Diagnosis and Management of Microvascular Dysfunction in Diabetes

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Introduction

- Microcirculation is an essential system that regulates oxygen and nutrients to cells and tissues in response to various environmental stimuli and pathophysiological conditions. Diabetes mellitus can cause **microvascular complications including nephropathy, neuropathy, and retinopathy**.
- Research studies have demonstrated that **functional microvascular dysfunction appears much earlier than structural alterations in vasculature in diabetes**. This finding of the progression from microvascular dysfunction to macrovascular disease establishes a foundation for screening and early diagnosis of diabetes by assessing microvascular function.
- This comprehensive review discusses technologies (laser Doppler, transcutaneous oximetry, infrared thermography and near-infrared spectroscopy) with computational methods (linear, nonlinear and machine learning approaches) for **diagnosing microvascular dysfunction in diabetes**.
- This review also evaluates current interventions (weight-bearing exercise, non-weight bearing exercise, vibration, and thermal therapy) used to **manage microvascular dysfunction in diabetes**.

Diagnosis of Microvascular Dysfunction in DM

1. **Laser Doppler flowmetry and imaging** is based on Doppler effect to monitor blood flow velocity in perfusion unit (e.g. Perimed PeriFlux 6000).
- **Blood flow**

2. **Transcutaneous oximetry** uses local heating to measure oxygen and carbon dioxide molecules in mmHg (e.g. Radiometer TCM).
- **Transcutaneous oxygen**

3. **Near-infrared spectroscopy** uses Beer-Lambert Law to assess the concentration of hemoglobin in the tissue in μM (e.g. Hitachi)
- **Oxygenation** (oxyhemoglobin and deoxy-hemoglobin)

4. **Infrared thermography** can measure the skin temperature in °F (e.g. FLIR).
- **Skin temperature**

5. **Computational methods** use signal and imaging processing to classify microvascular status, including linear (thermal index, wavelet analysis), nonlinear (sample entropy, fractal, correlation dimension) and machine learning (convolutional neural network, AlexNet, Vgg-19, ResNet-18) methods.
- **Complex microvascular dynamics**

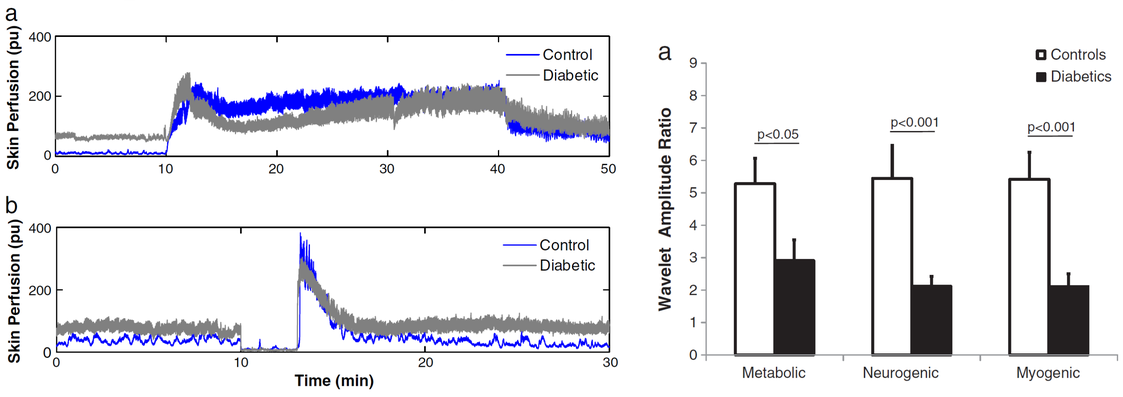


Fig 1. Blood flow response to thermal (left upper) and mechanical (left lower) stresses in diabetics and wavelet-based analysis indicating metabolic endothelial, neurogenic and vascular smooth muscle-based controls (right).

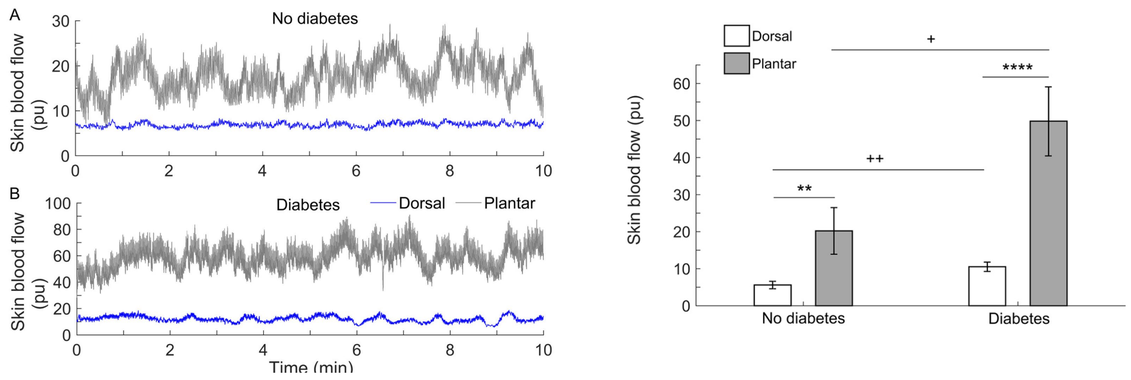


Fig 2. Dorsal and plantar blood flow in diabetics.

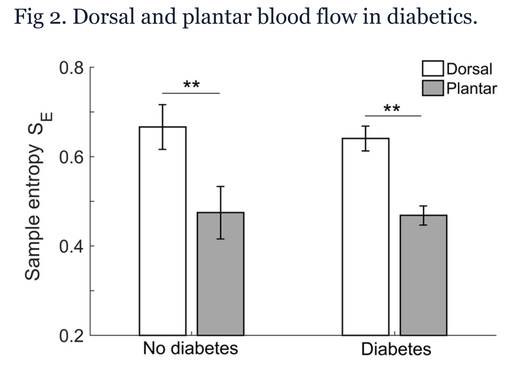


Fig. 5. Sample entropy of dorsal and plantar blood flow signals in the control group and the diabetes group. The symbols ** represents $p < 0.01$ using Wilcoxon signed-rank tests.

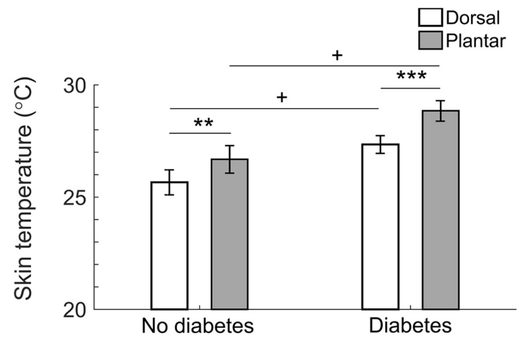


Fig. 6. Dorsal and plantar skin temperature in the control group and the diabetes group. The environmental temperature was maintained at 24 ± 2 °C. Data are represented as mean ± standard error. The symbols ** and *** respectively represent $p < 0.01$ and $p < 10^{-3}$ using Wilcoxon signed-rank tests; the symbol + represents $p < 0.05$ using Wilcoxon rank sum tests.

Fig 3. Sample entropy and thermal index of the dorsal and plantar blood flow in diabetics.

Management of Microvascular Dysfunction in DM

	Modality	Principle	Benefits	Guidelines (Dosage)
Intervention	Weight-bearing exercise [9,10,43,44]	Weight-bearing exercise is recommended to people with diabetes, including people at risk for diabetic foot ulcers.	- Activities of daily living can be integrated for exercise programs. - Weight-bearing activities stimulate plantar tissues to maintain sufficient stiffness.	- Both aerobic and resistance exercise [10]. - Moderate-to-rigorous intensity of exercise for 150 min per week [43]. - People who are physically inactive should start from breaking down sedentary time before pursuing exercise [9]. - Both upper and lower limb muscles [44].
	Non-weight-bearing exercise [9]	Non-weight-bearing exercise is needed for people with open diabetic foot ulcers.	- Non-weight-bearing activities may reduce risk for diabetic foot ulcers.	- With diabetic foot ulcers, non-weight-bearing exercise can promote wound healing.
	Local Vibration [45]	The use of vibration to stimulate blood flow control for improving microcirculation.	- Mechanical vibration improves blood flow to reduce tissue ischemia. - Patients do not need to exercise.	- Intermittent local vibration can be applied to plantar foot.
	Thermal Therapy [46]	The use of heat to induce a vasodilatory response for improving microcirculation.	- Thermal therapy improves blood flow to reduce tissue ischemia. - Patients do not need to exercise.	- Local heat like warm bath could induce thermal vasodilation for improving microcirculation. A careful assessment is needed to avoid overheating in people with diabetic neuropathy.

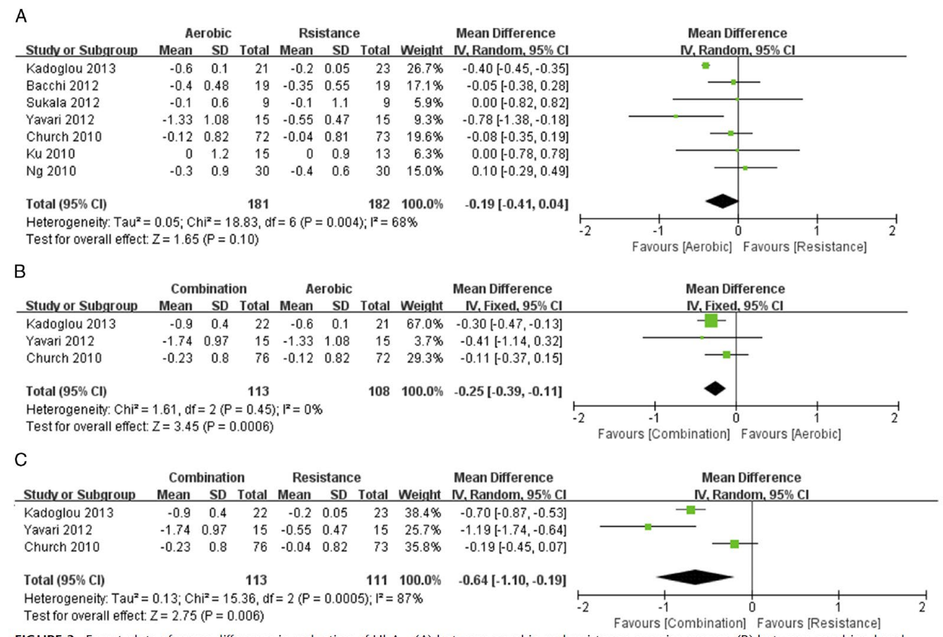


FIGURE 3. Forest plots of mean difference in reduction of HbA_{1c} (A) between aerobic and resistance exercise groups, (B) between combined and aerobic exercise groups, and (C) between combined and resistance exercise groups. df, degrees of freedom; IV, inverse variance.

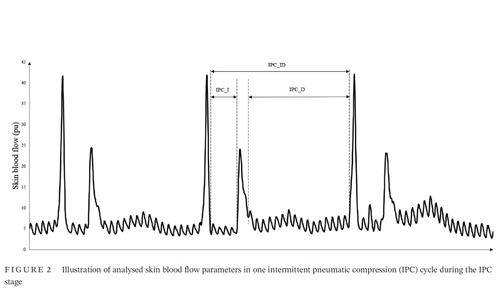


FIGURE 2 Illustration of analysed skin blood flow parameters in one intermittent pneumatic compression (IPC) cycle during the IPC stage

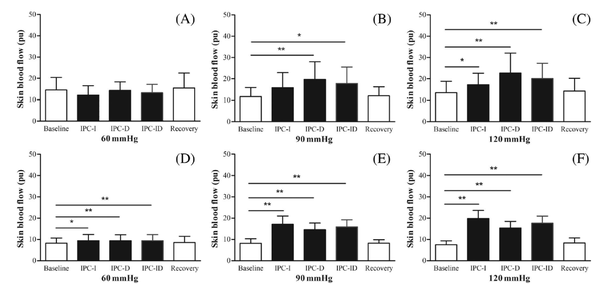


FIGURE 3 Foot skin blood flow (SBF) of diabetic subjects (A-C) and healthy subjects (D-F) in baseline, IPC, and recovery stages. * indicates there is a significant difference in SBF between the two corresponding stages, *$P < .05$, **$P < .01$. IPC_I: mean value of SBF in inflation periods during IPC stage; IPC_D: mean value of SBF in deflation periods during IPC stage; IPC_ID: mean value of SBF in inflation and deflation periods during IPC stage. IPC, intermittent pneumatic compression

Conclusion

In this comprehensive review, recent advances in imaging and optical technologies with computational methods used to diagnose microvascular dysfunction are reviewed. Research studies have demonstrated that local vibration and whole-body vibration can improve microcirculation in various pathological conditions, including diabetes. Due to the complex nature of microvascular regulation, various computational methods have been developed to shed light on the influence of diabetes on microvascular dysfunction. This comprehensive review will contribute to the diagnosis and management of microvascular dysfunction in diabetes.

References

1. Jan YK, Kelhofer N, Tu T, Mansuri O, Onyemere K, Dave S, and Pappu S. Diagnosis, pathophysiology and management of microvascular dysfunction in diabetes mellites. Diagnostics 2024, 14(24), 2830.
2. Jan YK, Shen S, Forearm RD, and Ennis WJ. Skin blood flow response to locally applied mechanical and thermal stresses in the diabetic foot. Microvascular Research 2013, 89, 40-46.
3. Jan YK, Liao F, Cheing GLY, Pu F, Ren W, Choi HMC. Differences in skin blood flow oscillations between the plantar and dorsal foot in people with diabetes mellitus and peripheral neuropathy. Microvascular Research 2019, 122, 45-51.
4. Liao F, An R, Pu F, Burns S, and Jan YK.. Effect of exercise on risk factors of diabetic foot ulcers: a systematic review and meta-analysis. American Journal of Physical Medicine and Rehabilitation 2019, 98, 102-116.
5. Ren W, Duan Y, Jan YK, Li J, Liu w, Pu F, and Fan Y. Effect of intermittent pneumatic compression with different inflation pressures on the distal microvascular responses of the foot in people with type 2 diabetes mellitus. International Wound Journal 2022, 9, 732628.