

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.)

Pressure and diabetic foot ulcers impose a significant burden on health care.^{1,2} Annual costs of prevention and treatment of ulcers exceed \$50 billion for the United States.^{3,4} These costs are likely to increase because of aging societies and the rise of diabetes.² 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.^{5,6} Most attention has been given to the loss of protective sensation^{1,7,8} and mechanical stress.^{1,9,10} 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.^{11,12} 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.¹³ 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.¹² Animal and human studies were both included. Articles in languages other

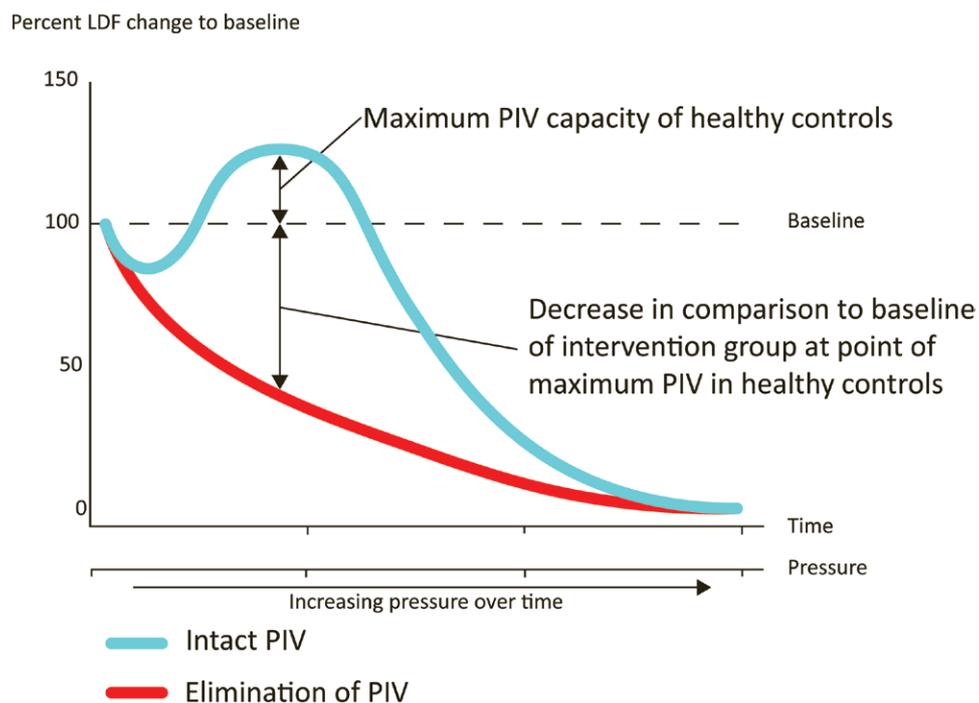


Fig. 1. Examples of perfusion curves during loading with a slowly increasing amount of pressure of subjects with and without pressure-induced vasodilation. The maximum pressure-induced vasodilation capacity is the maximum increase of blood flow in comparison to baseline in percentages. The decrease in 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.¹⁴ 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.^{15–18}

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,¹⁴ 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).¹⁹ 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.²⁰ Heterogeneity was investigated using the I^2 statistic.²¹ We defined $p < 0.05$ as statistically significant. In case of a limited amount of studies, no subgroup analysis

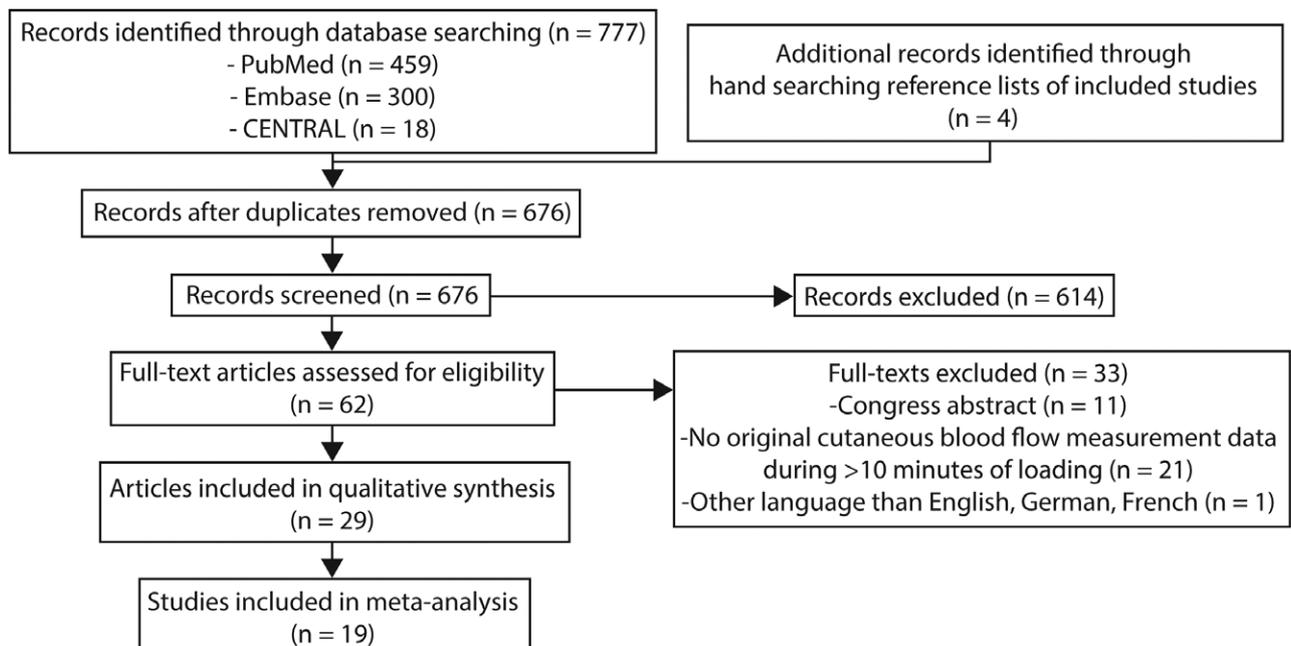


Fig. 2. Flow diagram of study selection.

would be performed. Statistical analyses were conducted using the meta package for R.¹⁹

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^{11,12,15–18,22–29} and 16 animal studies (described in 29 articles).^{25,30–44} A description of the setup used in most studies^{11,12,22–25,27,30–44} can be found in a methodology article by Fromy et al.⁴⁵ Studies originated from six independent research groups.^{11,12,15–18,22–44} 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,¹⁴ 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).²⁵ 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 ± 8 percent and 81 ± 15 percent ($p < 0.01$) of the compressed area.²⁵ Two studies assessed the influence of diabetic neuropathy on pressure-induced vasodilation and pressure ulcer formation in mice.^{31,34} Mice exposed to 8 weeks

		Study design	A1 Randomization	A2 Allocation concealment	A3 Comparability	A4 Confounding	A5 Identical conditions	A6 Blinding	A7 Data completeness	A8 Exposure completeness	A9 Outcome characterization	A10 Outcome assessment	A11 Threats to internal validity
Abraham 2001	HCT	NR	NR	N/A*	N/A*	N/A*	NR	+	++	++	++	+	
Begey 2018	EA	+	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Bergstrand 2014	HCT	NR	NR	N/A*	N/A*	N/A*	NR	++	++	+	+	+	
Danigo 2015	EA	+	NR	N/A*	N/A*	++	NR	++	++	++	++	+	
Demiot 2006	EA	+	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Demiot 2006, sorbinil	EA	+	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Demiot 2011	EA	+	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Fizanne 2003	EA	NR	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Fizanne 2004	EA	NR	NR	N/A*	N/A*	+	NR	+	++	+	++	+	
Fromy 1998	HCT	NR	NR	N/A*	N/A*	N/A*	NR	++	++	+	++	+	
Fromy 2000	EA	+	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Fromy 2002	HCT	NR	NR	N/A*	N/A*	N/A*	NR	++	++	+	++	+	
Fromy 2007	EA	NR	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Fromy 2010	HCT	NR	NR	N/A*	N/A*	N/A*	NR	+	++	+	++	+	
Fromy 2012, EA	EA	+	++	N/A*	N/A*	++	++	++	++	++	++	+	
Fromy 2012, HCT	HCT	+	++	N/A*	N/A*	N/A*	++	++	++	++	++	+	
Garry 2005	EA	NR	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Garry 2007	EA	NR	NR	N/A*	N/A*	+	NR	+	+	+	+	+	
Gaubert 2007	EA	NR	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Hagblad 2012	HCT	NR	NR	N/A*	N/A*	N/A*	NR	++	++	++	++	+	
Herrman 1999	EA	NR	NR	N/A*	N/A*	++	NR	++	++	+	+	+	
Humeau 2004	EA	NR	NR	N/A*	N/A*	++	NR	+	+	+	++	+	
Hsiu 2014	HCT	NR	NR	N/A*	N/A*	++	NR	+	++	+	+	+	
Källman 2015	HCT	NR	NR	N/A*	N/A*	N/A*	NR	++	++	++	++	+	
Källman 2016	HCT	NR	NR	N/A*	N/A*	N/A*	NR	++	++	+	+	+	
Koïtka 2004, DM1	HCT	NR	NR	N/A*	N/A*	N/A*	NR	++	++	+	++	+	
Koïtka 2004, temperature	HCT	+	NR	N/A*	N/A*	N/A*	NR	+	++	+	+	+	
Pelletier 2012	EA	NR	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Sae-Sia 2007	HCT	NR	NR	N/A*	N/A*	N/A*	NR	++	++	+	++	+	
Sigaudo-Roussel 2004	EA	NR	NR	N/A*	N/A*	++	NR	+	++	+	++	+	
Tzen 2013	HCT	NR	NR	N/A*	N/A*	N/A*	NR	++	++	++	++	+	

++ = Definitely low risk of bias + = Probably low risk of bias - = Probably high risk of bias NR = Not recorded
 -- = Definitely high risk of bias

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

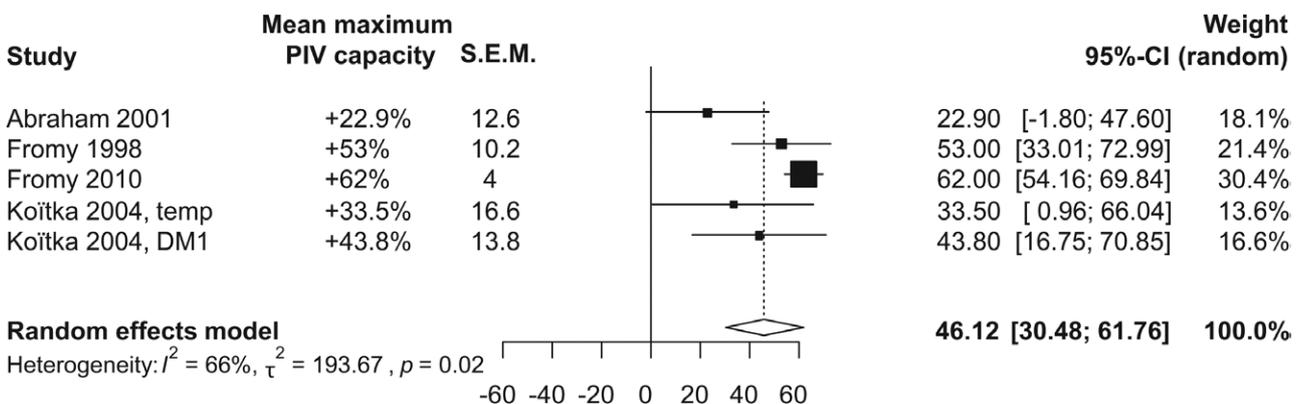


Fig. 4. Pooling of the mean maximum pressure-induced vasodilation capacities of human studies that used a pressure stimulus of 11.1 Pa/second.

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 ²²	8	4	4	23 ± 1	23 ± 13
Fromy et al., 1998 ¹²	10	NR	NR	NR	53 ± 10
Fromy et al., 2010 ²⁴	12	8	4	26 ± 1	62 ± 4
Koïtka et al., 2004 ¹¹	12	NR	NR	23 ± 1	44 ± 14
Koïtka et al., 2004 ²⁷	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 ³⁰	Between 4–9 for each group	All male	10–14	23 ± 6%
Danigo et al., 2015 ³¹	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 ³²	7–10 for every group	All male	12	42 ± 8%
Demiot et al., 2006 ³³	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 ³⁴	10	All male	5–6	35 ± 9%
Fizanne et al., 2004 ³⁶	5–10 for every group	NR	NR	60 ± 15%
Fromy et al., 2012 ²⁵	5–10 for every group	All male	NR	41 ± 3%
Garry et al., 2007 ⁴⁰	4–11 for every group	NR	NR	41 ± 6%
Gaubert et al., 2007 ⁴¹	5–13 for every group	All male	24–28	39 ± 6%
Sigaudo-Roussel et al., 2004 ⁴⁴	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 ³⁵	7–9 for every group	All male	NR	37 ± 10
Fizanne et al., 2004 ³⁶	5–10 for every group	All male	NR	60 ± 15
Fromy et al., 2000 ³⁷	9–20 for every group	NR	NR	25 ± 9
Fromy et al., 2007 ³⁸	5–13 for every group	All male	NR	40 ± 7
Pelletier et al., 2012 ⁴³	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 ($p < 0.001$).^{31,34} Pressure-induced

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

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 ²⁴	62 ± 4% (young subjects, 20–35 yr) vs. 12 ± 7% (older subjects, 60–75 yr)	<0.001
Diabetic neuropathy	Fromy et al., 2002 ²³	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 ³³	55 ± 6% (control mice) vs. no PIV (–33 ± 8%) in mice with diabetic neuropathy	<0.001
	Demiot et al., 2011 ³⁴	35 ± 9% vs. no PIV (exact PIV data NR) in mice with diabetic neuropathy	<0.001
	Danigo et al., 2015 ³¹	35 ± 8% vs. no PIV (–17 ± 7%) in mice with diabetic neuropathy	<0.001
Compression neuropathy	Pelletier et al., 2012 ⁴³	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 ²⁴	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 ²⁸	PIV in healthy subjects, decreased BF in SCI patients (exact PIV data NR)	<0.01
Pharmaceuticals			
ASIC3-antagonists (Diclofenac, Amiloride)	Fromy et al., 2012 ²⁵	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 ³⁵	37 ± 10% (control mice) vs. –20 ± 5% (mice treated with high-dose anesthesia)	<0.05
Miscellaneous			
Pain	Fromy et al., 2007 ³⁸	40 ± 7% (control rats) vs. –12 ± 6% (rats subjected to a pain stimulus)	<0.01
Low temperatures	Koítka et al., 2004 ²⁷	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 ³⁰	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.^{11,12,15–18,22–28} Using Office of Health Assessment and Translation methodology,¹³ 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.^{25,31,34} Fromy et al. showed that treatment with the diuretic amiloride eliminates pressure-induced vasodilation,²⁵ 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 ⁴³	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 α-LPA	Fromy et al., 2007 ³⁸	–31 ± 6% (pain) vs. 43 ± 10% (pain management with morphine)	<0.001
	Demiot et al., 2006 ³²	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 ³³	–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 ³⁴	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 ³¹	–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; $p = 0.003$).⁴⁶ 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.^{3,4} As tissue without pressure-induced vasodilation is prone to ulcer formation^{25,31,34} 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).^{33,37} 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).²⁴ This was attributed to aging-associated neuropathy,²⁴ and is thought to contribute to the susceptibility of the elderly to pressure ulcer formation.⁴⁷ Similarly, pressure-induced vasodilation is impaired in various other neuropathies such as diabetic or compression neuropathy.^{28,31,33,34,43} Pressure-induced vasodilation deterioration seems to aggravate with progression of neuropathy in

neuropathic conditions.^{23,43} 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.¹¹ In spinal cord injury, loss of pressure-induced vasodilation is complete and immediate.²⁸ 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^{5,6} as seen in diabetic feet¹ (Fig. 6) or pressure ulcers of patients with spinal cord injury.⁴⁸

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,⁴⁹ 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,⁵⁰ 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,^{51,52} 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.⁵³

Innervated tissue displays pressure-induced vasodilation,¹² whereas noninnervated tissue does not.²⁸ 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,^{54,55} many centers do not regularly apply innervated flaps. As an example, free muscle flaps are still widely

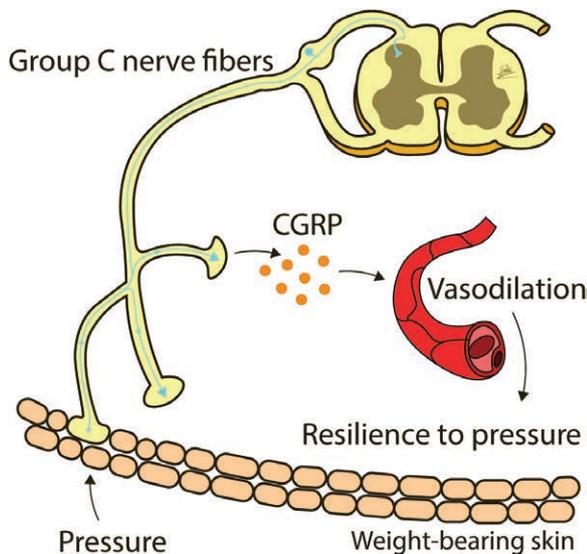


Fig. 5. Pressure-induced vasodilation in healthy skin. Pressure is detected by sensory nerves. This results in the release of the neuropeptide calcitonin gene-related peptide. This induces vasodilation, increasing tissue resilience against tissue compression. CGRP, calcitonin gene-related peptide.

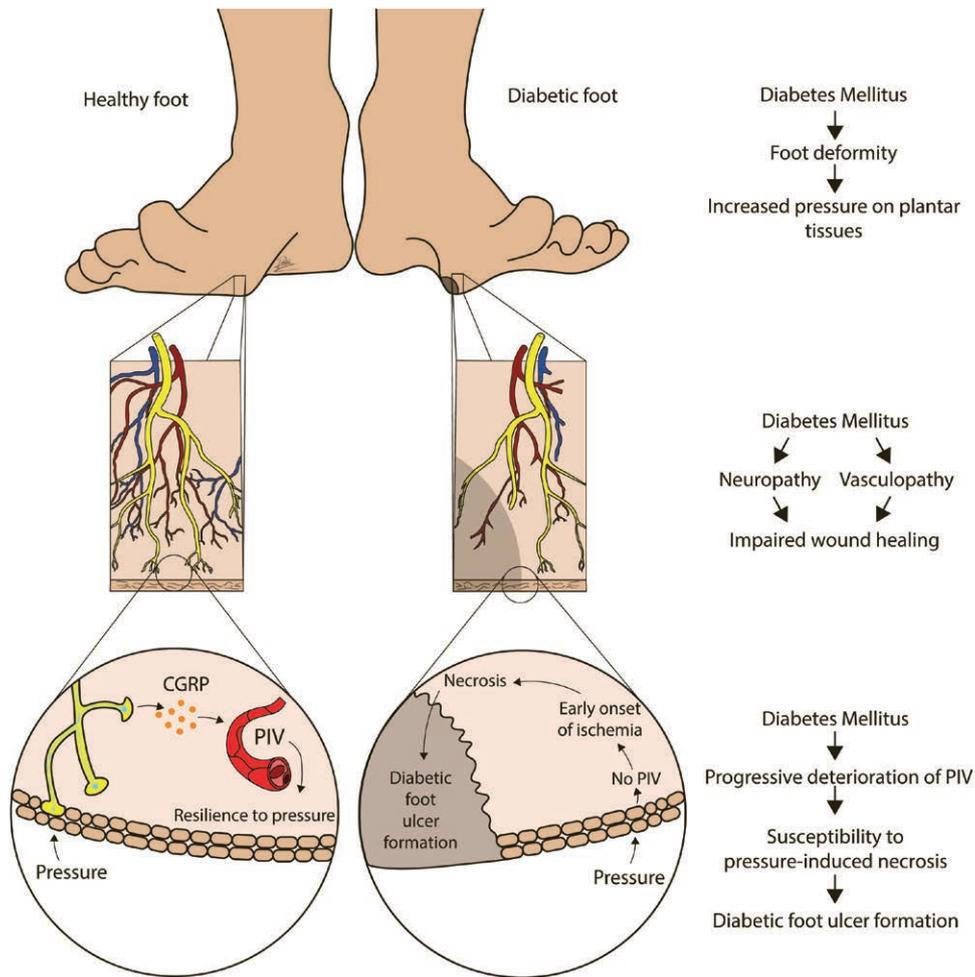


Fig. 6. Proposed diabetic foot ulcer pathogenesis model. Diabetes leads to increased exposure to high plantar pressures, combined with elimination of pressure-induced vasodilation. This results in a susceptibility to ulcerations as a result of pressure-induced necrosis. *CGRP*, calcitonin gene-related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

used in reconstruction of the weight-bearing foot,⁵⁶ and noninnervated local flaps are still widely used in pressure ulcer reconstruction in patients with spinal cord injury.⁵⁷ 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.⁵⁸ 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.⁵⁸ These results are in line with other studies where innervated pedicled flap are also reported to remain recurrence-free.^{59–68} In contrast, studies of noninnervated local flaps in such patient populations reveal recurrence rates of up to 82 percent within several years.^{69–73} Similarly,

there are many studies that report an absence of ulceration with use of free innervated flaps in weight-bearing foot reconstruction,^{74–86} whereas ulceration is reported to develop in free noninnervated fasciocutaneous flaps^{87–89} or free muscle flaps covered with skin grafts.^{90,91} 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.^{92,93} Motor neuropathy results in an increased exposure to plantar mechanical stress.¹ 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,⁹⁴⁻⁹⁹ as has recently been reviewed by Nickerson.¹⁰⁰ 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.⁴³ Moreover, improvement of sensibility was consistently associated with improvement of pressure-induced vasodilation in the studies included in this review.^{31-34,43} 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,¹⁰⁰ 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.³¹⁻³⁴ This suggests that treatment with such pharmaceuticals (i.e., α -lipoic acid,³² erythropoietin,³⁴ candesartan,³¹ and sorbinil³³) 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,^{101,102} a considerable number of patients receive diclofenac for perioperative pain management.¹⁰¹⁻¹⁰³ However, use of diclofenac (a nonsteroidal antiinflammatory drug) eliminated pressure-induced vasodilation,²⁵ 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.^{25,31,34} Moreover, treatment with amiloride also leads to significantly more pressure ulcers in hospitalized patients.⁴⁶ 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,³⁸ 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.¹⁰¹⁻¹⁰³

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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