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# A Systematic Review and Meta-Analysis of the Pressure-Induced Vasodilation Phenomenon and Its Role in the Pathophysiology of Ulcers

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**Background:** Physiologic studies show that tissue perfusion increases during moderate amounts of tissue compression. This is attributed to sensory nerves initiating a vasodilatory cascade referred to as pressure-induced vasodilation.

**Methods:** PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched for studies investigating perfusion during pressure exposure longer than 10 minutes. Retrieved studies were assessed using the Office of Health Assessment and Translation Risk of Bias Rating Tool for Human and Animal Studies. Results were pooled with random effects models. The body of evidence was rated using the Office of Health Assessment and Translation approach.

**Results:** Twenty-nine articles were included, of which 19 articles were included in meta-analyses. The evidence indicates that moderate amounts of tissue compression have the capacity to increase perfusion in healthy humans by 46 percent (95 percent CI, 30 to 62 percent). Using the Office of Health Assessment and Translation approach, the authors found a high level of confidence in the body of evidence. Pressure-induced vasodilation blockade was associated with increased pressure ulcer formation. Pressure-induced vasodilation was impaired by neuropathy and by the drugs diclofenac and amiloride.

**Conclusions:** This systematic review and meta-analysis indicates that healthy humans have the capacity to increase local perfusion in response to mechanical stress resulting from tissue compression. Because pressure-induced vasodilation is mediated by sensory nerves, pressure-induced vasodilation emphasizes the importance of sensory innervation for durable tissue integrity. Pressure-induced vasodilation impairment seems to provide a complementary explanation for the susceptibility of neuropathic tissues to pressure-induced lesions. (*Plast. Reconstr. Surg.* 144: 669e, 2019.)

**P**ressure and diabetic foot ulcers impose a significant burden on health care.<sup>1,2</sup> Annual costs of prevention and treatment of ulcers exceed \$50 billion for the United States.<sup>3,4</sup> These costs are likely to increase because of aging societies and the rise of diabetes.<sup>2</sup> Improved understanding of the physiology behind ulcer formation may provide windows of opportunity for new preventive

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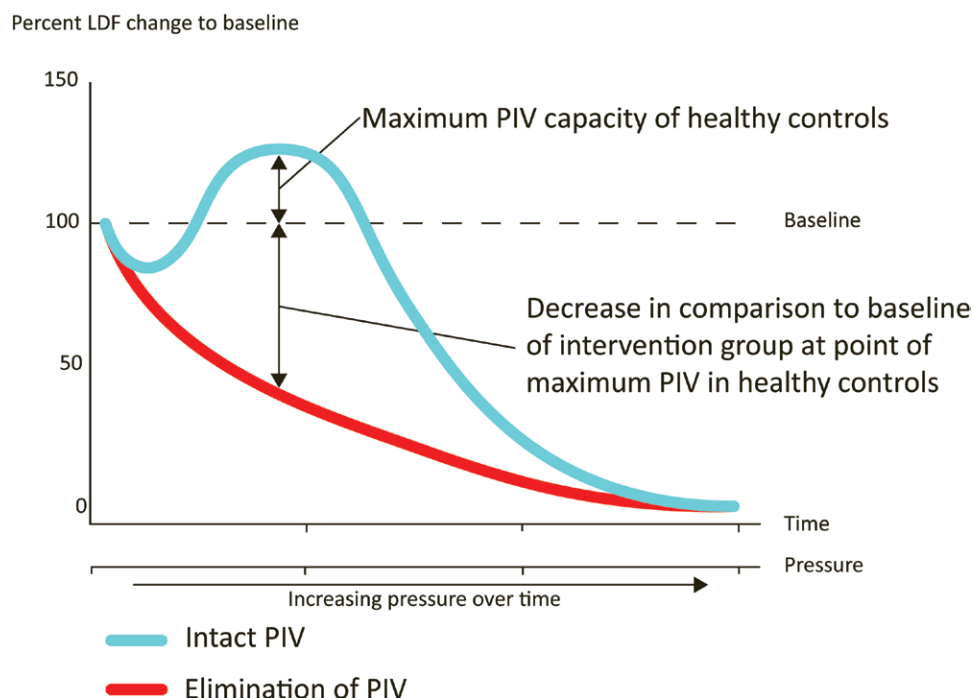
and treatment options. Nevertheless, the reason why certain groups, such as patients with neuropathy, are at increased risk of developing ulcerations remains the subject of debate.<sup>5,6</sup> Most attention has been given to the loss of protective sensation<sup>1,7,8</sup> and mechanical stress.<sup>1,9,10</sup> However, some studies report that a moderate amount of tissue compression increases blood flow in healthy tissue, a phenomenon called pressure-induced vasodilation. These studies also demonstrated that pressure-induced vasodilation cannot be induced in neuropathic tissues.<sup>11,12</sup> We hypothesize that moderate amounts of pressure increase local blood flow in subjects with healthy neurovascular status, and that a lack of pressure-induced vasodilation may lead to necrosis and the formation of ulcers during tissue compression. To summarize the evidence on pressure-induced vasodilation, we conducted a systematic review and meta-analysis of animal and human studies that measured perfusion with laser Doppler flowmetry during more than 10 minutes of tissue compression.

## PATIENTS AND METHODS

This systematic review and meta-analysis was performed in concordance with the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>13</sup> As this concerns a literature study, no ethical approval was required. No review protocol for this meta-analysis was published or registered before this study was undertaken. The PubMed, Embase, and Cochrane Central Register of Controlled Trials databases were searched on April 30, 2018, with terms relating to pressure-induced vasodilation, including the Medical Subject Headings terms “Pressure” and “Vasodilation.” (See **Appendix, Supplemental Digital Content 1**, which shows the search strategy, <http://links.lww.com/PRS/D717>.) No restrictions were used.

Titles and abstracts were screened by two independent reviewers (P.R.Z. and S.F.M.B.). The full text of potentially eligible articles was reviewed for eligibility based on predefined inclusion criteria by both reviewers. Studies were included when they provided cutaneous laser Doppler flowmetry measurements of tissue that was subjected to more than 10 minutes of mechanical stress from constant or increasing pressure exposure, as studies suggest that it takes 10 minutes for pressure-induced vasodilation to occur.<sup>12</sup> Animal and human studies were both included. Articles in languages other



**Fig. 1.** Examples of perfusion curves during loading with a slowly increasing amount of pressure of subjects with and without pressure-induced vasodilation. The maximum pressure-induced vasodilation capacity is the maximum increase of blood flow in comparison to baseline in percentages. The decrease in comparison to baseline at the point of maximum pressure-induced vasodilation is also represented. *LDF*, laser Doppler flowmetry; *PIV*, pressure-induced vasodilation.

than English, German, and French were excluded, as were duplicates, congress abstracts, and articles without original data. References from included articles were assessed for eligibility.

Two reviewers (P.R.Z. and S.F.M.B.) critically appraised each study using the Office of Health Assessment and Translation Risk of Bias Tool for Human and Animal Studies. Discrepancies were resolved through discussion to reach final risk of bias ratings for each item.<sup>14</sup> Based on the design of an individual study, a number of items are rated to be at definitely high, probably high, probably low, or definitely low risk of bias. When studies did not report the necessary information, “not reported” was recorded.

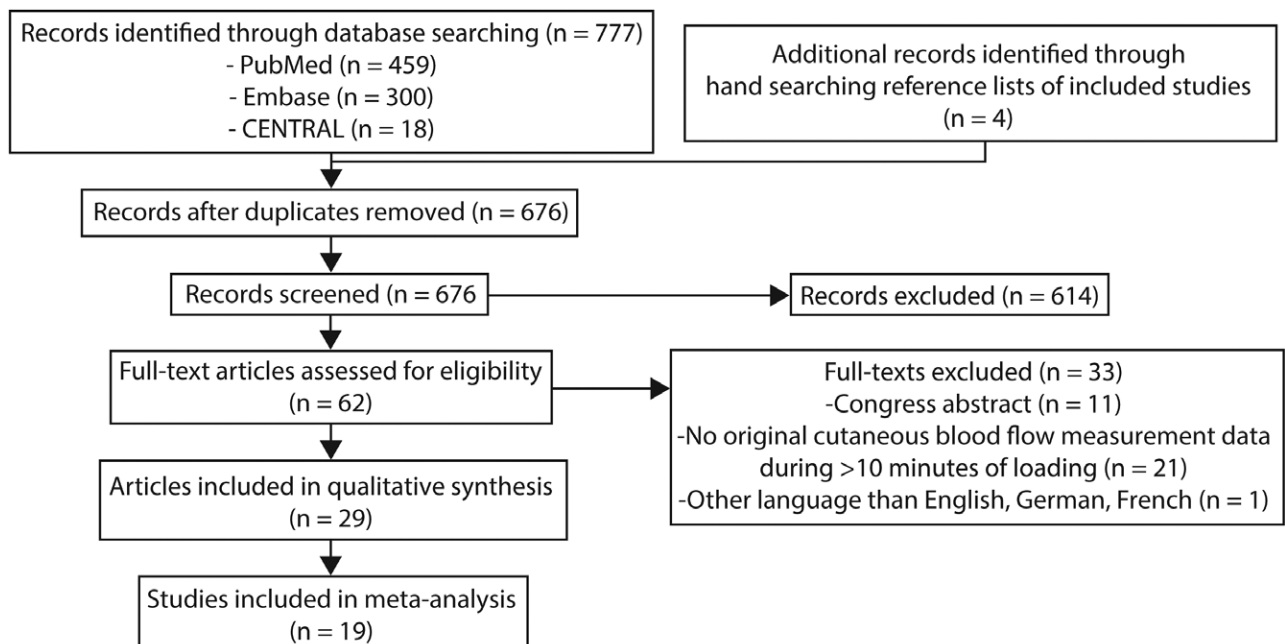
Two reviewers (P.R.Z. and S.F.M.B.) extracted data in predefined evidence tables for comparison. Disagreements were resolved through discussion. Data collection included sample size, study groups and their characteristics (e.g., age, sex, animal species), pressure stimulus characteristics, room and/or skin temperature during the measurements, location of measurement, and physiologic targets of interest in case of studies investigating pressure-induced vasodilation physiology.<sup>15–18</sup>

The primary outcome of interest was the maximum increase of blood flow during pressure loading in comparison to baseline of healthy subjects (Fig. 1), as measured by laser Doppler flowmetry. Secondary outcomes were whether pressure-induced vasodilation could be measured at deeper tissue sites, factors found to impact blood flow responses during pressure exposure and

corresponding changes in blood flow, physiologic mediators necessary for a full pressure-induced vasodilation response, and the results from experimental pressure ulcer induction tests in animals with or without blockage of pressure-induced vasodilation. In case of discrepancies between studies, we sought contact with the authors for clarification. We graded our confidence in the body of evidence using the Office of Health Assessment and Translation approach,<sup>14</sup> an adaptation of the Grading of Recommendations, Assessment, Development and Evaluation Working Group guidelines.

### Statistical Analysis

Mean maximum pressure-induced vasodilation capacities and the standard errors of the mean of healthy subjects were pooled using generic inverse variance meta-analysis when studies used an identical setup and concerned the same species category (i.e., humans, rats, or mice).<sup>19</sup> Data from subjects with compromised neurovascular status were excluded from these meta-analyses. The mean decrease of blood flow in comparison to baseline of diabetic mice, at the same amount of pressure where healthy controls had maximum pressure-induced vasodilation (Fig. 1), was also pooled using generic inverse variance meta-analysis. To account for anticipated heterogeneity, we pooled effect sizes using random effects meta-analysis.<sup>20</sup> Heterogeneity was investigated using the  $I^2$  statistic.<sup>21</sup> We defined  $p < 0.05$  as statistically significant. In case of a limited amount of studies, no subgroup analysis



**Fig. 2.** Flow diagram of study selection.



would be performed. Statistical analyses were conducted using the meta package for R.<sup>19</sup>

## RESULTS

The search retrieved 777 records. After removal of duplicates, 676 records were screened and 614 were excluded based on title and abstract. A total of 62 full-text articles was assessed for eligibility. Four additional records were identified from the reference lists of included studies. A total of 29 articles were included. An overview of the systematic review process is presented in Figure 2.

We included 14 human<sup>11,12,15–18,22–29</sup> and 16 animal studies (described in 29 articles).<sup>25,30–44</sup> A description of the setup used in most studies<sup>11,12,22–25,27,30–44</sup> can be found in a methodology article by Fromy et al.<sup>45</sup> Studies originated from six independent research groups.<sup>11,12,15–18,22–44</sup> A comprehensive overview of all included studies is provided as Supplemental Digital Content 2 and 3. (See Table, Supplemental Digital Content 2, which shows a summary of included animal studies, <http://links.lww.com/PRS/D718>. See Table, Supplemental Digital Content 3, which shows a summary of included human studies, <http://links.lww.com/PRS/D719>.) A summary of the risk of bias assessment is presented in Figure 3.

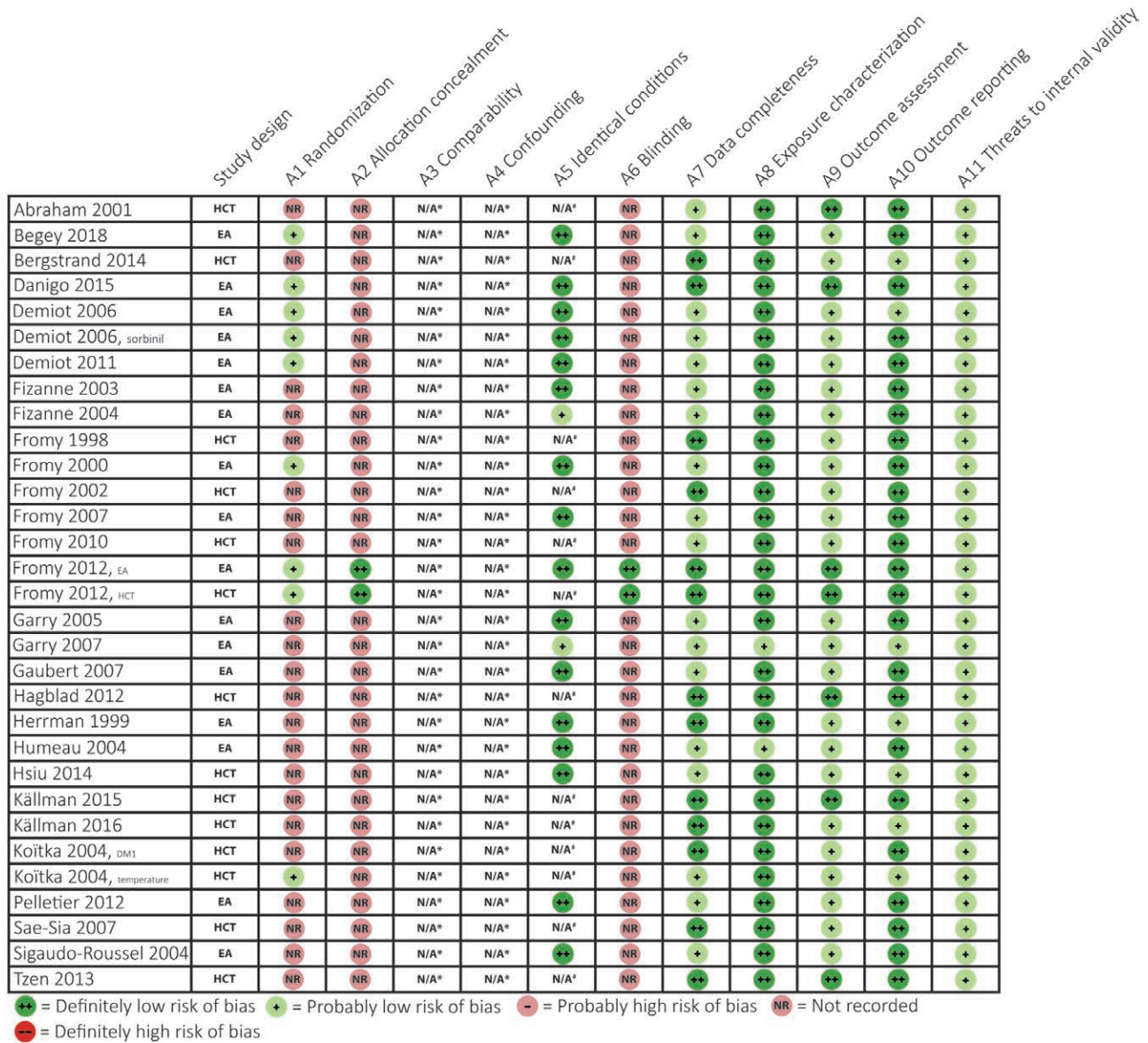
### Pressure-Induced Vasodilation

The pooled maximum pressure-induced vasodilation capacity of healthy humans showed an increase of 46 percent (95 percent CI, 30 to 62 percent) in comparison to baseline blood flow in response to a progressive pressure stimulation of 11.1 Pa/second (Fig. 4). A brief summary of these studies is provided in Table 1. In healthy mice, the pooled maximum pressure-induced vasodilation capacity was 39 percent (95 percent CI, 34 to 45 percent) in response to a progressive pressure stimulus of 2.2 Pa/second. (See Figure, Supplemental Digital Content 4, which shows a pooling of the mean maximum pressure-induced vasodilation capacities of mouse studies that used a pressure stimulus of 2.2 Pa/second, <http://links.lww.com/PRS/D720>.) A brief summary of these studies is provided in Table 2. In healthy rats, the pooled maximum pressure-induced vasodilation capacity was 47 percent (95 percent CI, 28 to 66 percent) in response to a progressive pressure stimulus of 11.1 Pa/second. (See Figure, Supplemental Digital Content 5, which shows a pooling of the mean maximum pressure-induced vasodilation capacities of rat studies that used a pressure stimulus of 11.1 Pa/second, <http://links.lww.com/PRS/D721>.)

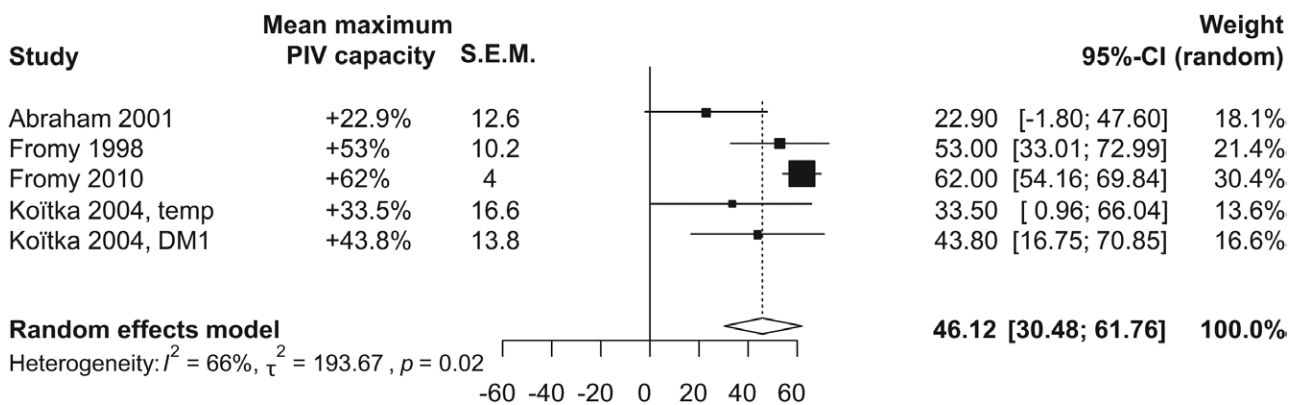
A brief summary of these studies is provided in Table 3. According to the evidence judgment by the Office of Health Assessment and Translation approach,<sup>14</sup> we found a high level of confidence in the body of evidence to support the notion that moderate amounts of pressure increase perfusion in subjects with healthy neurovascular status. (See Table, Supplemental Digital Content 6, which shows rating of pressure-induced vasodilation body of evidence according to the Office of Health Assessment and Translation approach, <http://links.lww.com/PRS/D722>.) The pooled decrease of blood flow in diabetic mice at the pressure stimulus that induced maximum pressure-induced vasodilation in healthy mice (0.4 kPa) showed a decrease of –24 percent (95 percent CI, –40 to –8 percent). [See Figure, Supplemental Digital Content 7, which shows a pooled decrease in blood flow of diabetic mice exposed to the amount of pressure that induced maximum pressure-induced vasodilation in healthy mice (0.4 kPa), <http://links.lww.com/PRS/D723>.] A brief summary of these studies is provided in Table 2. A summary of the studies that identified factors that impair or eliminate pressure-induced vasodilation is presented in Table 4, whereas a summary of the studies that identified treatments able to restore pressure-induced vasodilation in animal models is presented in Table 5. A visual summary of the physiologic studies is presented. (See Figure, Supplemental Digital Content 8, which shows an overview of physiologic mediators involved in pressure-induced vasodilation, <http://links.lww.com/PRS/D724>.)

### Influence of Pressure-Induced Vasodilation on Ulcer Formation

Fromy et al. examined the influence of pressure-induced vasodilation on pressure ulcer formation by comparing the incidence of pressure ulcers after 4 hours of ischemic skin compression, and demonstrated that mice with pressure-induced vasodilation developed fewer pressure ulcers than those without pressure-induced vasodilation (60 percent versus 100 percent).<sup>25</sup> Moreover, the cutaneous area with a loss of perfusion was significantly smaller in mice with pressure-induced vasodilation ( $33 \pm 14 \text{ mm}^2$ ) than in mice without pressure-induced vasodilation ( $144 \pm 26 \text{ mm}^2$ ;  $p < 0.01$ ), corresponding to  $19 \pm 8$  percent and  $81 \pm 15$  percent ( $p < 0.01$ ) of the compressed area.<sup>25</sup> Two studies assessed the influence of diabetic neuropathy on pressure-induced vasodilation and pressure ulcer formation in mice.<sup>31,34</sup> Mice exposed to 8 weeks



**Fig. 3.** Quality assessment of included studies with the Office of Health Assessment and Translation Risk of Bias Tool for Human and Animal Studies.



**Fig. 4.** Pooling of the mean maximum pressure-induced vasodilation capacities of human studies that used a pressure stimulus of 11.1 Pa/second.

**Table 1. Brief Summary of the Human Studies with Healthy Volunteers Included in Meta-Analysis**

Reference	Sample Size	Sex		Age (yr)	Maximal PIV (%)
		Male	Female		
Abraham et al., 2001 <sup>22</sup>	8	4	4	23 ± 1	23 ± 13
Fromy et al., 1998 <sup>12</sup>	10	NR	NR	NR	53 ± 10
Fromy et al., 2010 <sup>24</sup>	12	8	4	26 ± 1	62 ± 4
Koïtka et al., 2004 <sup>11</sup>	12	NR	NR	23 ± 1	44 ± 14
Koïtka et al., 2004 <sup>27</sup>	10	6	4	25 ± 1	34 ± 17
Pooled maximum PIV capacity					46†

NR, not reported; PIV, pressure-induced vasodilation.

\*All subjected to a 11.1-Pa/second pressure stimulus.

†95% CI, 30 to 62 percent ( $F = 66$  percent).**Table 2. Brief Summary of the Studies with Healthy and Diabetic Mice Included in Meta-Analysis\***

References	Groups with Sample Size	Sex Distribution	Age (wk)	Maximal PIV†
Begey et al., 2018 <sup>30</sup>	Between 4–9 for each group	All male	10–14	23 ± 6%
Danigo et al., 2015 <sup>31</sup>	20 for each group G: STZ-induced diabetes of 8 wk in duration vs. healthy controls	All male	5–6	Healthy controls: 35 ± 8% at 0.4 kPa STZ-induced DM: -17 ± 7% at 0.4 kPa ( $p < 0.001$ )
Demiot et al., 2006 <sup>32</sup>	7–10 for every group	All male	12	42 ± 8%
Demiot et al., 2006 <sup>33</sup>	10 for each group G: STZ-induced diabetes of 8 wk in duration vs. healthy controls	All male	NR	Healthy controls: 55 ± 6% at 0.4 kPa STZ-induced DM: -33 ± 8% at 0.4 kPa ( $p < 0.001$ )
Demiot et al., 2011 <sup>34</sup>	10	All male	5–6	35 ± 9%
Fizanne et al., 2004 <sup>36</sup>	5–10 for every group	NR	NR	60 ± 15%
Fromy et al., 2012 <sup>25</sup>	5–10 for every group	All male	NR	41 ± 3%
Garry et al., 2007 <sup>40</sup>	4–11 for every group	NR	NR	41 ± 6%
Gaubert et al., 2007 <sup>41</sup>	5–13 for every group	All male	24–28	39 ± 6%
Sigaud-Roussel et al., 2004 <sup>44</sup>	9–12 for every group	All male	NR	34 ± 13%
Pooled decrease in diabetic mice at 0.4 kPa				-24%‡
Pooled maximum PIV of healthy mice at 0.4 kPa				39%§

DM, diabetes mellitus; NR, not reported; PIV, pressure-induced vasodilation; STZ, streptozotocin (method to induce diabetes in laboratory animals); G, groups.

\*All subjected to a 2.2-Pa/second pressure stimulus.

†Values are given as ± SEM.

‡95% CI, -40 to -8 percent ( $F = 60$  percent).§95% CI, 34 to 45 percent ( $F = 42$  percent).**Table 3. Brief Summary of the Studies with Healthy Rats Included in Meta-Analysis\***

References	Sample Size	Sex Distribution	Age	Maximal PIV (%)†
Fizanne et al., 2003 <sup>35</sup>	7–9 for every group	All male	NR	37 ± 10
Fizanne et al., 2004 <sup>36</sup>	5–10 for every group	All male	NR	60 ± 15
Fromy et al., 2000 <sup>37</sup>	9–20 for every group	NR	NR	25 ± 9
Fromy et al., 2007 <sup>38</sup>	5–13 for every group	All male	NR	40 ± 7
Pelletier et al., 2012 <sup>43</sup>	10	All male	NR	74 ± 7
Pooled maximum PIV capacity				47‡

NR, not reported; PIV, pressure-induced vasodilation.

\*All subjected to an 11.1-Pa/second pressure stimulus.

†Values are given as ± SEM.

‡95% CI, 28 to 66 percent ( $F = 83$  percent).

of diabetes lost their capacity to display pressure-induced vasodilation, and this loss was accompanied by a significantly increased susceptibility to ulcer formation ( $p < 0.001$ ).<sup>31,34</sup> Pressure-induced

vasodilation restoration with candesartan or human recombinant erythropoietin treatment was accompanied by a regained ability to resist pressure ulcer formation ( $p < 0.05$ ).<sup>31,34</sup>



**Table 4. Overview of Factors That Impair or Eliminate Pressure-Induced Vasodilation**

PIV Impairing Factor	Reference	Results*	<i>p</i>
Neuropathy			
Aging-associated neuropathy	Fromy et al., 2010 <sup>24</sup>	62 ± 4% (young subjects, 20–35 yr) vs. 12 ± 7% (older subjects, 60–75 yr)	<0.001
Diabetic neuropathy	Fromy et al., 2002 <sup>23</sup>	In patients with diabetic neuropathy, BF was significantly lower than baseline at a PS of 0.8 kPa, vs. 6.5 kPa in healthy controls (exact PIV data NR)	
	Demiot et al., 2006 <sup>33</sup>	55 ± 6% (control mice) vs. no PIV (–33 ± 8%) in mice with diabetic neuropathy	<0.001
	Demiot et al., 2011 <sup>34</sup>	35 ± 9% vs. no PIV (exact PIV data NR) in mice with diabetic neuropathy	<0.001
	Danigo et al., 2015 <sup>31</sup>	35 ± 8% vs. no PIV (–17 ± 7%) in mice with diabetic neuropathy	<0.001
Compression neuropathy	Pelletier et al., 2012 <sup>43</sup>	70 ± 7% (control rats) vs. 25 ± 8% after 1 mo of CN ( <i>p</i> < 0.001), and no PIV (exact PIV data NR) after 6 mo of CN	<0.001
Peripheral neuropathy (not otherwise specified)	Fromy et al., 2010 <sup>24</sup>	62 ± 4% (young subjects, 20–35 yr) vs. –31 ± 10% (subjects with neuropathy, 60–75 yr)	<0.001
Spinal cord injury	Sae-Sia et al., 2007 <sup>28</sup>	PIV in healthy subjects, decreased BF in SCI patients (exact PIV data NR)	<0.01
Pharmaceuticals			
ASIC3-antagonists (Diclofenac, Amiloride)	Fromy et al., 2012 <sup>25</sup>	PIV in controls, no PIV with mice and humans treated with diclofenac or amiloride (exact PIV data NR)	
High-dose anesthesia	Fizanne et al., 2003 <sup>35</sup>	37 ± 10% (control mice) vs. –20 ± 5% (mice treated with high-dose anesthesia)	<0.05
Miscellaneous			
Pain	Fromy et al., 2007 <sup>38</sup>	40 ± 7% (control rats) vs. –12 ± 6% (rats subjected to a pain stimulus)	<0.01
Low temperatures	Koïtka et al., 2004 <sup>27</sup>	51 ± 15% (subjects with very high skin temperature, 36 ± 0.1°C) and 34 ± 11% (high, 33.9 ± 0.1°C) vs. –31 ± 7% (intermediate, 32.6 ± 0.1°C) and –40 ± 7% (low skin temperature, 29 ± 0.3°C)	<0.001
High-salt diet	Begey et al., 2018 <sup>30</sup>	23 ± 6% (control mice) vs. –4 ± 4% (high-salt diet mice)	<0.01

ASIC3, acid-sensing ion channel 3; BF, blood flow; CN, compression neuropathy; NR, not reported; PIV, pressure-induced vasodilation; PS, pressure stimulus; SCI, spinal cord injury.

\*Values are given as ± SEM.

## DISCUSSION

This systematic review and meta-analysis indicates that pressure-induced vasodilation increases tissue blood flow during exposure to mechanical stress.<sup>11,12,15–18,22–28</sup> Using Office of Health Assessment and Translation methodology,<sup>13</sup> a high level of confidence in the body of evidence was found to support this notion. We identified three

basic research studies that indicate that pressure-induced vasodilation protects against ulcer formation.<sup>25,31,34</sup> Fromy et al. showed that treatment with the diuretic amiloride eliminates pressure-induced vasodilation,<sup>25</sup> and Roustit et al. have demonstrated that amiloride treatment is indeed associated with increased formation of pressure ulcers in hospitalized patients (OR, 1.88; 95

**Table 5. Overview of Treatments Capable of Restoring Pressure-Induced Vasodilation in Animal Studies**

PIV-Restoring Treatment	Reference	Results	<i>p</i>
Nerve decompression	Pelletier et al., 2012 <sup>43</sup>	25 ± 8% (1 mo of CN) vs. 74 ± 12% (1 mo after ND); no PIV could be induced (6 mo of CN, exact PIV data NR) vs. 31 ± 7% (1 mo after ND)	<0.01
Pain management	Fromy et al., 2007 <sup>38</sup>	–31 ± 6% (pain) vs. 43 ± 10% (pain management with morphine)	<0.001
α-LPA	Demiot et al., 2006 <sup>32</sup>	No PIV could be induced in mice with 1 wk of DM, whereas PIV capacity was preserved (exact PIV data NR) in mice treated with α-LPA	<0.05
Sorbinil	Demiot et al., 2006 <sup>33</sup>	–33 ± 8% (8 wk of DM) versus 43 ± 7% (8 wk of DM with 2 wk sorbinil treatment)	<0.001
rhEPO	Demiot et al., 2011 <sup>34</sup>	No PIV could be induced in mice with 8 wk of DM, whereas mice receiving 2 wk of rhEPO treatment their PIV capacity was restored (exact PIV data NR)	<0.05
Candesartan	Danigo et al., 2015 <sup>31</sup>	–17 ± 7% (8 weeks of DM) vs. 27 ± 11% (8 wk of DM with 2 wk of candesartan treatment)	<0.05

PIV, pressure-induced vasodilation; CN, compression neuropathy; ND, nerve decompression; NR, not reported; α-LPA, alpha-lipoic acid; DM, streptozotocin-induced diabetes mellitus; rhEPO, recombinant human erythropoietin.



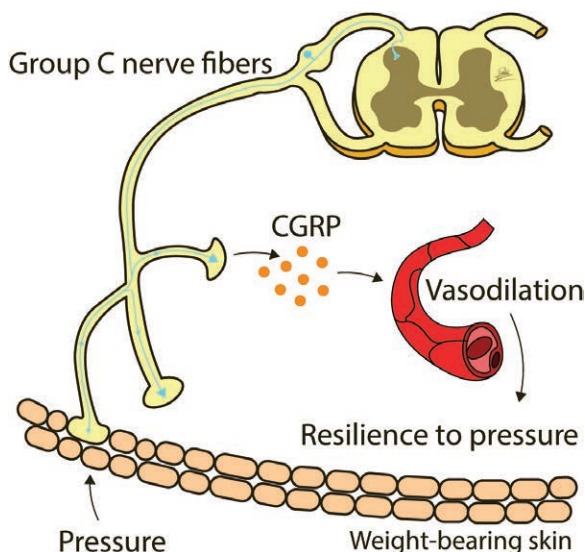
percent CI, 1.23 to 2.86;  $p = 0.003$ ).<sup>46</sup> This study provides clinical human evidence for the concept that pressure-induced vasodilation protects against pressure ulcers.

Many plastic surgeons are regularly confronted with problematic ulcers in their practice, and problematic ulcers impose a significant burden to society.<sup>3,4</sup> As tissue without pressure-induced vasodilation is prone to ulcer formation<sup>25,31,34</sup> and pressure-induced vasodilation can be influenced both positively and negatively by the factors summarized in this review, knowledge of pressure-induced vasodilation should be considered crucial to plastic surgeons treating such defects. For pressure-induced vasodilation to occur, individuals need to possess healthy sensory nerves and healthy vascular endothelium (Fig. 5).<sup>33,37</sup> Although young and healthy individuals all display pressure-induced vasodilation, pressure-induced vasodilation deteriorates with aging because otherwise healthy individuals aged 60 to 75 years display less pressure-induced vasodilation than younger adults (20 to 35 years).<sup>24</sup> This was attributed to aging-associated neuropathy,<sup>24</sup> and is thought to contribute to the susceptibility of the elderly to pressure ulcer formation.<sup>47</sup> Similarly, pressure-induced vasodilation is impaired in various other neuropathies such as diabetic or compression neuropathy.<sup>28,31,33,34,43</sup> Pressure-induced vasodilation deterioration seems to aggravate with progression of neuropathy in

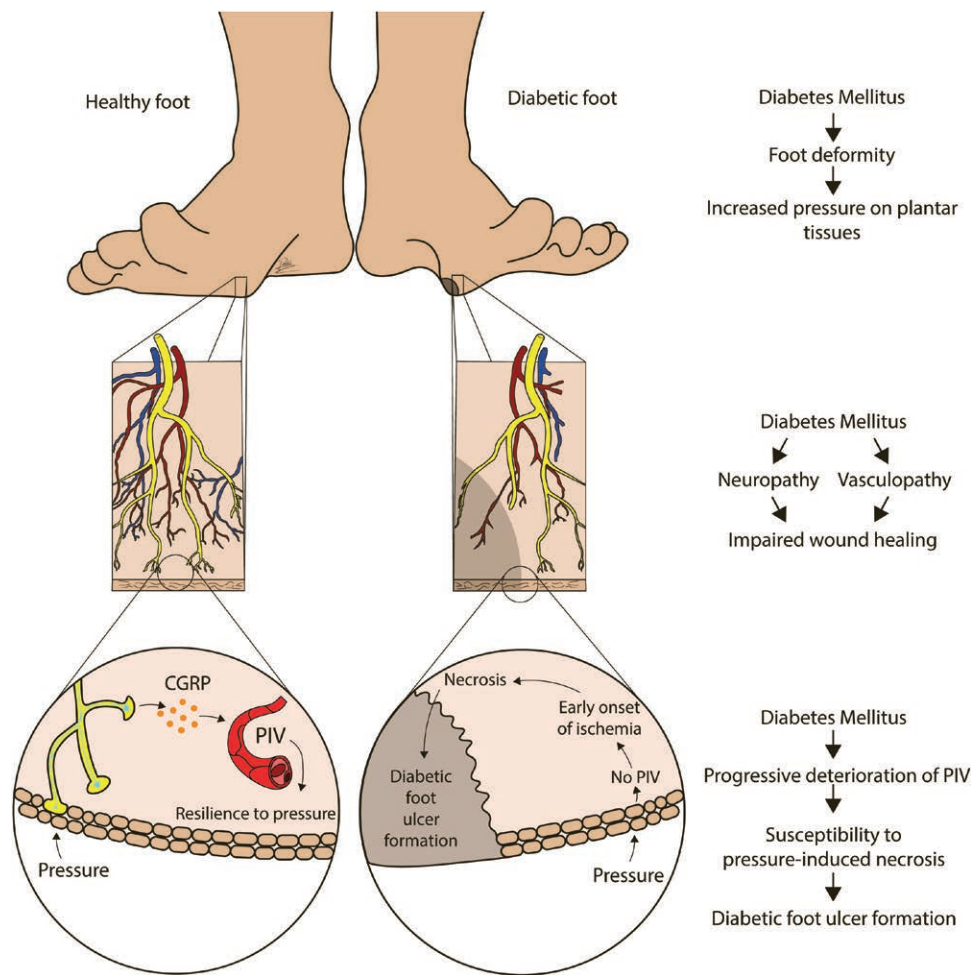
neuropathic conditions.<sup>23,43</sup> In young individuals with type 1 diabetes (mean age, 22 years), pressure-induced vasodilation seems impaired already at a young age because of endothelial dysfunction.<sup>11</sup> In spinal cord injury, loss of pressure-induced vasodilation is complete and immediate.<sup>28</sup> Although bacteria or the patient's vascular status are also likely to be important factors, pressure-induced vasodilation seems to underscore the importance of sensory innervation for preservation of tissue integrity during mechanical stress, such as from compression or shearing forces. Loss of pressure-induced vasodilation may therefore partly explain the susceptibility of neuropathic tissue to ulcerations<sup>5,6</sup> as seen in diabetic feet<sup>1</sup> (Fig. 6) or pressure ulcers of patients with spinal cord injury.<sup>48</sup>

When interpreting the results of this review, it is important to take into account that all studies included in our meta-analysis used laser Doppler flowmetry. As this technique only measures perfusion up to 1-mm depth,<sup>49</sup> these experiments provide measurements of only superficial skin perfusion. In these experiments, moderate amounts of compression increased perfusion as a result of vasodilation, whereas further compression led to ischemia as a result of vessel compression despite the presence of vasodilatory mediators (Fig. 1). Because skin is relatively robust tissue that is not easily deformed in comparison with more pliable tissues such as fat,<sup>50</sup> it is therefore likely that a certain amount of compression may increase blood flow in superficial skin, while deeper located subcutaneous fat may still be exposed to ischemia. Combined with other factors such as differences in metabolic demand or perfusion rates between different types of tissue,<sup>51,52</sup> this could be an explanation for the disease course of deep tissue injuries. Deep tissue injury is the phenomenon where skin integrity initially remains intact, whereas injury from mechanical stress does occur beneath the skin. In case of continued exposure, the overlying skin also deteriorates, after which a much larger defect is witnessed.<sup>53</sup>

Innervated tissue displays pressure-induced vasodilation,<sup>12</sup> whereas noninnervated tissue does not.<sup>28</sup> This implies that innervated flaps should be used for reconstruction of weight-bearing surfaces whenever possible (e.g., in heel reconstruction or pressure ulcer reconstruction in patients with spinal cord lesions). Although innervated flaps have been advocated for decades,<sup>54,55</sup> many centers do not regularly apply innervated flaps. As an example, free muscle flaps are still widely



**Fig. 5.** Pressure-induced vasodilation in healthy skin. Pressure is detected by sensory nerves. This results in the release of the neuropeptide calcitonin gene-related peptide. This induces vasodilation, increasing tissue resilience against tissue compression. CGRP, calcitonin gene-related peptide.



**Fig. 6.** Proposed diabetic foot ulcer pathogenesis model. Diabetes leads to increased exposure to high plantar pressures, combined with elimination of pressure-induced vasodilation. This results in a susceptibility to ulcerations as a result of pressure-induced necrosis. *CGRP*, calcitonin gene-related peptide; *PIV*, pressure-induced vasodilation.

used in reconstruction of the weight-bearing foot,<sup>56</sup> and noninnervated local flaps are still widely used in pressure ulcer reconstruction in patients with spinal cord injury.<sup>57</sup> However, there is literature to suggest favorable results associated with innervated flaps. As an example, Thomson et al. reported the results of innervated pedicled fasciocutaneous thigh flaps for pressure ulcer reconstruction.<sup>58</sup> Although all their paraplegic patients worked as administrative secretaries and were reported to be chair-bound at least 8 hours per day, all four remained ulcer-free despite an extensive follow-up length from 9 to 18 years.<sup>58</sup> These results are in line with other studies where innervated pedicled flap are also reported to remain recurrence-free.<sup>59–68</sup> In contrast, studies of noninnervated local flaps in such patient populations reveal recurrence rates of up to 82 percent within several years.<sup>69–73</sup> Similarly,

there are many studies that report an absence of ulceration with use of free innervated flaps in weight-bearing foot reconstruction,<sup>74–86</sup> whereas ulceration is reported to develop in free noninnervated fasciocutaneous flaps<sup>87–89</sup> or free muscle flaps covered with skin grafts.<sup>90,91</sup> This review suggests that innervated flaps not only provide protective sensation, but may also provide increased tissue durability as a result of pressure-induced vasodilation.

Foot ulcers are a common problem in diabetics.<sup>92,93</sup> Motor neuropathy results in an increased exposure to plantar mechanical stress.<sup>1</sup> The combination of increased exposure to mechanical stress with concomitant loss of pressure-induced vasodilation could thus be seen as an explanatory model for the pathogenesis of diabetic foot ulcers (Fig. 6). Although there are currently no clinical data regarding pressure-induced

vasodilation in patients that have undergone lower extremity nerve decompression, patients have been reported to display improved sensibility, nerve conduction velocity, transcutaneous oxygen pressures, and even a decreased incidence of diabetic foot ulcerations,<sup>94–99</sup> as has recently been reviewed by Nickerson.<sup>100</sup> Interestingly, in this context, Pelletier et al. showed that pressure-induced vasodilation could be restored with nerve decompression in their animal study regarding a compression neuropathy model.<sup>43</sup> Moreover, improvement of sensibility was consistently associated with improvement of pressure-induced vasodilation in the studies included in this review.<sup>31–34,43</sup> We therefore hypothesize that improvement of pressure-induced vasodilation may be one of the mechanisms of action behind the efficacy of lower extremity nerve decompression for ulcer prevention. Although lower extremity nerve decompression is not embraced by most clinicians or academics caring for diabetes and its complications,<sup>100</sup> improvement of pressure-induced vasodilation would provide a solid rationale to support lower extremity nerve decompression treatment. Pressure-induced vasodilation could also be restored with pharmaceutical treatment in diabetic mouse models.<sup>31–34</sup> This suggests that treatment with such pharmaceuticals (i.e.,  $\alpha$ -lipoic acid,<sup>32</sup> erythropoietin,<sup>34</sup> candesartan,<sup>31</sup> and sorbinil<sup>33</sup>) may have the potential to help prevent ulcerations.

As diclofenac is one of the most frequently prescribed nonsteroidal antiinflammatory drug outside of the United States,<sup>101,102</sup> a considerable number of patients receive diclofenac for perioperative pain management.<sup>101–103</sup> However, use of diclofenac (a nonsteroidal antiinflammatory drug) eliminated pressure-induced vasodilation,<sup>25</sup> as did use of amiloride (a diuretic), and a loss of pressure-induced vasodilation resulted in a susceptibility to pressure ulcer formation in animal studies.<sup>25,31,34</sup> Moreover, treatment with amiloride also leads to significantly more pressure ulcers in hospitalized patients.<sup>46</sup> This suggests that by replacing diclofenac with an alternative nonsteroidal antiinflammatory drug, or amiloride with an alternative diuretic, ulcers may be prevented. As pressure-induced vasodilation could also not be induced during pain stimuli, and this suggests that adequate pain management may also assist in preventing ulcer formation,<sup>38</sup> this should not be performed at the expense of adequate pain management.

This review provides an overview of pressure-induced vasodilation for introduction of

this phenomenon to the medical and surgical community. However, this review has several limitations. All human studies used for meta-analysis had sample sizes of less than 15 per group. Although the finding that moderate amounts of tissue compression increased perfusion was reported consistently, we observed heterogeneity between studies regarding the amount of perfusion increase, whereas the limited number of studies precluded further subgroup analysis. Many studies provided only a visual presentation of their data in figures, instead of numerical data, precluding meta-analysis. As there are no official guidelines available for pressure-induced vasodilation measurements, studies used a variety of measurement setups. Uniform pressure-induced vasodilation measurement technique would improve comparability and would also increase the potential of pressure-induced vasodilation measurement for outcome assessment (e.g., after lower extremity nerve decompression or innervated flap transfer to weight-bearing surfaces).

As pressure-induced vasodilation has not been related to plastic surgery before, several data gaps exist regarding pressure-induced vasodilation in plastic surgery. Future studies could explore pressure-induced vasodilation between innervated and noninnervated flaps, and before and after lower extremity nerve decompression in diabetic feet. Moreover, we did not identify studies that assessed the influence of diclofenac on pressure ulcer formation, despite its widespread use in perioperative pain management.<sup>101–103</sup>

## CONCLUSIONS

Pressure-induced vasodilation seems to be a protective mechanism that increases tissue blood flow during exposure to mechanical stress and provides protection against ulcer formation. Because pressure-induced vasodilation is mediated by sensory nerves, pressure-induced vasodilation appears to emphasize the importance of sensory innervation for durable tissue integrity.

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## REFERENCES

- Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376:2367–2375.
- Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: A major and snowballing threat to public health and the economy. *Wound Repair Regen*. 2009;17:763–771.
- American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013;36:1033–1046.
- Padula WV, Makic MB, Wald HL, et al. Hospital-acquired pressure ulcers at academic medical centers in the United States, 2008–2012: Tracking changes since the CMS nonpayment policy. *Jt Comm J Qual Patient Saf*. 2015;41:257–263.
- Ashrafi M, Baguneid M, Bayat A. The role of neuromediators and innervation in cutaneous wound healing. *Acta Derm Venereol*. 2016;96:587–594.
- Barker AR, Rosson GD, Dellon AL. Wound healing in denervated tissue. *Ann Plast Surg*. 2006;57:339–342.
- Ducic I, Hung V, Dellon AL. Innervated free flaps for foot reconstruction: A review. *J Reconstr Microsurg*. 2006;22:433–442.
- Bus SA. The role of pressure offloading on diabetic foot ulcer healing and prevention of recurrence. *Plast Reconstr Surg*. 2016;138(Suppl):179S–187S.
- Cichowitz A, Pan WR, Ashton M. The heel: Anatomy, blood supply, and the pathophysiology of pressure ulcers. *Ann Plast Surg*. 2009;62:423–429.
- Ricci JA, Bayer LR, Orgill DP. Evidence-based medicine: The evaluation and treatment of pressure injuries. *Plast Reconstr Surg*. 2017;139:275e–286e.
- Kořtka A, Abraham P, Bouhanick B, Sigaudo-Roussel D, Demiot C, Saumet JL. Impaired pressure-induced vasodilation at the foot in young adults with type 1 diabetes. *Diabetes* 2004;53:721–725.
- Fromy B, Abraham P, Saumet JL. Non-nociceptive capsaicin-sensitive nerve terminal stimulation allows for an original vasodilatory reflex in the human skin. *Brain Res*. 1998;811:166–168.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009;339:b2700.
- Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspect*. 2014;122:711–718.
- Källman U, Bergstrand S, Ek AC, Engström M, Lindgren M. Blood flow responses over sacrum in nursing home residents during one hour bed rest. *Microcirculation* 2016;23:530–539.
- Källman U, Engström M, Bergstrand S, et al. The effects of different lying positions on interface pressure, skin temperature, and tissue blood flow in nursing home residents. *Biol Res Nurs*. 2015;17:142–151.
- Hagblad J, Folke M, Lindberg LG, Lindén M. Technical issues related to the long-term monitoring of blood flow at different depths using LDF and PPG. *Physiol Meas*. 2012;33:985–996.
- Bergstrand S, Källman U, Ek AC, et al. Pressure-induced vasodilation and reactive hyperemia at different depths in sacral tissue under clinically relevant conditions. *Microcirculation* 2014;21:761–771.
- Schwarzer G. meta: An R package for meta-analysis. *R News* 2007;7:40–45.
- Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
- Abraham P, Fromy B, Merzeau S, Jardel A, Saumet JL. Dynamics of local pressure-induced cutaneous vasodilation in the human hand. *Microvasc Res*. 2001;61:122–129.
- Fromy B, Abraham P, Bouvet C, Bouhanick B, Fressinaud P, Saumet JL. Early decrease of skin blood flow in response to locally applied pressure in diabetic subjects. *Diabetes* 2002;51:1214–1217.
- Fromy B, Sigaudo-Roussel D, Gaubert-Dahan ML, et al. Aging-associated sensory neuropathy alters pressure-induced vasodilation in humans. *J Invest Dermatol*. 2010;130:849–855.
- Fromy B, Lingueglia E, Sigaudo-Roussel D, Saumet JL, Lazdunski M. ASIC3 is a neuronal mechanosensor for pressure-induced vasodilation that protects against pressure ulcers. *Nat Med*. 2012;18:1205–1207.
- Hsiu H, Hsu WC, Hsu CL, Bau JG. Microcirculatory complexity responses to the application of skin-surface-contacting pressure stimulation around normal blood pressure. *J Med Biol Eng*. 2014;34:164–171.
- Kořtka A, Legrand-Fernandez MS, Abraham P, et al. Low skin temperature impairs the cutaneous vasodilator response to local progressive pressure strain. *Microvasc Res*. 2004;67:203–206.
- Sae-Sia W, Wipke-Tevis DD, Williams DA. The effect of clinically relevant pressure duration on sacral skin blood flow and temperature in patients after acute spinal cord injury. *Arch Phys Med Rehabil*. 2007;88:1673–1680.
- Tzen YT, Brienza DM, Karg PE, Loughlin PJ. Effectiveness of local cooling for enhancing tissue ischemia tolerance in people with spinal cord injury. *J Spinal Cord Med*. 2013;36:357–364.
- Begey AL, Liu KL, Lo M, et al. Cutaneous and renal vasodilatory response to local pressure application: A comparative study in mice. *Microvasc Res*. 2018;115:44–51.
- Danigo A, Nasser M, Bessaguet F, et al. Candesartan restores pressure-induced vasodilation and prevents skin pressure ulcer formation in diabetic mice. *Cardiovasc Diabetol*. 2015;14:26.
- Demiot C, Fromy B, Saumet JL, Sigaudo-Roussel D. Preservation of pressure-induced cutaneous vasodilation by limiting oxidative stress in short-term diabetic mice. *Cardiovasc Res*. 2006;69:245–252.
- Demiot C, Tartas M, Fromy B, Abraham P, Saumet JL, Sigaudo-Roussel D. Aldose reductase pathway inhibition improved vascular and C-fiber functions, allowing for pressure-induced vasodilation restoration during severe diabetic neuropathy. *Diabetes* 2006;55:1478–1483.
- Demiot C, Sarrazy V, Javellaud J, et al. Erythropoietin restores C-fiber function and prevents pressure ulcer formation in diabetic mice. *J Invest Dermatol*. 2011;131:2316–2322.
- Fizanne L, Fromy B, Preckel MP, Sigaudo-Roussel D, Saumet JL. Effect of isoflurane on skin-pressure-induced vasodilation. *J Vasc Res*. 2003;40:416–422.
- Fizanne L, Sigaudo-Roussel D, Saumet JL, Fromy B. Evidence for the involvement of VPAC1 and VPAC2 receptors in pressure-induced vasodilation in rodents. *J Physiol*. 2004;554:519–528.
- Fromy B, Merzeau S, Abraham P, Saumet JL. Mechanisms of the cutaneous vasodilator response to local external pressure



- application in rats: Involvement of CGRP, neurokinins, prostaglandins and NO. *Br J Pharmacol*. 2000;131:1161–1171.
38. Fromy B, Sigaudou-Roussel D, Baron C, Roquelaure Y, Leftheriotis G, Saumet JL. Neuroendocrine pathway involvement in the loss of the cutaneous pressure-induced vasodilation during acute pain in rats. *J Physiol*. 2007;579:247–254.
  39. Garry A, Sigaudou-Roussel D, Merzeau S, Dumont O, Saumet JL, Fromy B. Cellular mechanisms underlying cutaneous pressure-induced vasodilation: In vivo involvement of potassium channels. *Am J Physiol Heart Circ Physiol*. 2005;289:H174–H180.
  40. Garry A, Fromy B, Blondeau N, et al. Altered acetylcholine, bradykinin and cutaneous pressure-induced vasodilation in mice lacking the TREK1 potassium channel: The endothelial link. *EMBO Rep*. 2007;8:354–359.
  41. Gaubert ML, Sigaudou-Roussel D, Tartas M, Berrut G, Saumet JL, Fromy B. Endothelium-derived hyperpolarizing factor as an in vivo back-up mechanism in the cutaneous microcirculation in old mice. *J Physiol*. 2007;585:617–626.
  42. Herrman EC, Knapp CF, Donofrio JC, Salcido R. Skin perfusion responses to surface pressure-induced ischemia: Implication for the developing pressure ulcer. *J Rehabil Res Dev*. 1999;36:109–120.
  43. Pelletier J, Fromy B, Morel G, Roquelaure Y, Saumet JL, Sigaudou-Roussel D. Chronic sciatic nerve injury impairs the local cutaneous neurovascular interaction in rats. *Pain*. 2012;153:149–157.
  44. Sigaudou-Roussel D, Demiot C, Fromy B, et al. Early endothelial dysfunction severely impairs skin blood flow response to local pressure application in streptozotocin-induced diabetic mice. *Diabetes*. 2004;53:1564–1569.
  45. Fromy B, Abraham P, Saumet JL. Progressive calibrated pressure device to measure cutaneous blood flow changes to external pressure strain. *Brain Res Brain Res Protoc*. 2000;5:198–203.
  46. Roustit M, Genty C, Lepelley M, et al. Amiloride treatment and increased risk of pressure ulcers in hospitalized patients. *Br J Clin Pharmacol*. 2016;82:1685–1687.
  47. Allman RM. Pressure ulcers among the elderly. *N Engl J Med*. 1989;320:850–853.
  48. Solovyev A, Mi Q, Tzen YT, Brienza D, Vodovotz Y. Hybrid equation/agent-based model of ischemia-induced hyperemia and pressure ulcer formation predicts greater propensity to ulcerate in subjects with spinal cord injury. *PLoS Comput Biol*. 2013;9:e1003070.
  49. Eun HC. Evaluation of skin blood flow by laser Doppler flowmetry. *Clin Dermatol*. 1995;13:337–347.
  50. Joodaki H, Panzer MB. Skin mechanical properties and modeling: A review. *Proc Inst Mech Eng H*. 2018;232:323–343.
  51. Messner F, Hautz T, Blumer MJF, et al. Critical ischemia times and the effect of novel preservation solutions HTK-N and TiProtec on tissues of a vascularized tissue isograft. *Transplantation*. 2017;101:e301–e310.
  52. Khiabani KT, Kerrigan CL. Differing flow patterns between ischemically challenged flap skin and flap skeletal muscle: Implications for salvage regimens. *Plast Reconstr Surg*. 2002;109:220–227.
  53. Stekelenburg A, Gawlitta D, Bader DL, Oomens CW. Deep tissue injury: How deep is our understanding? *Arch Phys Med Rehabil*. 2008;89:1410–1413.
  54. Esser JFS. *Biological or Artery Flaps of the Face*. Monaco: Institut Esser de Chirurgie Structrice; 1931.
  55. Dibbell DG. Use of a long island flap to bring sensation to the sacral area in young paraplegics. *Plast Reconstr Surg*. 1974;54:220–223.
  56. Fox CM, Beem HM, Wiper J, Rozen WM, Wagels M, Leong JC. Muscle versus fasciocutaneous free flaps in heel reconstruction: Systematic review and meta-analysis. *J Reconstr Microsurg*. 2015;31:59–66.
  57. Sameem M, Au M, Wood T, Farrokhyar F, Mahoney J. A systematic review of complication and recurrence rates of musculocutaneous, fasciocutaneous, and perforator-based flaps for treatment of pressure sores. *Plast Reconstr Surg*. 2012;130:67e–77e.
  58. Thomson HG, Azhar Ali M, Healy H. The recurrent neurotrophic buttock ulcer in the meningomyelocele paraplegic: A sensate flap solution. *Plast Reconstr Surg*. 2001;108:1192–1196.
  59. Cochran JH Jr, Edstrom LE, Dibbell DG. Usefulness of the innervated tensor fascia lata flap in paraplegic patients. *Ann Plast Surg*. 1981;7:286–288.
  60. Coleman JJ III, Jurkiewicz MJ. Methods of providing sensation to anesthetic areas. *Ann Plast Surg*. 1984;12:177–186.
  61. Dibbell DG, McCraw JB, Edstrom LE. Providing useful and protective sensibility to the sitting area in patients with meningomyelocele. *Plast Reconstr Surg*. 1979;64:796–799.
  62. Lesavoy MA, Dubrow TJ, Korn HN, Cedars MG, Castro DJ. “Sensible” flap coverage of pressure sores in patients with meningomyelocele. *Plast Reconstr Surg*. 1990;85:390–394; discussion 395–396.
  63. Spear SL, Kroll SS, Little JW III. Bilateral upper-quadrant (intercostal) flaps: The value of protective sensation in preventing pressure sore recurrence. *Plast Reconstr Surg*. 1987;80:734–736.
  64. Lüscher NJ, de Roche R, Krupp S, Kuhn W, Zäch GA. The sensory tensor fasciae latae flap: A 9-year follow-up. *Ann Plast Surg*. 1991;26:306–310; discussion 311.
  65. Posma AN. The innervated tensor fasciae latae flap in patients with meningomyelocele. *Ann Plast Surg*. 1988;21:594–596.
  66. Rosen JM, Mo ST, Liu A. Experience with the island inferior gluteal thigh flap compared with other local flaps for the reconstruction of the pelvic area. *Ann Plast Surg*. 1990;24:498–509.
  67. Santanelli Di Pompeo F, Longo B, Pagnoni M, Laporta R. Sensate anterolateral thigh perforator flap for ischiatic sores reconstruction in meningomyelocele patients. *Microsurgery*. 2015;35:279–283.
  68. Tellioglu AT, Tekdemir I, Akyuz M, et al. Ischial pressure sores treated with a sensate gracilis myocutaneous flap. *Eur J Plast Surg*. 2000;23:132–134.
  69. Schryvers OI, Stranc MF, Nance PW. Surgical treatment of pressure ulcers: 20-year experience. *Arch Phys Med Rehabil*. 2000;81:1556–1562.
  70. Relander M, Palmer B. Recurrence of surgically treated pressure sores. *Scand J Plast Reconstr Surg Hand Surg*. 1988;22:89–92.
  71. Tavakoli K, Rutkowski S, Cope C, et al. Recurrence rates of ischial sores in para- and tetraplegics treated with hamstring flaps: An 8-year study. *Br J Plast Surg*. 1999;52:476–479.
  72. Disa JJ, Carlton JM, Goldberg NH. Efficacy of operative cure in pressure sore patients. *Plast Reconstr Surg*. 1992;89:272–278.
  73. Mehta A, Baker TA, Shoup M, et al. Biplanar flap reconstruction for pressure ulcers: Experience in patients with immobility from chronic spinal cord injuries. *Am J Surg*. 2012;203:303–306; discussion 306–307.
  74. Wyble EJ, Yakuboff KP, Clark RG, Neale HW. Use of free fasciocutaneous and muscle flaps for reconstruction of the foot. *Ann Plast Surg*. 1990;24:101–108.
  75. Noever G, Brüser P, Köhler L. Reconstruction of heel and sole defects by free flaps. *Plast Reconstr Surg*. 1986;78:345–352.
  76. Reigstad A, Hetland KR, Bye K, Waage S, Røkkum M, Husby T. Free flaps in the reconstruction of foot injury: 4 (1-7) year follow-up of 24 cases. *Acta Orthop Scand*. 1994;65:103–106.

77. Harris PG, Letrosne E, Caouette-Laberge L, Egerszegi EP. Long-term follow-up of coverage of weight bearing surface of the foot with free muscular flap in a pediatric population. *Microsurgery* 1994;15:424–429.
78. Ulusal BG, Lin YT, Ulusal AE, Lin CH, Yen JT. Reconstruction of foot defects with free lateral arm fasciocutaneous flaps: Analysis of fifty patients. *Microsurgery* 2005;25:581–588.
79. Santanelli F, Tenna S, Pace A, Scuderi N. Free flap reconstruction of the sole of the foot with or without sensory nerve coaptation. *Plast Reconstr Surg*. 2002;109:2314–2322; discussion 2323–2324.
80. Potparić Z, Rajčić N. Long-term results of weight-bearing foot reconstruction with non-innervated and reinnervated free flaps. *Br J Plast Surg*. 1997;50:176–181.
81. Sinha AK, Wood MB, Irons GB. Free tissue transfer for reconstruction of the weight-bearing portion of the foot. *Clin Orthop Relat Res*. 1989;242:269–271.
82. Duncan MJ, Zuker RM, Manktelow RT. Resurfacing weight bearing areas of the heel: The role of the dorsalis pedis innervated free tissue transfer. *J Reconstr Microsurg*. 1985;1:201–208.
83. Löfstrand JG, Lin CH. Reconstruction of defects in the weight-bearing plantar area using the innervated free medial plantar (instep) flap. *Ann Plast Surg*. 2018;80:245–251.
84. Oh SJ, Moon M, Cha J, Koh SH, Chung CH. Weight-bearing plantar reconstruction using versatile medial plantar sensate flap. *J Plast Reconstr Aesthet Surg*. 2011;64:248–254.
85. Zelken JA, Lin CH. An algorithm for forefoot reconstruction with the innervated free medial plantar flap. *Ann Plast Surg*. 2016;76:221–226.
86. Song B, Chen J, Han Y, et al. The use of fabricated chimeric flap for reconstruction of extensive foot defects. *Microsurgery* 2016;36:303–309.
87. Perttunen J, Rautio J, Komi PV. Gait patterns after free flap reconstruction of the foot sole. *Scand J Plast Reconstr Surg Hand Surg*. 1995;29:271–278.
88. Rautio J, Kekoni J, Hämäläinen H, Härmä M, Asko-Seljavaara S. Mechanical sensibility in free and island flaps of the foot. *J Reconstr Microsurg*. 1989;5:119–125.
89. Roth JH, Urbaniak JR, Koman LA, Goldner JL. Free flap coverage of deep tissue defects of the foot. *Foot Ankle* 1982;3:150–157.
90. Sönmez A, Bayramiçli M, Sönmez B, Numanoğlu A. Reconstruction of the weight-bearing surface of the foot with nonneurosensory free flaps. *Plast Reconstr Surg*. 2003;111:2230–2236.
91. Öztürk S, Bayram Y, Möhür H, Deveci M, Sengezer M. Evaluation of late functional results of patients treated with free muscle flaps for heel defects caused by land-mine explosions. *Plast Reconstr Surg*. 2005;116:1926–1936.
92. Vinik AI. Diabetic neuropathy: Pathogenesis and therapy. *Am J Med*. 1999;107:17S–26S.
93. Dellon AL, Muse VL, Nickerson DS, et al. Prevention of ulceration, amputation, and reduction of hospitalization: Outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy. *J Reconstr Microsurg*. 2012;28:241–246.
94. Aszmann O, Tassler PL, Dellon AL. Changing the natural history of diabetic neuropathy: Incidence of ulcer/amputation in the contralateral limb of patients with a unilateral nerve decompression procedure. *Ann Plast Surg*. 2004;53:517–522.
95. Dellon AL, Muse VL, Nickerson DS, et al. Prevention of ulceration, amputation, and reduction of hospitalization: Outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy. *J Reconstr Microsurg*. 2012;28:241–246.
96. Nickerson DS. Low recurrence rate of diabetic foot ulcer after nerve decompression. *J Am Podiatr Med Assoc*. 2010;100:111–115.
97. Nickerson DS, Rader AJ. Low long-term risk of foot ulcer recurrence after nerve decompression in a diabetes neuropathy cohort. *J Am Podiatr Med Assoc*. 2013;103:380–386.
98. Nickerson DS, Rader AJ. Nerve decompression after diabetic foot ulceration may protect against recurrence: A 3-year controlled, prospective analysis. *J Am Podiatr Med Assoc*. 2014;104:66–70.
99. Zhang W, Zhong W, Yang M, Shi J, Guowei L, Ma Q. Evaluation of the clinical efficacy of multiple lower-extremity nerve decompression in diabetic peripheral neuropathy. *Br J Neurosurg*. 2013;27:795–799.
100. Nickerson DS. Nerve decompression and neuropathy complications in diabetes: Are attitudes discordant with evidence? *Diabet Foot Ankle* 2017;8:1367209.
101. McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: An examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS Med*. 2013;10:e1001388.
102. Allen SC, Ravindran D. Perioperative use of nonsteroidal anti-inflammatory drugs: Results of a UK regional audit. *Clin Drug Investig*. 2009;29:703–711.
103. Derry S, Wiffen PJ, Moore RA. Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2015;7:CD004768.