A Preliminary Study to Evaluate the Effect of Pulsed Radio Frequency Field Treatment on Lower Extremity Peri–Ulcer Skin Microcirculation of Diabetic Patients

Harvey N. Mayrovitz, PhD
Parry B. Larsen, MD

Abstract: To determine the potential effects of pulsed radio frequency field (PRFF) treatment on peri–ulcer microcirculation, this preliminary study measured laser Doppler (LD) red blood cell (RBC) perfusion, volume and velocity, and skin temperature in 15 subjects with diabetes (DM), each of whom had an ulcer on the foot or toe of one limb for at least eight weeks duration. These measurements were made at a peri–ulcer site and contralateral nonulcerated limb site prior to and at the end of a single 45 minute PRFF treatment protocol. The contralateral site was used to control for any systemic changes that might occur during treatment interval unrelated to the treatment itself. All subjects had DM ≥ five years and nine of these had lower extremity arterial disease in the ulcer bearing limb as judged by noninvasive vascular testing which included measurements of ankle brachial indices (ABI) and total leg pulsatile flow measured by magnetic resonance flowmetry. The overall data on this initial group of patients showed that at the peri–ulcer site, the single treatment produced an increase in LD perfusion which occurred mainly due to an increased volume component; there was no significant increase in any LD parameter at the contralateral control site nor was there an increase in skin temperature at either site. The LD increase occurred even though the peri–ulcer pretreatment perfusion and volume were much greater than at the contralateral control site. This suggests peri–ulcer vasodilation, perhaps in response to ulcer metabolic needs. Nonetheless, PRFF still caused a further increase in perfusion. Since volume component of the LD measurement is related to the microvessel number with active RBC flow, its increase due to PRFF suggests either further arteriolar dilation and/or selective recruitment of previously non–perfused vessels. These preliminary findings may suggest that if resting perfusion is marginally inadequate to promote timely ulcer healing, the incremental perfusion might potentially aid the healing process. More work to specifically relate PRFF treatment to perfusion changes and ulcer healing outcomes is clearly indicated.

WOUNDS 1995;7(3):90–93

Introduction

There is increasing evidence suggesting the possible beneficial effect of pulsed electromagnetic fields as an aid in the treatment of certain types of chronic wounds.[1–2] The mechanisms whereby such effects may be realized have remained allusive. There is some data suggesting that positive effects on cellular processes related to the wound healing cascade may be involved. These include acceleration of collagen formation and angiogenesis,[3] and increased activation of neutrophils[4] and monocytes.[5] There is also evidence of electrical augmentation of epidermal cell locomotion[6] and fibroblast motility.[7] Effects of pulsed radio frequency fields on ion fluxes, particularly calcium ion,[8] appear to play a role in vascular processes

From the Miami Heart Research Institute, Department of Vascular Research and Wound Healing Center, Miami Beach, FL.

Address correspondence to:

Harvey N. Mayrovitz, PhD
Chief, Microvascular and
Physiological Studies
Miami Heart Research Institute
4701 N. Meridian Ave.
Miami Beach, FL 33140
Phone (305) 674–3175

leading to field-induced vasodilation,[9] a finding which is consistent with emerging links of calcium ion to endothelial cell-mediated dilation.[10] Previous studies by authors on the effect of pulsed radio frequency field (PRFF) on the microcirculation of forearm skin of normal subjects demonstrated an increase in red blood cell (RBC) flux as measured by laser Doppler (LD) fluxmetry.[11] However, since the composite LD signal includes components which are dependent on the mean speed of moving RBC as well as their number density within the sampled volume,[12-14] the question as to which perfusion component was affected was left unanswered. Differential responses of these two components may give further clues as to the involved mechanisms.[15-16] In addition, it is unclear if the response to PRFF treatment of volar forearm of normal subjects could reliably be extrapolated to other sites or to patients with coexistent tissue or circulatory compromise. The present preliminary study was undertaken to deal with these specific issues as related to diabetic patients with coexisting lower extremity ulcers by evaluating the LD response to a single PRFF treatment in the region of the ulcer.

Methods

Experimental. Laser Doppler (Vasamedics, model BPM2) RBC perfusion,[17-22] the separate volume (RBC concentration) and velocity components, and skin temperature (Baily, BAT8) were measured in 15 diabetic (DM) subjects with lower extremity ulcers. Subjects studied had only one ulcer present which was located either on the foot or toe. Measurements were made on the peri-ulcer skin using a plastic laser probe positioned approximately one centimeter from the ulcer margin and also at a corresponding skin site on the contralateral non-ulcerated limb. Measurements were made at both sites prior to PRFF treatment of the ulcer bearing site and near the end of 45 minutes of continuous treatment. The contralateral site was used to control for any systemic changes that might occur during the treatment interval unrelated to the treatment itself. The settings of the PRFF unit (EPi, SofPulse) which uses a frequency of 27.12mHz were set to maximum pulse rate (600 pulses/sec) and maximum peak power with the actuator containing the coil positioned 1.5cm from the surface of the ulcer. Separate measurements indicate that under these conditions the RMS magnetic field strength during each 65 μsec pulse is about one Gauss near the skin surface. All subjects studied had diabetes mellitus for at least five years and had an ulcer with a duration not less than eight weeks; five were female, and the group age (mean and S.E.M.) was 62.3 ± 3.4. Prior to treatment, each subject's leg arterial status was evaluated by measuring the ankle-brachial systolic blood pressure index (ABI) using Doppler ultrasound and by measuring pulsatile leg blood flow using the method of magnetic resonance flowmetry[23-25] (MRF, Metriflo model AFM100). Leg blood flow was measured at five below-knee sites as previously described[26] and an arterial status index (ASI) was derived from the blood flow measurement. This index, which is sensitive to both the amplitude and width of leg blood flow pulse has been shown to permit stratification as to the presence of lower extremity arterial disease (LEAD) or normal leg status (NORM)[27] and correlates with resting ABI. Of the 15 subjects evaluated, nine were classified as having LEAD according to both ABI and ASI criteria (ABI < 0.9, ASI < 4.5). It should be noted that microvascular deficits could exist in any DM subject in spite of a normal ASI or ABI.

Analysis. Laser Doppler data reported are the five minute averages obtained prior to treatment and during the last five minutes of treatment at the peri-ulcer site and the corresponding contralateral non-ulcerated site. Statistical testing for differences between measurements on the same leg before and at the end of treatment were done using the nonparametric Wilcoxon test with a rejection of the null hypothesis (no difference) at the p=0.05 level. Additional tests were done to compare the LD values at the ulcer site vs. the contralateral site during these same time intervals. All LD data is reported in arbitrary units (AU) since acceptable calibration procedures have not yet been fully developed.[14]

Results

The main results of this study are summarized in Table 1. A significant increase in LD perfusion mainly due to a treatment-related increase in the volume component was found for the treated ulcer site (ULCR); no significant increase in skin temperature was detected. No increase in any LD parameter of the contralateral control site

Table 1
Summary of overall laser Doppler and skin temperature findings

Parameter	ULCR Site		CONT Site		ULCR vs CONT (p values)	
	Pre	Post	Pre	Post	Pre	Post
Perfusion	10.7 (2.9)	12.0* (2.5) [0.049]	4.3 (1.0)	4.6 (0.9) [0.173]	0.006	0.003
Volume	1.37 (0.21)	1.92* (0.20) [0.017]	0.93 (0.16)	1.20 (0.13) [0.776]	0.002	0.001
Velocity	1.56 (0.25)	1.62 (0.20) [0.142]	1.19 (0.10)	1.20 (0.15) [0.543]	0.280	0.057
Skin Temp	31.2 (0.8)	31.7 (0.7) [0.398]	31.3 (0.5)	31.3 (0.5) [0.485]		

Data: mean and S.E.M. from 15 subjects with lower limb ulcers; values are five minutes average before PRFF treatment (PRE) and near the end of a 45 minute treatment (PST). LD parameters: Perfusion, Volume, and Velocity in arbitrary units; Skin Temp (°C). []=p value between PRE and PST, *=$p<0.05$.

(CONT) was detected indicating the absence of systemic or other confounding effects which might be responsible for the perfusion increase noted at the ulcer site. The pretreatment levels of both perfusion and volume at the ulcer site were significantly greater than values at the contralateral sites ($p<0.001$).

Discussion

A single 45 minute PRFF treatment of lower extremity ulcer sites in this diabetic group resulted in a significant increase in peri–ulcer laser Doppler RBC perfusion as measured during the final five minutes of the treatment interval. This increase occurred in spite of the fact that as a group, the peri–ulcer pretreatment LD perfusion and volume were much greater than at the corresponding contralateral non–ulcer sites. This likely indicates that the peri–ulcer microvasculature was significantly vasodilated; perhaps as a physiological response to meet the increased metabolic needs of the ulcer and/or associated with a localized inflammatory response. Similar findings have been reported for the peri–ulcer microcirculation in patients with venous ulcers.[16] However, in the present group there was neither a history or any evidence for the presence of venous disease in any subject and all ulcers treated were distal to the malleolus. In the 15 subjects studied, in spite of the already vasodilated state of the peri–ulcer skin, PRFF treatment was still able to produce a further increase in RBC perfusion. The primary response noted was associated with an increase in the volume component. The physiological significance of this component is related to the number of microvessels with an active RBC flow within the tissue measurement area. An increase in this parameter subsequent to PRFF treatment may indicate further arteriolar dilation and/or selective recruitment of previously non-perfused capillaries and/or other microvessels. Since no significant increase in the velocity component was detected, a significant increase in local arteriolar vasodilation is unlikely, suggesting that microvessel recruitment may be the primary mechanism for the observed perfusion increase. Under conditions in which non–aided

perfusion is marginally inadequate to promote timely ulcer healing, the increased perfusion may potentially be useful as an aid to the healing process. These initial preliminary findings using a single PRFF treatment provide the basis and suggest the need for an expanded study in which the relationship of PRFF treatment can be related to perfusion changes and ulcer healing outcomes.

Acknowledgement

The authors thank Electropharmacology Inc. (EPi) for the loan of the SofPulse device. The excellent technical and coordinating efforts of Marie Delgado, RN, and Connie Ingram, RN, are also gratefully acknowledged.

References

1. Vodovnik L, Karba R. Treatment chronic wounds by means of electric and electromagnetic fields. *Med Biol Eng Comp* 1992;30:257–66.
2. Bassett CAL. Beneficial effects of electromagnetic fields. *J Cell Biochem* 1993;51:387–93.
3. Ottani V, Pasquale V, Govoni P, et al. Effects of pulsed extremely low frequency magnetic fields on skin wounds in the rat. *Bioelectromagnetics* 1988;9:53–62.
4. Bobanovic F, Simcic S, Kotnik V, Vodonik L. Pulsed electric current enhances the phorbolester–induced oxidative burst in human neutrophils. *FEBS letters* 1992;311:95–8.
5. Cossarizza A, Angioni A, Petragilia F, et al. Exposure to low frequency pulsed electromagnetic fields increases interleukin–1 and interleukin–6 production by human peripheral blood mononuclear cells. *Exp Cel Res* 1993;204:385–7.
6. Cooper MS, Schliwa M. Electrical and ionic controls of tissue cell locomotion in the electric fields. *J Neuroscience Res* 1985;13:223–44.
7. Nuccitelli R, Erickson CA. Embryonic cell motility can be guided by physiological electric fields. *Exp Cell Res* 1983;147:195–201.
8. Adey WR. Biological effects of electromagnetic fields. *J Cell Biochem* 1993;51:410–6.
9. Miura M, Ocada J. Non–thermal vasodilation by radio frequency burst–type electromagnetic field radiation in the frog. *J Physiol* (Lond) 1991;435:257–73.
10. Falcone JC, Kuo L, Meininger GA. Endothelial cell calcium increases during flow–induced dilation in isolated arterioles. *Am J Physiol* 1993;264:H653–9.
11. Mayrovitz HN, Larsen PB. Effects of pulsed electromagnetic fields on skin microvascular blood perfusion. *WOUNDS* 1992;4:197–202.
12. Nilsson GE, Tenland T, Oberg PA. A new instrument for continuous measurement of tissue blood flow by light beating spectroscopy. *ICEEE Trans Biomed Eng* 1980;27:12–9.
13. Bonner R, Nossal R. Model for laser Doppler measurements of blood flow in tissue. *Applied Optics* 1980;20:2097–2107.
14. Mayrovitz HN. Assessment of the microcirculation: Laser Doppler and transcutaneous oxygen. *J Vasc Tech* 1994;18:269–75.
15. Rendell M, Bergman T, O'Donnell G. Microvascular blood flow, volume, and velocity measured by laser Doppler techniques in IDDM. *Diabetes* 1989;38:819–24.
16. Mayrovitz HN, Larsen PB. Periwound skin microcirculation of venous ulcers. *Microvasc Res* 1994;48:114–23.
17. Nilsson GE, Tenland T. Evaluation of a laser Doppler flowmetry for measurement of tissue blood flow. *IEEE Trans Biomed Eng* 1980;27:597–604.
18. Smits GJ, Romans RJ, Lombard JH. Evaluation of laser Doppler flowmetry as a measure of tissue blood flow. *J Appl Physiol* 1986;61:666–72.
19. Salumet JL, Dittmar A, Leftheriotis G. Noninvasive measurement of skin blood flow: Comparison between plethysmograph, laser Doppler flowmeter and heat thermal clearance method. *Int J Microcirc: Clin Exp* 1986;5:73–83.
20. Shepherd AP, Riedel GL, Kiel JW, et al. Evaluation of an infrared laser–Doppler blood flowmeter. *Am J Physiol* 1989;252:G832–9.
21. Bonner RF, Nossal R. Principles of laser–Doppler flowmetry. In: Shepard AP, Oberg PA (eds). *Laser–Doppler Blood Flowmetry*. Kluwer Academic Publishers:1991:17–45.
22. Mayrovitz HN, Regan MB. Gender differences in facial skin blood perfusion during basal and heated conditions determined by laser Doppler fluxmetry. *Microvasc Res* 1993;45:211–8.
23. Battocletti JH. Blood flow measurement by NMR. *CRC Crit Rev Biomed Engr* 1986;13:311–67.
24. Bendick PJ, Price JL, Glover JL. An objective measure of heomdynamic improvement after angioplasty. *Arch Surg* 1992;127:806–11.
25. Kerr TM, Cranely JJ, Johnson JR, et al. Measurement of blood flow rates in the lower extremities using a nuclear magnetic resonance based instrument. *J Vasc Surg* 1991;14:649–57.
26. Mayrovitz HN, Larsen PB. Leg blood flow in patients with venous ulcers: Relationship to site and ulcer area. *WOUNDS* 1994;6:195–200.
27. Rice KI, Money SR, Pendleton DW, et al. Resting arterial status index predicts exertional arterial compromise. *J Vasc Tech* 1994 (in press).