

Cardiovascular Topics

A novel method that can be used in both the diagnosis and treatment of peripheral arterial disease in diabetics: vibration-mediated dilation

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Abstract

Objective: The growing incidence of diabetes and the increasing life expectancy of the diabetic population worldwide has increased the number of diabetic vascular complications occurring in cardiology practice. As current treatment and prevention methods are less effective in this patient group, there is a need for new treatment methods in this area. Exercise, which reduces metabolic and vascular problems associated with diabetes, often becomes impossible, especially in advanced-stage patients who need exercise the most. Since exercise and flow-mediated dilation (FMD) are effective by stimulating mechanotransduction mechanisms on the endothelium, it can be expected that the same mechanisms could also be stimulated by direct vibration.

Methods: In order to test this hypothesis, in this study, a group of 20 type 2 diabetes patients (11 males, age 56.80 ± 11.05 years and diagnosed for 15.35 ± 8.61 years) were examined via the application of FMD and vibration-mediated dilation (VMD). We performed vibration for five minutes with 20-Hz frequency and 3-mm vertical amplitude, to the same side forearm, with a 30-minute interval. Using a 10-MHz linear echo probe, brachial artery diameter and flow velocities were recorded for 10 minutes before and at two-minute intervals after the FMD and VMD applications. Then brachial artery flow and resistance were calculated at each stage.

Results: In the first minute after FMD and VMD applications, brachial artery diameter and flow velocities increased significantly, and vascular resistance decreased significantly. None of the corresponding FMD or VMD parameters in the

first minute was different. The artery diameters in the first minute after FMD and VMD were increased by 6.04 ± 5.29 and $5.49 \pm 5.21\%$, respectively. At the tenth minute, these values decreased to 1.73 ± 3.21 and $2.05 \pm 3.31\%$. In the FMD series, all parameters except brachial artery diameter returned to their baseline values after the fourth minute. After VMD, all parameters also decreased after the first minute, but the recovery was much slower. At each stage after the first minute, the VMD averages were higher than the baseline value and their corresponding FMD values.

Conclusion: The results of this study indicated that vibration may be a powerful, long-lasting and feasible treatment option in patients with peripheral perfusion failure, developed due to diabetic macro- and microvascular complications.

Keywords: vibration-mediated dilation, flow-mediated dilation, diabetes mellitus, arterial haemodynamics, endothelial function, peripheral arterial disease

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Diabetes mellitus is a problem that is increasing in frequency to a level that can be defined as an epidemic in the world due to increasing and aging populations, increasing average body mass index, decreasing physical activity levels and changing nutritional habits, and it is expected to increase even more in the future. As the disease progresses, it causes vascular complications, involving almost all vascular segments, becoming a source of serious mortality and morbidity.^{1,2} Diabetic cardiovascular disease has become a growing and challenging subgroup of cardiovascular diseases. Therefore, there is a need for increased effort to understand and treat it, and new solutions are needed.

Even in diabetics who carefully follow their treatment plan, plasma glucose levels fluctuate more than in healthy individuals.¹ In general, despite treatment, the average glucose level in extracellular fluids remains high and intracellular levels remain low. Metabolic abnormalities cause direct or indirect structural and functional abnormalities in the tissues as the duration of diabetes is prolonged. Therefore, prolonged duration of diabetes accumulates the chronic effects of the disease and leads to late complications.^{2,3}

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Apart from metabolic fluctuations, vascular complications are the main determinants of mortality and morbidity in diabetic patients. In diabetic patients, atherosclerosis occurs two to four times more frequently, is more diffuse (widespread along the vessel) and has a more rapid course than in non-diabetic patients. It is more difficult to treat with medical, interventional or surgical therapies.⁴

Insulin resistance and hyperglycaemia, which develop years before manifest diabetes occurs, facilitate the development of atherosclerosis by causing an increase in oxygen radicals, a decrease in endothelial nitric oxide synthesis, a tendency to inflammation, platelet activation and the development of prothrombotic conditions.⁵ Therefore, macrovascular complications may have progressed when manifest diabetes is more recent.⁶

In healthy individuals, adaptive mechanisms in the vascular system generally equalise the perfusion required and provided by tissues over the long term. An acute increase in demand is met by increased perfusion provided by micro- and macrovascular vasodilation. If the increase in demand is chronic or if acute increases in demand are repeated frequently, angiogenesis is stimulated in the microvasculature and the capillary vascular network is enriched. The vessel diameters of the macrovascular vessels that deliver blood to the microvascular space enlarge structurally. Therefore both the chronically increasing need for perfusion and the increased acute perfusion that develop on this basis can be adequately met at a higher level.^{7,8}

All these changes develop sequentially, with microvascular dilation initiated by the metabolic needs, a decrease in vascular resistance, an increase in flow and shear stress (SS), and mechanochemical transduction mechanisms starting from the endothelial surface and continuing inside the cell. As a result, angiogenesis in the microvascular segments, whose primary task is substance exchange, with the participation of all cells and matrix proteins participating in the vasculature, and an increase in diameter in macrovascular segments, whose primary task is to deliver blood to this area, make it possible to restore the balance between perfusion need and supply.⁹ When the tissue is perfused more than it needs, dilator mechanisms are inhibited and capillary number decreases in the long term. Vascular resistance increases and perfusion decreases, approaching the amount needed.¹⁰

Perfusion demand–supply balance is most commonly analysed through the oxygen demand–supply balance of tissues. Acute or chronic increases or recurrent acute increases in tissue oxygen demand stimulate vascular adaptation mechanisms, resulting in acute or chronic adaptation of tissue perfusion.¹¹ Decreased demand, on the other hand, stimulates functional and/or structural changes that decrease perfusion by acting in the opposite direction. The relationship between tissue oxygen demand and perfusion is so strong that tissue oxygenation immediately comes to mind in acute or chronic perfusion changes. This strong relationship makes it easy to overlook other factors affecting perfusion.

In the first years of diabetes in patients, hyperperfusion in tissues and organs is notable. Renal hyperperfusion in early diabetes is a typical example.¹² The myocardium has also been shown to be hyperperfused under basal conditions in the first decade of diabetes.¹³ Years later, microvascular desquamation, loss of glomeruli in the kidney and thickening of precapillary

arteriolar walls in other tissues lead to increased microvascular resistance, decreased basal perfusion and replacement of hyperperfusion by microvascular hypoperfusion. During this phase, the ability to adapt to acute increases in demand is also reduced. This is manifested in the heart as a decrease in coronary flow reserve.¹³

Microvascular changes lead to significant organ dysfunction, including retinopathy, nephropathy, neuropathy and cardiomyopathy. When concomitant macrovascular problems are added, clinical symptoms worsen. Since oxygen transport is not impaired in diabetes, hypoxia is not the cause of early hyperperfusion. However, the task of circulation is not only to provide oxygen–carbon dioxide gas exchange in tissues. Indispensable substances for life must also be transported.

In diabetes, absolute or relative insulin insufficiency usually causes the cell to become glycopaenic. It is likely that the hyperperfusion seen in diabetes during the first decade is due to intracellular glycopaenia stimulating mechanisms that increase perfusion, as hypoxia does. However, the stimulation of perfusion does not cease because the increased perfusion does not meet the demand due to impaired transmembrane transport of glucose. However, the increased perfusion causes the tissue to be ‘over-perfused’ in terms of oxygen and other transports that are not impeded in their entry into the cell. The perception of excess perfusion then starts to stimulate the mechanisms that limit it.

Years of stimulation of the mechanisms that limit hyperperfusion ultimately lay the groundwork for diabetic microvascular complications, characterised by microvascular desquamation and increased vascular resistance. The microvascular insufficiency that develops is added to macrovascular complications in the form of diffuse and anatomically difficult-to-remediate diffuse stenoses, magnifying the perfusion problem associated with diabetes.

In proportion to the intensity and duration of exercise, it facilitates the ability of the striated muscle to take up blood glucose by insulin-dependent and non-insulin-dependent pathways during and in the hours following exercise. In addition, micro- and macrovascular resistance decreases in striated muscles and other organs with increased output during exercise. At the rate of repetition, structural and functional changes compatible with high flow rate begin to occur in the micro- and macrovascular segments of the vascular system. Since the increase in perfusion during exercise develops with or even after the increase in demand, it does not warn of excess perfusion.

Exercise reduces the low- to high-density lipoprotein cholesterol ratio, triglyceride levels and excess weight. Because of these multifaceted effects, exercise both reduces metabolic disorders and facilitates the control of vascular complications in diabetics.¹⁴ Even if the response to exercise is blunted compared to non-diabetics, exercise is highly recommended in diabetics due to the versatility of the effect and the limitation of alternative treatment options.

However, advancing age, decreased muscle strength, concomitant peripheral and/or coronary artery diseases, mechanical orthopaedic problems facilitated by chronic obesity, and trophic lower-extremity ulcers that develop in some patients may not infrequently limit or even render impossible the exercise capacity of patients. Therefore, it can be said that new tools and applications that will increase the treatment possibilities of

diabetes-related vascular complications are needed more than in non-diabetic patient groups.

The vascular effects of exercise can be simulated with the flow-mediated dilation (FMD) test. During this test, forearm ischaemia is induced by raising a sphygmomanometer cuff, wrapped around the forearm below the elbow, above the systolic arterial pressure for five minutes. Microvascular dilation secondary to ischaemia decreases microvascular resistance; flow velocities increase markedly when flow is allowed.

Increased flow velocity increases the friction of blood against the vessel wall (SS). Special structures on the endothelial surface sense the increase in SS. Following an interaction process involving microtubules and actin filaments that form the cytoskeleton, mechanochemical processes, defined as mechanotransduction, develop. As a result, nitric oxide (NO) is released and vasodilation is stimulated. Perfusion of the tissue increases. Hyperperfusion eliminates ischaemia in the tissue within minutes; increased flow returns to basal values, and dilation ends.¹⁵

In diabetics, induction of ischaemia by frequent and repetitive exercise and therefore favourable metabolic and functional/vascular changes cannot always be induced. Not infrequently, exercise limitations and the already ischaemic state of peripheral tissues limit or even prevent this. Even if exercise is not possible, stimulation of the mechanisms that would be stimulated by exercise by means other than exercise may initiate the changes hoped to be achieved by exercise and may open new therapeutic possibilities in diabetics.

Even if the vascular response to exercise is initially stimulated by ischaemia, SS perception and perception-sensitive mechanisms play an important role in the spread of the effect to the vasculature and dilation of macro- and microsegments. The endothelium senses the level of SS by receptors or structures that continuously detect it.¹⁶ The increase in this perception stimulates mechanisms that result in acute vasodilation, chronic microvascular enrichment and macrovascular diameter increase.¹⁷

The structures that sense SS on the luminal surface of the endothelium are consistent with the mechanical character of the stimulus and are referred to as mechanosomes.¹⁸ The SS-induced mechanical stimulus perceived through these sensors or receptors is transferred through the cytoskeleton onto intracellular mechanotransduction mechanisms, leading to the synthesis of NO and other specific chemical responses.¹⁹⁻²²

The mechanical character of SS and the mechanisms stimulated by this effect suggest that these mechanisms can be stimulated by direct mechanical stimuli instead of induction of ischaemia in patients who cannot exercise. For this purpose, vibration can be used to stimulate the tissues in which increased circulation is desired. Moreover, since such a stimulus will affect all vascular segments, it can be expected to be effective in all micro- and macrovascular segments, similar to the induction of ischaemia. Since vibration has been used in physiotherapy clinics for many years for various purposes, vibration was performed with the devices used in these clinics and at tested frequencies.

The security concerns of its implementation would also not be significant.²³ In this study, vibration-mediated dilation (VMD) and other local haemodynamic parameter changes in the vascular system in a group of diabetic patients were investigated by comparing the baseline values with the results of FMD application, applied to the same arm in the same patients for comparison.

Methods

The study included 20 patients in sinus rhythm, aged between 30 and 80 years, with a diagnosis of type 2 diabetes mellitus for at least one year, who gave written informed consent, and who had echocardiographic left ventricular ejection fraction above 35%. Patients with definite or suspected subclavian artery stenosis, atheroma plaque or wall calcification in the brachial artery on ultrasonographic control, insufficient co-operation, functional capacity III or IV heart failure according to the New York Heart Association classification, unstable angina, atrial fibrillation or irregular heart rhythm due to frequent extrasystoles were excluded.

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by Istanbul University's Istanbul Faculty of Medicine ethics committee (decision date and number: 19.06.2020 2020/755). The clinical trial registration number is NCT05492071 (<https://www.clinicaltrials.gov>).

After physical examination and laboratory tests, it was ensured that the patients included in the study had not consumed tea, coffee or cigarettes within half an hour before the examination. In all patients, two-dimensional ultrasonographic imaging of the left brachial artery of the left arm was performed in the supine position using a GE Vingmed Vivid 7[®] echocardiography device and a 10-MHz linear probe under ECG monitoring. The flow of the same artery was recorded with pulsed Doppler echocardiography. The measurement site was marked with a pen. Basal heart rate, brachial artery diameter, and highest, lowest and mean flow velocities were measured and recorded in all patients.

For FMD measurement, the cuff pressure of a sphygmomanometer cuff wrapped just below the left elbow was increased to 50 mmHg above the patient's previously measured systolic arterial pressure. Forearm perfusion was stopped for five minutes by controlling the disappearance of the radial artery pulse. In the first minute, immediately after cuff release, and at

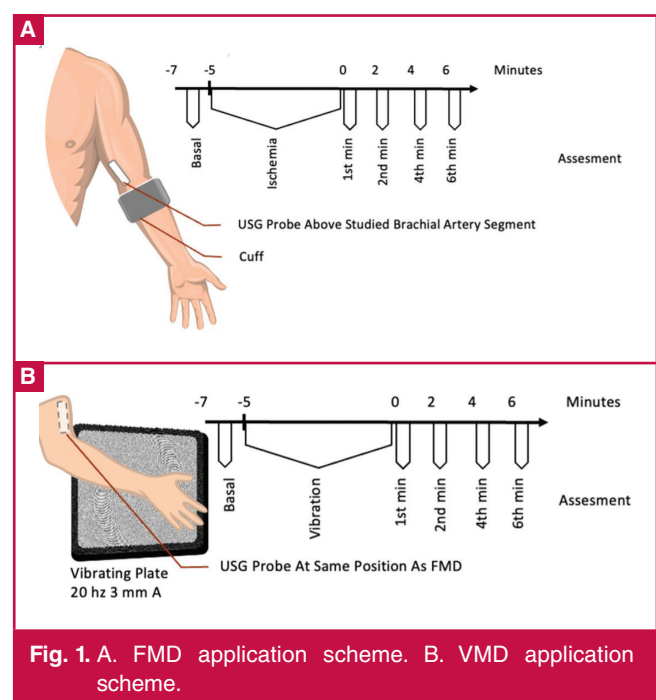


Fig. 1. A. FMD application scheme. B. VMD application scheme.



Fig. 2. Demonstration of applying vibration to the forearm.

two-minute intervals until the 10th minute (second, fourth, sixth, eighth and 10th minutes), the same parameters were measured and recorded again from the point where baseline measurements were previously recorded (Fig. 1A).

For VMD measurement, the same side forearm of the patient was placed on the Power Plate vibration device 30 minutes after the last FMD measurement and exposed to vibration with a frequency of 20 Hz and a vertical amplitude of 3 mm for five minutes. In the first minute, immediately after the vibration was terminated, and at two-minute intervals until the 10th minute, the same measurements were made from the same point in the same position and recorded (Figs 1B, 2).

Considering that the short-axis cross-section of the brachial artery is circular, cross-sectional areas (πr^2) were calculated in cm^2 , based on the diameters (2r) at each stage. The artery's minute flow rate (ml/min) was calculated by multiplying this area by the mean flow rate (cm/s) and taking 60 times the result. Forearm vascular resistance ($\text{dyn}/\text{s}/\text{cm}^2$) was calculated by dividing the mean arterial pressure by this flow rate and multiplying the result by 80. Calculations were repeated for all

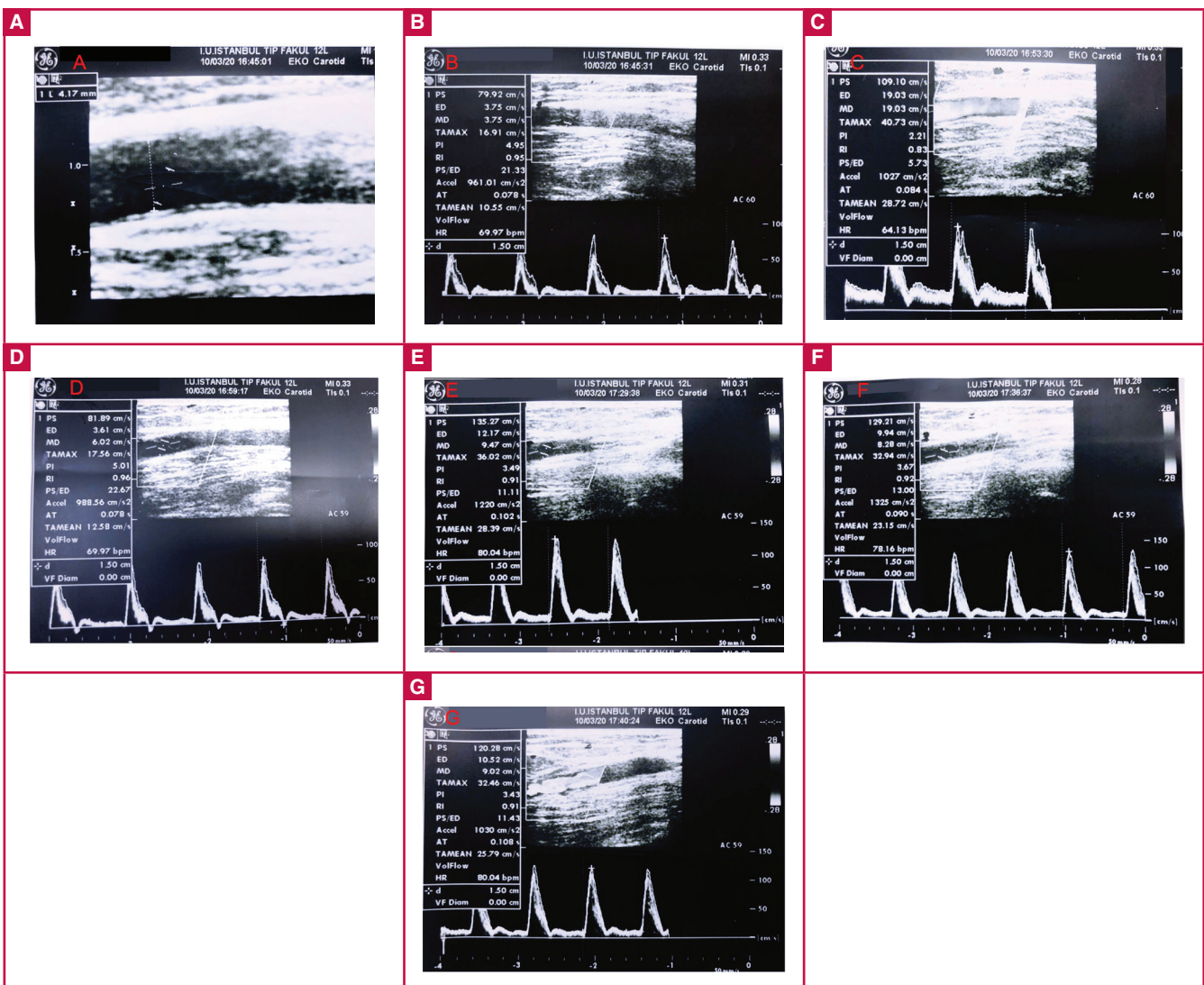


Fig. 3. A. Measurement of the brachial artery basal diameter. B. Brachial artery basal flow recording. C. FMD first-minute flow recording. D. FMD sixth-minute flow recording. E. VMD first-minute flow recording. F. VMD sixth-minute flow recording. G. VMD 10th-minute flow recording.

Table 1. Demographic and baseline parameters in the patient group

Parameters	Number	Mean	Standard deviation
Age (years)	20	56.8	11.05
Diabetes duration (years)	20	15.35	8.61
Gender, (M/F)	20	11/9	
Weight (kg)	20	81.95	18.97
Height (cm)	20	167.2	7.77
Body mass index (kg/m ²)	20	29.31	6.64
Fasting glucose (mg/dl)	20	203.15	77.44
HbA _{1c} (%)	19	8.92	1.83
Creatinine (mg/dl)	20	0.9	0.35
Microalbuminuria (mg/l)	17	121.88	268.67
CRP (mg/l)	20	4.45	5.21
LDL-C (mg/dl)	20	118.55	36.31
Systolic arterial pressure (mmHg)	20	127	14.82
Diastolic arterial pressure (mmHg)	20	74.75	9.24
Mean arterial blood pressure (mmHg)	20	92.2	9.81
Ischaemic heart disease, <i>n</i> (%)	20	6 (30)	
Heart failure, <i>n</i> (%)	20	2 (10)	
Hypertension, <i>n</i> (%)	20	13 (65)	
Vasodilator usage, <i>n</i> (%)	20	10 (50)	
Statin usage, <i>n</i> (%)	20	12 (60)	
HbA _{1c} , glycated haemoglobin; CRP, C-reactive protein; LD-C, low-density lipoprotein cholesterol.			

measurement phases after baseline, FMD and VMD.

Since there was no information in the literature on VMD application, it was observed that the vascular changes that occurred after vibration could continue even after 30 minutes, albeit attenuated, in the pilot applications performed to decide on the method. However, since it was observed that arterial diameter returned to baseline values in 10 to 12 minutes and flow velocities returned to baseline values in three to four minutes in all patients after FMD application, it was planned to perform both methods after similar baseline values. Therefore, FMD

was performed first and recordings were taken from the patients for 10 minutes at two-minute intervals (Fig. 3A–D), followed by a 30-minute break. VMD was then performed and the same parameters were recorded at the same stages (Fig. 3E–G).

Statistical analysis

Continuous (parametric) variables are expressed as mean ± standard deviation and categorical (non-parametric) variables are expressed as number and percentage. The means of different stages obtained by the same method or at the same stage obtained by different methods were compared by paired *t*-test since they were obtained from the same patient group. The limit for statistical significance was accepted as *p* < 0.05.

Results

The average age of the 20 diabetic patients included in the study was 56.80 ± 11.05 years. The age at diagnosis of diabetes was 15.35 ± 8.61 years and the male-to-female ratio was 11/9 (55/45%). The other baseline demographics and laboratory characteristics are given in detail in Table 1.

The brachial artery diameter showed maximum dilation in the first minute after both FMD and VMD treatments. The increase in diameter gradually decreased in the following minutes. However, the averages were still higher than the baseline value, even at 10 minutes. The differences between the baseline averages and the first-, second-, fourth-, sixth- and 10th-minute values were significant in both series. The effects of FMD and VMD on brachial artery diameter were similar. There was no significant difference between the series at all stages (Fig. 4A, Table 2).

In both series, maximum deviation (increase) in mean flow velocity from baseline was observed within the first minute. In the FMD series, the increase returned to baseline at a similar

Table 2. Comparison of vascular parameters in terms of FMD and VMD methods

Stage/method	Diameter (cm)	Mean velocity (cm/s)	Peak velocity (cm/s)	Min velocity (cm/s)	Flow (ml/min)	Resistance (10 ³ dyn/s/cm ²)
Baseline/FMD	0.378 ± 0.054	10.15 ± 4.29	77.089 ± 14.09	2.42 ± 3.04	67.87 ± 33.21	145.136 ± 91.32
Baseline/VMD	0.378 ± 0.054	10.16 ± 4.29	77.21 ± 14.22	2.42 ± 3.04	67.82 ± 33.13	145.33 ± 91.18
<i>p</i> -value	0.59	0.16	0.25	1.00	0.58	0.84
Minute 1/FMD	0.399 ± 0.052	22.76 ± 5.96	104.14 ± 13.36	11.93 ± 9.5	168.50 ± 45.46	47.35 ± 15.55
Minute 1/VMD	0.397 ± 0.051	21.14 ± 7.18	113.56 ± 20.33	8.45 ± 7.42	157.68 ± 63.77	55.03 ± 24.31
<i>p</i> -value	0.18	0.35	0.004	0.20	0.36	0.15
Minute 2/FMD	0.394 ± 0.054	12.96 ± 5.02	93.09 ± 16.97	4.82 ± 4.85	96.44 ± 45.04	95.75 ± 50.25
Minute 2/VMD	0.394 ± 0.054	21.02 ± 9.23	120.42 ± 20.43	8.45 ± 7.42	151.28 ± 64.40	59.98 ± 31.67
<i>p</i> -value	0.48	< 0.001	< 0.001	0.002	< 0.001	< 0.001
Minute 4/FMD	0.391 ± 0.052	10.48 ± 3.88	85.39 ± 13.81	2.35 ± 2.67	76.32 ± 29.10	129.85 ± 129.54
Minute 4/VMD	0.391 ± 0.052	20.23 ± 6.45	114.24 ± 19.97	8.49 ± 8.47	143.92 ± 46.87	57.70 ± 24.23
<i>p</i> -value	0.19	< 0.001	< 0.001	0.001	< 0.001	0.008
Minute 6/FMD	0.388 ± 0.053	9.60 ± 3.73	79.91 ± 13.62	2.63 ± 2.71	68.12 ± 28.02	133.87 ± 73.96
Minute 6/VMD	0.389 ± 0.053	19.41 ± 7.47	112.32 ± 22.39	7.11 ± 6.72	137.41 ± 55.33	62.98 ± 28.28
<i>p</i> -value	0.33	< 0.001	< 0.001	0.001	< 0.001	< 0.001
Minute 8/FMD	0.387 ± 0.052	10.53 ± 3.57	76.66 ± 15.14	2.42 ± 3.04	76.53 ± 34.83	118.87 ± 64.13
Minute 8/VMD	0.389 ± 0.052	17.69 ± 6.83	107.97 ± 19.94	7.39 ± 6.71	129.50 ± 59.31	72.50 ± 40.27
<i>p</i> -value	0.19	< 0.001	< 0.001	< 0.001	0.001	0.01
Minute 10/FMD	0.384 ± 0.054	10.79 ± 3.75	77.39 ± 16.33	1.86 ± 2.42	77.88 ± 36.43	120.45 ± 70.12
Minute 10/VMD	0.385 ± 0.054	17.28 ± 6.06	105.76 ± 25.93	5.54 ± 4.60	123.89 ± 53.49	72.11 ± 37.55
<i>p</i> -value	0.35	< 0.001	< 0.001	0.002	0.001	0.003

FMD, flow-mediated dilation; VMD, vibration-mediated dilation.

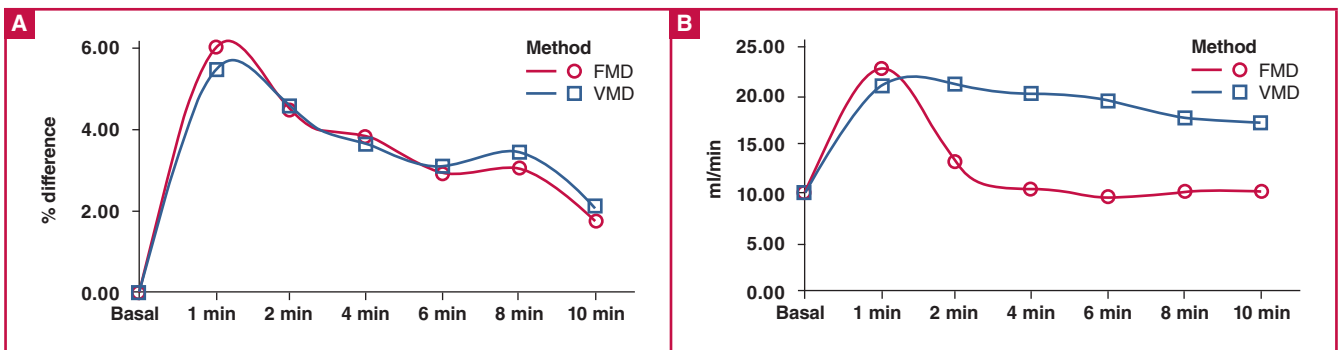


Fig. 4. A. Brachial artery diameter before and after FMD and VMD. B. Brachial artery mean flow velocity before and after FMD and VMD.

rate in the next two phases. It remained at baseline values after the fourth minute. In this series, only the difference between the first- and second-minute averages from baseline was significant (Fig. 4B, Table 2).

In the VMD series, the first-minute values showed a similar increase to that in FMD. However, the return to normal in the later stages was slower. In this series, starting from the first minute and including the tenth minute, the mean values were higher than the baseline value in all recording phases and the differences were highly significant. From the second minute onwards, VMD averages were higher than FMD averages. From the fourth minute onwards, the differences between the two series were significant.

Brachial artery peak (early systolic maximum) flow velocity was highest in the first minute in the FMD series. Then it decreased and returned to baseline value at six minutes. The differences between the first-, second- and fourth-minute averages and baseline values were significant.

In the VMD series, peak flow velocity reached its highest value at two minutes. Afterwards, it was observed to decrease slowly. Nevertheless, averages of all stages from the first to the 10th minute were higher than the baseline value and the differences were highly significant. Compared to the FMD series, VMD averages were higher in all follow-up phases. The differences were highly significant in all follow-up phases, starting from the first minute to 10 minutes (Fig. 5A, Table 2).

The lowest (minimum end-diastolic) brachial artery flow velocity showed a maximum increase in the first minute compared to baseline in the FMD series. It decreased rapidly

in the following stages and returned to baseline at four minutes. While the first-minute mean was significantly different from baseline, the subsequent stages showed no significant difference.

In the VMD series, end-diastolic velocity maintained its peak in the first minute at two minutes. It decreased with a slow slope in the following stages. Starting from the first minute, the averages of all stages were higher than baseline and the differences were significant. Although FMD mean was higher in the first minute, the difference from VMD was not significant. However, VMD averages were higher and the differences were significant at all stages, starting from the second minute to 10 minutes (Fig. 5B, Table 2).

In both series, maximum increase in brachial artery flow rate was observed in the first minute compared to baseline. In the FMD series, the increase decreased rapidly in the following stages and returned to baseline values at the fourth minute. The first- and second-minute averages of the FMD series were significantly different compared to baseline. In the VMD series, all stage averages were higher than baseline and the differences were highly significant. VMD averages were higher than the FMD series averages in all follow-up stages, starting from the second minute and including the 10th minute. The differences were significant in the second minute and at later stages (Fig. 6A, Table 2).

Forearm vascular resistance decreased by more than half compared to baseline in the first minute in both series. The first-minute mean was significantly different from baseline in both series. In the FMD series, the difference between the mean stage at the fourth minute and beyond, and baseline was not

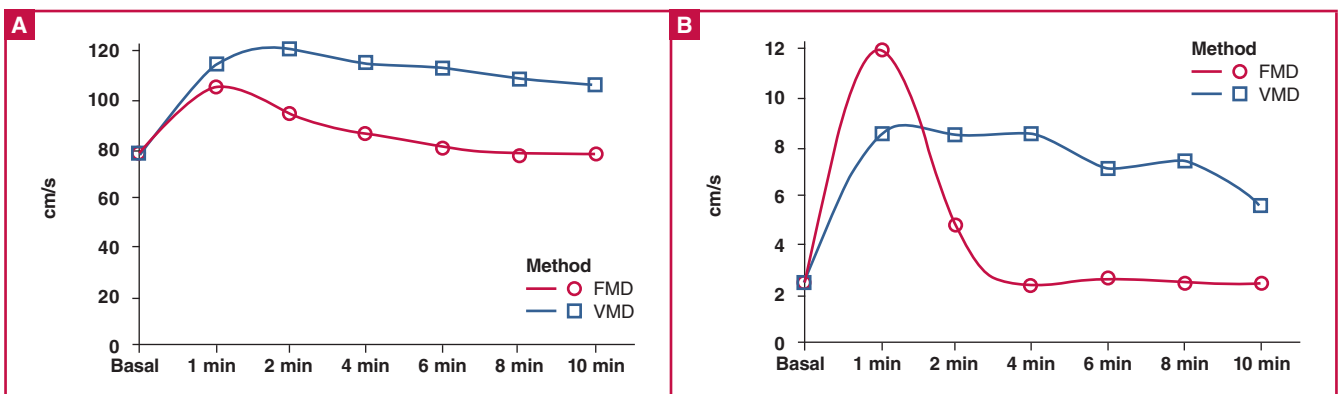


Fig. 5. A. Brachial artery peak flow velocity (cm/s) before and after FMD and VMD. B. Brachial artery lowest flow velocity (cm/s) before and after FMD and VMD.

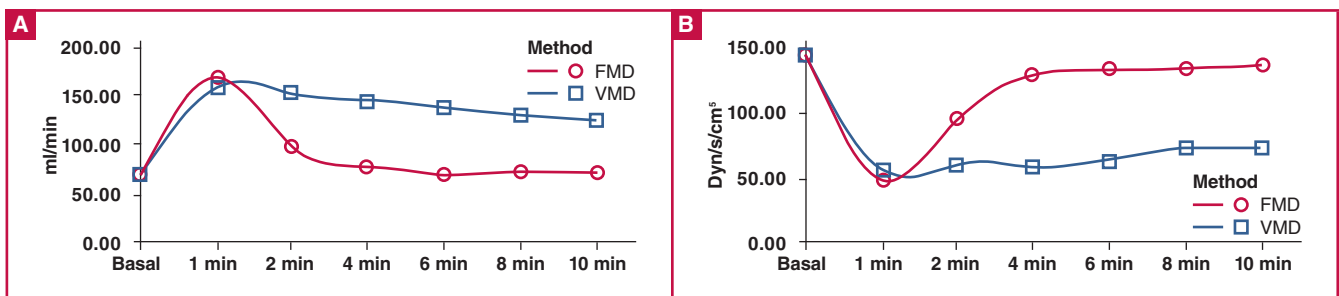


Fig. 6. A. Brachial artery flow (ml/min) before and after FMD and VMD. B. Forearm vascular resistance (dyn/s/cm²) before and after FMD and VMD.

significant. In the VMD series, a similar decrease in the mean in the first minute started to approach baseline in the later stages, as in the FMD series. However, the rate of change was much slower. The mean values of all stages were lower than baseline and the differences were highly significant. The VMD series averages were lower than the FMD series at the stages after the first minute. The VMD averages were significantly lower than the FMD averages in all subsequent stages, starting from the second minute (Fig. 6B, Table 2).

Discussion

FMD is defined as endothelium-dependent macrovascular dilation, largely caused by NO release, caused by transient ischaemia-induced flow, and hence, increased SS.¹⁵ FMD is also seen in type 2 diabetes patients; however, the amount is lower than in non-diabetic patients.^{24,25} Results reported in type 1 diabetes patients are contradictory.^{26,27} There is more consensus that the FMD response is blunted in type 1 diabetes patients with microalbuminuria and impaired glycaemic control than in non-diabetics.²⁸ It is likely that the FMD response is also related to the duration of diabetes. In manifest diabetics, the FMD response is reduced, whereas in those with early stages of the disease, such as impaired fasting glucose and/or impaired glucose tolerance, the response is similar to that of non-diabetics.²⁹

In the literature, we have not found any studies that quantitatively examined the vascular response to vibration in diabetics as in the FMD example. Although lower than in non-diabetic patients, the fact that diabetic patients have a dilation response to flow increase in the macrovascular area indicates that sensitivity to increased SS persists to some extent in these patients. FMD is a diagnostic rather than a therapeutic procedure. It cannot be used against macro- and microvascular problems that are difficult to treat as the duration of diabetes increases.

Exercise can help stimulate the mechanisms induced by FMD. Exercise creates relative ischaemia in the tissues, although not as deep as in FMD. Therefore, the need for perfusion increases. The increased need triggers acute functional responses. If the stimulus is chronic and repeated frequently, chronic structural changes are also stimulated. Exercise also helps regulate diabetes metabolism. However, exercise is more restricted, especially in diabetics who have the most vascular problems and therefore need the positive effects of exercise the most. Exercise becomes impossible in most advanced diabetes patients.

The character of endothelial surface mechanoreceptors that detect SS in the macro- and microvascular areas and the

mechanochemical (mechanotransductive) processes that develop within the cell with their stimulation and cause the release of vasodilator mediators, especially NO, suggest that these structures may also be open to mechanical stimuli other than SS. This mechanical stimulation method may be vibration. Although there is no study examining the vascular effects of vibration similar to FMD, there are data suggesting that it could have such effects.

It has been shown that vibration applied at low intensity for half an hour a day accelerated the healing of skin wounds in diabetic mice, and that this effect was achieved by stimulating granulation tissue and angiogenesis.³⁰ Refractory neuropathic pain due to diabetes in humans was greatly reduced with whole-body vibration.³¹

This study was not aimed at evaluating the change in vascular effects with diabetes, caused by current and vibration, but whether vibration was effective in the diabetic patient group. For this reason, the effectiveness of the application was controlled by the change in parameters examined compared to the basal values, and the non-diabetic control group was not included in the study.

There was no significant difference between the mean stages after FMD and vibration application at any stage. Because of the similarity in the amount and pattern of dilation, vibration application and the response obtained were likened to FMD application and named VMD. The macrovascular dilator effect of VMD was similar to FMD but differed from it in local haemodynamic parameters.

Unlike the FMD series, after the first minute, the mean values approached the baseline mean with a much slower slope. Averages at all stages after VMD were higher than the baseline value, as in the first minute, and the differences were highly significant. It was observed that VMD and FMD serial averages were separated after the first minute, with VMD remaining higher.

The difference between VMD and FMD was highly significant in the second minute and onwards. Although brachial artery dilation was similar to FMD, the fact that the mean velocity remained higher for longer than in the VMD series can only be explained by the difference in the microvascular effect of vibration. The finding suggests that the effect of this type of stimulus on the microvascular space disappears later.

It was observed that brachial artery flow, which is pulsatile, as in other arteries, reached its early systolic (maximum, peak) velocity in the second minute, not in the first minute, as in the VMD series. In the VMD series, peak velocity averages started to decrease after the second minute. In the FMD series, only the

first- and second-minute averages were significantly different from baseline, whereas in the VMD series, the averages for all stages were significantly higher than baseline.

This finding suggests that the cellular and vascular processes that determine the peak velocity continue for some time after the end of vibration, increasing the cumulative effect, and that this effect is stronger and longer lasting than the ischaemia-related changes that occur during FMD and it recovers rapidly.

Brachial artery minimum (end-diastolic) flow velocity was significantly higher than baseline in the first and second minute in the FMD series and similar in the subsequent stages. In the VMD series, the lowest velocity averages of all stages were significantly higher than the basal value of this velocity. VMD averages were higher than FMD averages in all subsequent stages, starting from the second minute. The effect of VMD on the lowest (end-diastolic) flow velocity also lasted longer than in FMD.

The fact that VMD application decreased vascular resistance in diabetic patients in a similar way to FMD, but unlike FMD, its effect lasted longer, could be due to the difference between its effect in the microvascular area, since its macrovascular dilator effect is the same. According to the results of the study, vibration for five minutes initially increased forearm perfusion by a similar amount compared to ischaemia for the same duration. Unlike ischaemia, the effect of vibration on all velocity, flow and resistance parameters lasted longer.

The fact that the ischaemia-induced flow parameters, except for the increase in diameter, returned to basal value at the fourth minute, while the vibration-induced effect still persisted at the 10th minute, and the differences between flow parameters, although the brachial artery diameter increase during VMD was the same as FMD, indicate that the cause of this difference should be sought in the microvascular area.

Although extrapolation of the available data and observations of pilot applications made before the study indicate that the duration of effect in VMD was four to five times longer than in FMD (up to 20 to 30 minutes), new series with a long enough follow-up period are needed for more reliable information. However, the available data are also sufficient to conclude that the area under the curve of vibration-induced changes was larger (the total effect was greater).

The fact that flow velocities (peak, minimum and mean) were significantly higher after VMD than after FMD after four minutes indicates that SS was also higher after four minutes in this series. However, it is not clear why arterial diameters did not show any difference in the phases when flow velocities returned to baseline after FMD. This may have been due to the fact that the macrovascular dilation that develops with the increase in SS may not accompany the change in SS at the same rate. In other words, the dilation that continues to some extent despite the decrease in SS after the fourth minute in the FMD series may be the continuation of the response to the increase in SS in the first minutes. In this case, the diameter difference between the FMD and VMD series will be seen in longer follow ups.

Another possibility is that the method of measurement may have affected the diameter measurement. In the study, we could not use one of the special edge detection programmes that determines the endothelial edge by itself and gives the diameter by averaging multiple measurements in a segment. Although the use of the same method in both measurement series reduced the

influence of the choice of measurement method on the results, the limited number of patients studied prevented this possibility from being completely ruled out. Depending on the size of the observation, the reliability of the conclusions will increase.

The results show that vibration produced effects that were similar to those that occur during exercise and that persisted for several times the duration of the applied vibration, indicating that this application could be used for therapeutic purposes. Repeated applications are likely to cause structural and functional changes in macro- and microvascular areas in the direction of increasing perfusion. The fact that vibration can easily be applied in patients who are unable to exercise is promising for diabetic patients with micro- and macrovascular complications.

In diabetic patients with perfusion insufficiency due to peripheral vascular problems, vibration can be expected to have acute and chronic perfusion-enhancing effects. The development of the method and application tools may make it possible to use the method for chronic visceral ischaemia other than in the extremities. In addition to diabetes, repeated vibration may be attempted in atherosclerosis patients, those with senile vascular problems, and in athletes to improve fitness and the scleroderma.

The study has some limitations. Subgroup analyses could not be performed due to the limited patient group. The non-invasive arterial pressure considered for vascular resistance may theoretically differ slightly from the invasive and simultaneous brachial artery pressure. In addition, manual measurement of brachial artery diameter by edge detection and not by devices with automatic measuring programmes may be considered as a source of error. However, although it had an effect on individual measurements, averages were less affected by these measurements. We tried to compensate for the lack of use of diameter measuring programmes by being meticulous in our measurements.

Conclusion

In the extremities where vibration was applied in diabetic patients, the large arteries had significantly increased perfusion, with effects on the microvascular area. Moreover, this effect was not inferior to that of FMD, which acted by induction of ischaemia, was considered to simulate exercise, and lasted much longer. While FMD cannot be used for therapeutic purposes, and exercise can be limited or not performed in patients with advanced perfusion insufficiency, despite their increased needs, vibration can easily be applied to all patients at the desired frequency. Repeated vibration is likely to stimulate macro- and microvascular perfusion-enhancing structural changes, as with repeated exercise. Repeated VMD in diabetic patients with macro- and microvascular complications appears to be a candidate for an easily applicable, beneficial, effective and powerful treatment modality for this difficult-to-treat patient group.

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