative treatments with possibly higher medical expenses. Matsuzaki et al.<sup>15</sup> reported no difference between major and minor amputations in overall prognosis of the patients with dialysis due to diabetic nephropathy even if the wound had healed.

This study revealed that severe infection, but not diabetic, is a crucial factor that prevents ulcer healing in spite of high SPP. It is feasible that other factors, such as thinning dermis arising from diabetic neuropathy, venous stasis, and inadequate application of local wound treatments may also be hindering the wound healing process regardless of SPP.<sup>16</sup> Combinations with

recently developed biological medications, such as cultured allogeneic keratinocytes<sup>17</sup> and autologous platelet-rich plasma<sup>18,19</sup> along with treatments to directly improve blood flow may help overcome such conditions and promote ulcer healing.

### Limitation

Our study is retrospective, observational and an analysis of single institute. A further prospective study taking into account the modalities of vascular intervention in multiple centres is warranted for more solid evidences for our criteria.

### Conclusion

The combination of SPP and careful evaluation of infection may be a good parameter to predict the prognosis and to decide the appropriate treatment for ischaemic skin ulcers, regardless of the complication of DM.

### Continued Professional Development reflective questions

- Why could skin perfusion pressure (SPP) values provide appropriate

decision-making for leg amputation or for conservative treatment of ischaemic foot ulcers?

- How would you assess the condition of a foot ulcer?
- What would your standard approach for treating leg amputation due to a refractory foot ulcer be?

Declaration of interest

Nothing to declare.

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## Figure Legends

### Figure 1

No difference between patients with diabetes mellitus (DM) (●) and those without DM (°) was observed. Foot ulcers of 3 out of 5 patients complicated with severe infection (×) failed to heal in spite of exceptionally high skin perfusion pressure (SPP) values > 60 mmHg.

### Figure 2

Difference of glycated haemoglobin (HbA1c) between the ulcer healed group and the ulcer non-healed group.

### Figure 3

Skin perfusion pressure (SPP) values of the patients with foot ulcers before and after bypass operation and bone marrow mesenchymal stem cell transplantation (BMT).

#### Figure 4

Probability curve of healing on the basis of given skin perfusion pressure (SPP) values, excluding those of 5 toes with severe infections.

#### Figure 5

Receiver operating characteristic (ROC) curve analysis. The points from 31 to 43 of skin perfusion pressure (SPP) values were equally near the left top in the curve and those points had high sensitivity and high specificity. The point of 31 was the highest sensitivity among them. It is suitable for cut-off value at foot ulcer screening. The point of 43 was the highest specificity among them. Surgeries for revascularisation should aim for an increase of SPP value to 43 mmHg or higher. Area under the curve: 0.9134

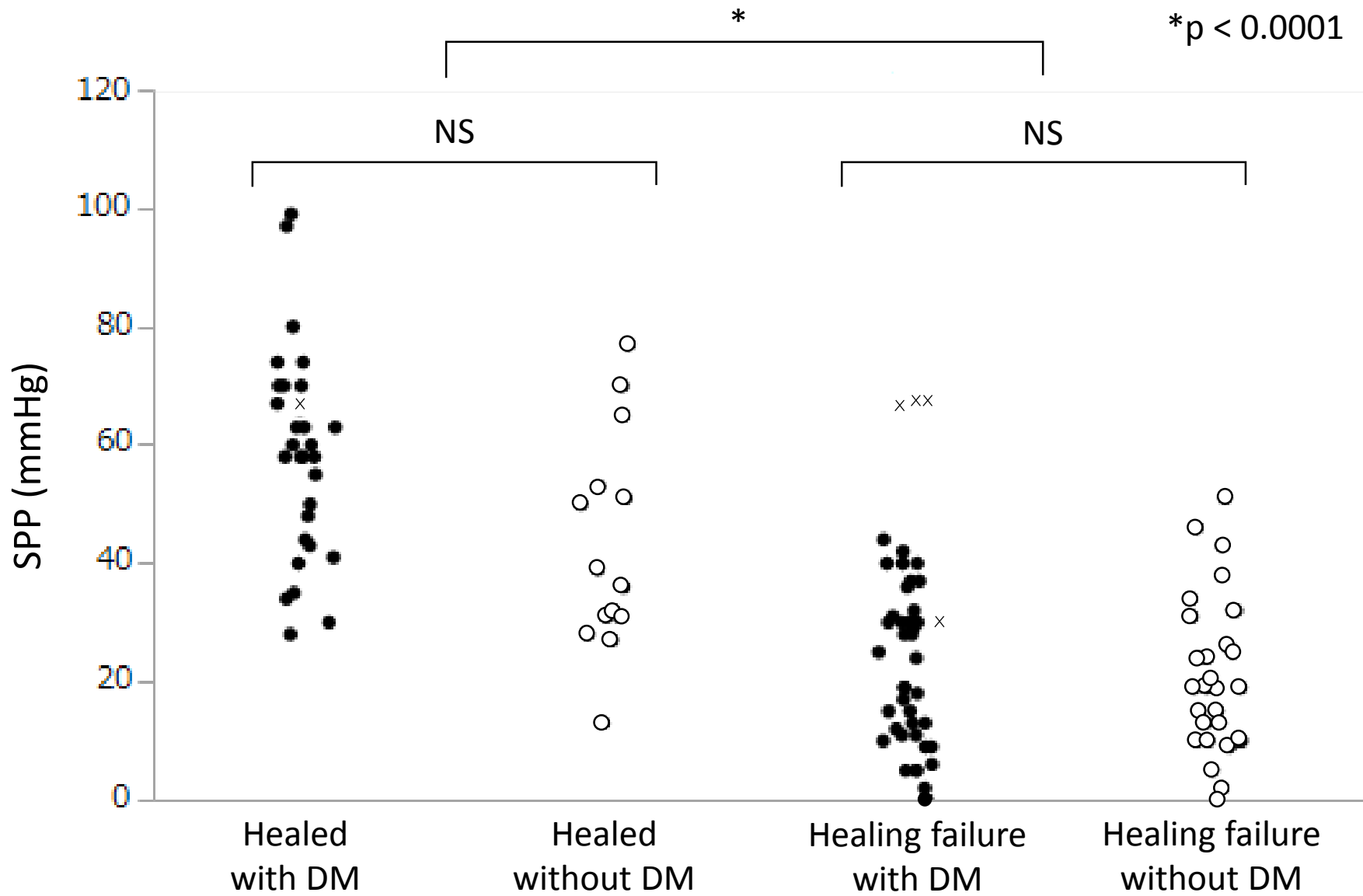


Fig 1

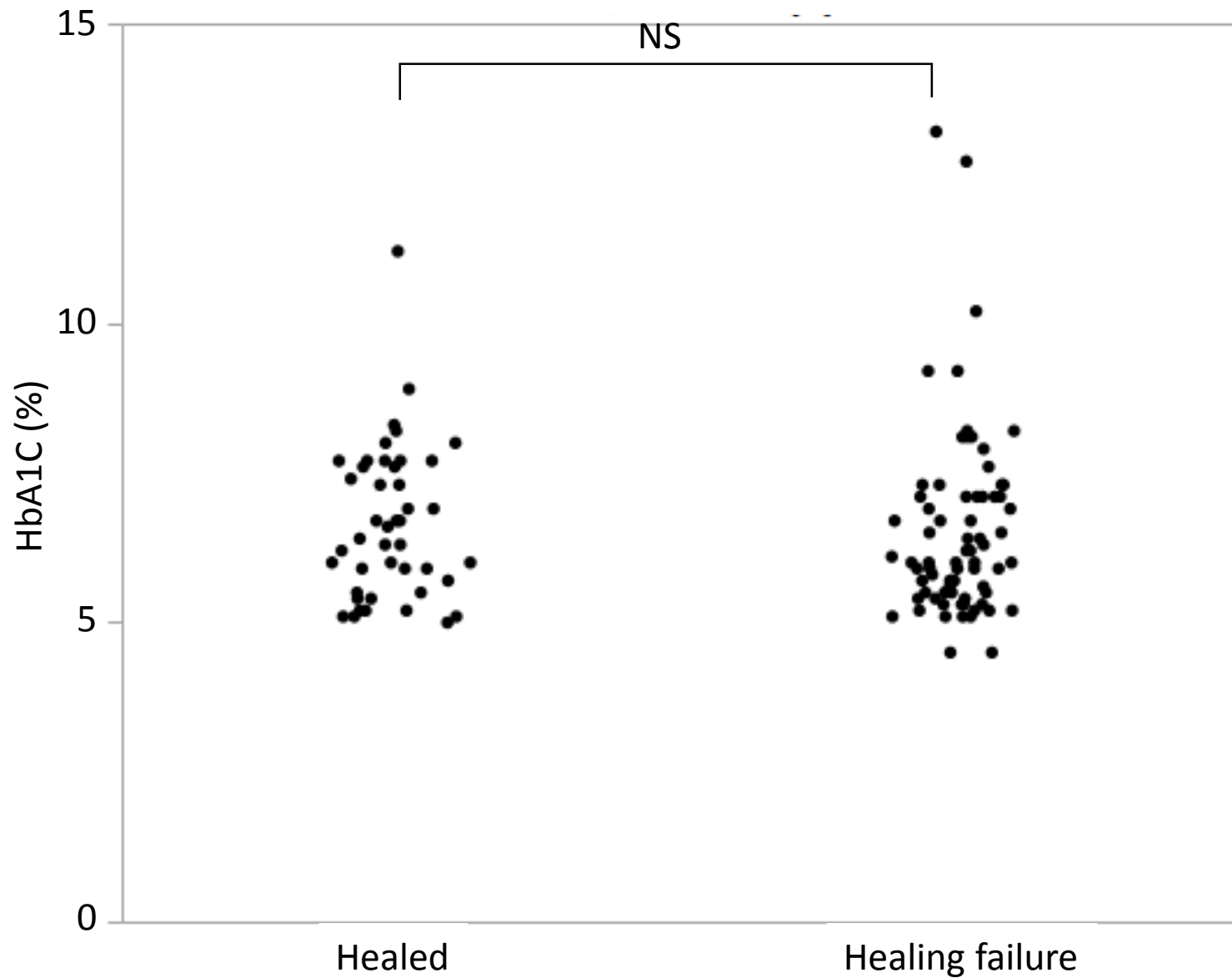


Fig 2

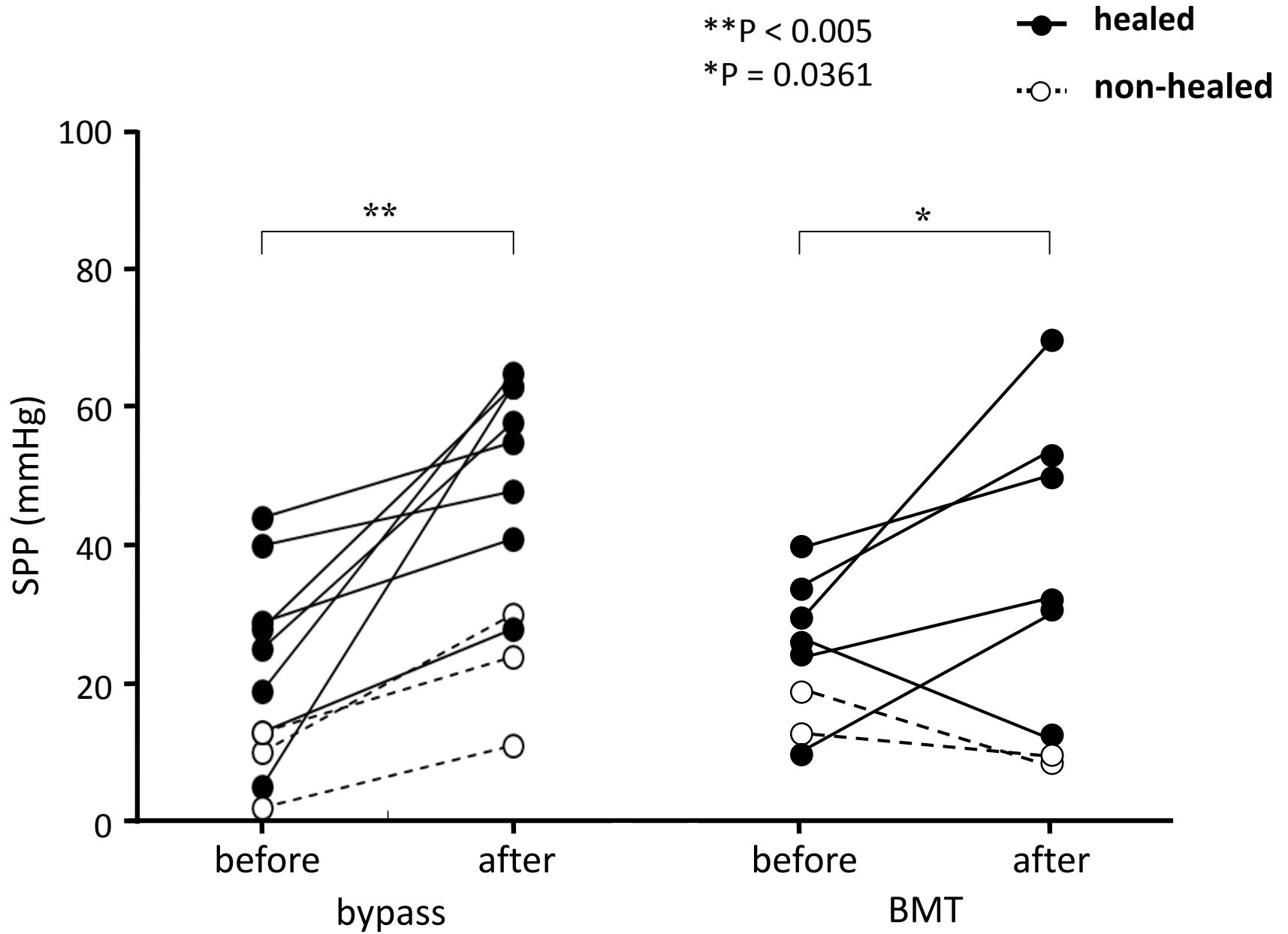


Fig 3



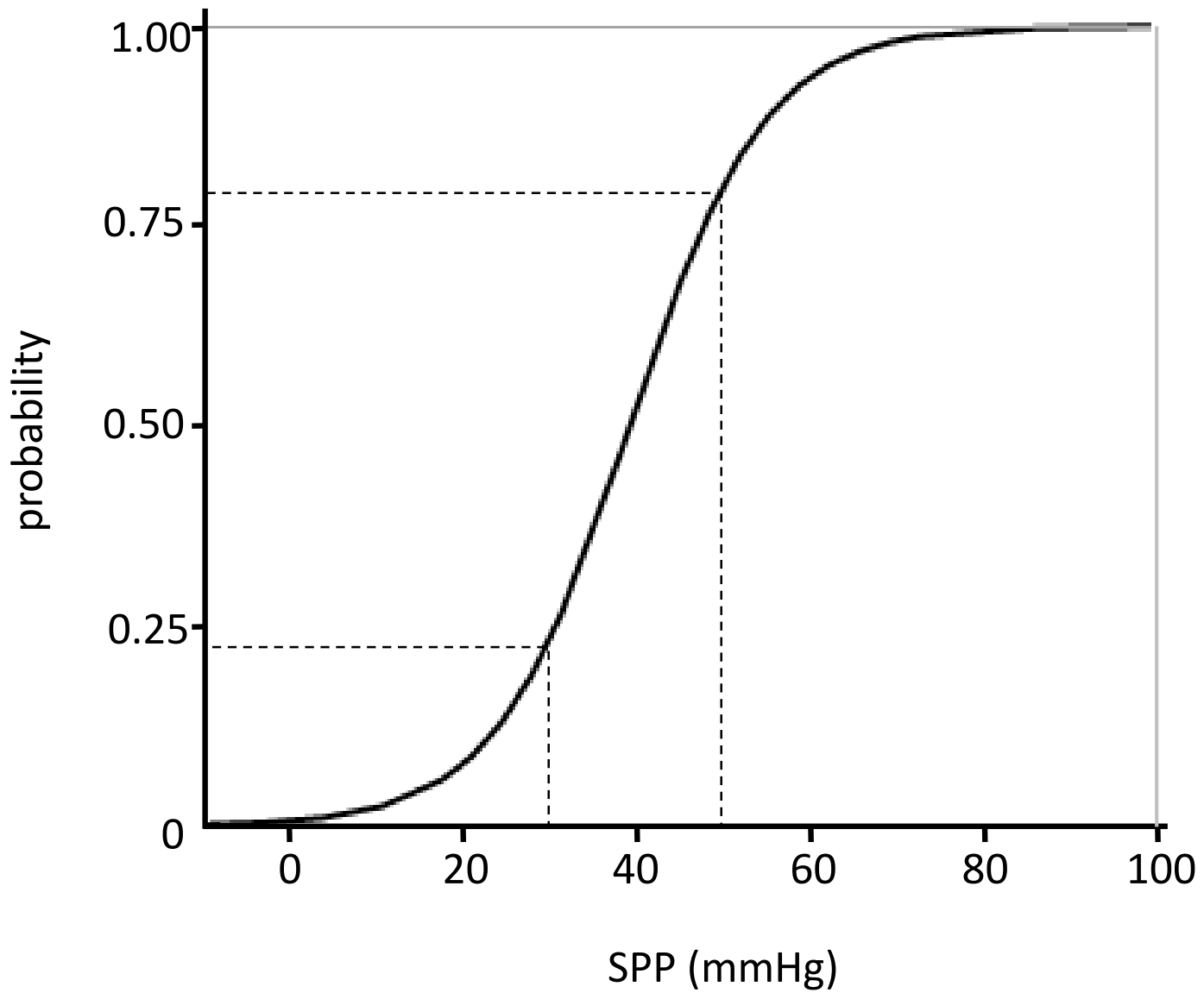


Fig 4

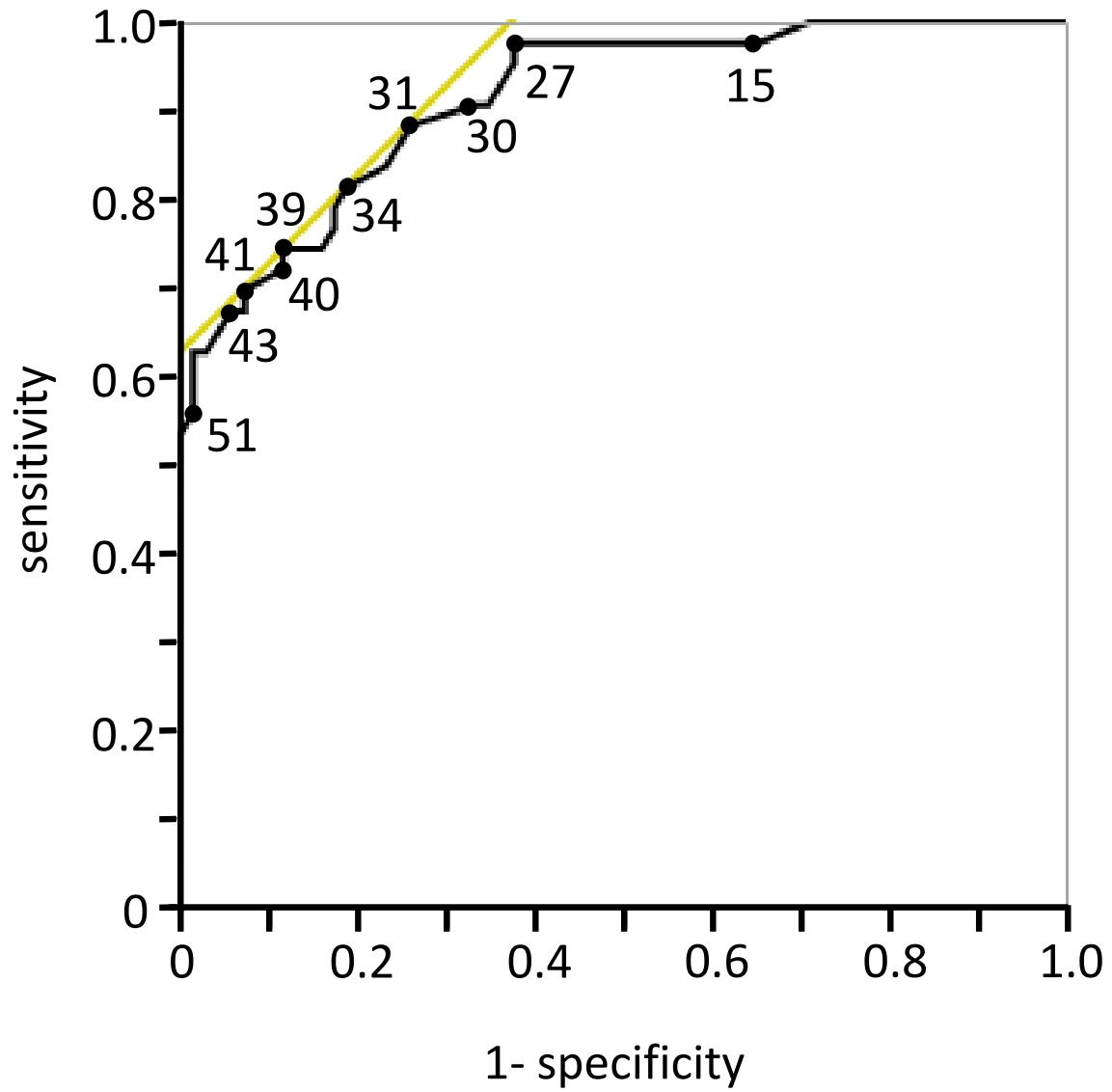


Fig 5