Forearm Hemodynamics and Responses to Exercise in Middle-aged Adult-onset Diabetic Patients

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SUMMARY

Much of the difficulty in assessing the progress of diabetic angiopathy and effects of experimental modes of therapy arises from the lack of quick, simple, inexpensive, and noninvasive tests to perform on the circulatory system of human subjects. We report here on values obtained by the use of mercury-in-rubber strain gauge plethysmography on 15 middle-aged, adult-onset diabetics who had minimal clinical evidence of microangiopathy. Standard tests are described for assessing forearm vascular function at rest, during tonic exercise of the fingers, and after interrupted repetitive exercise of the fingers. When matched against a similar aged nondiabetic group, the diabetics had slightly higher forearm vascular resistance at each level of exercise, a marked reduction (~ 50 per cent) in capillary filtration coefficient, which is believed to be related to vascular filtering surface area, and a slight reduction in venous capacitance at all levels of exercise. The method of mercury-in-rubber strain gauge venous occlusion plethysmography provides the clinician with a sensitive and inexpensive tool with which to follow the evolution of angiopathy in diabetic patients. DIABETES *27*:726-31, July, 1978.

In the 113 years since Marchal de Calvi theorized diabetic gangrene to be a disorder of the circulation,[1] there are today no standard methods for evaluating microcirculatory function in the routine office practice of diabetic patient management. At best the consequences of microcirculatory dysfunction are assessed by measuring compositional changes in blood, histologic changes in organs, or biochemical changes in tissue—but the nature of the actual disorder of the microcirculation itself remains obscure owing to lack of simple and inexpensive methodology. The inadequacy of current methods for evaluating the vasculopathy in vivo is itself partly responsible for the enigma of the relationship between insulin therapy, blood sugar, and time to the progress of the disease.[2]

Basic microcirculatory research has recently developed or refined at least three powerful tools with great potential for elucidating the natural history of diabetic angiopathy: intravital microscopy,[3] tracer washout techniques,[4-6] and mercury-in-rubber strain gauge plethysmography.[7,8] In this report we summarize our use of the latter and most widely applicable technique in assessing vascular behavior in a group of middle-aged adult-onset diabetics. The results provide new information about diabetic circulatory function and furthermore provide a simple and inexpensive standardized set of exercise tests that can be used in the practitioner's office to evaluate and follow human peripheral circulatory function.

MATERIALS AND METHODS

The techniques and their justifications have been reported elsewhere;[9] however, for purposes of familiarizing clinicians with specific details of the procedures, we present them here. The patient or volunteer lies in a bed with the head and neck elevated to a 30° position in a quiet, well-lit room. A 30 cm. blood pressure cuff is wrapped around the upper arm, and a slightly stretched (about 10 per cent), mercury-in-rubber Silastic strain gauge is wrapped around the mid-forearm and held in place with nonallergenic tape. The patient's elbow rests on the bed, with the hand slightly elevated by a cushion so as to leave the

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strain gauge untouched by bedclothes. The terminals of the gauge are connected to the resistance posts of a model 270 Parks Electronics plethysmograph (Beaverton, Ore.), with the voltage across the strain gauge displayed on a K-61-Soltec multipen recorder (North Hollywood, Calif.). After balancing the strain gauge the blood pressure cuff is abruptly inflated to 40 mm.Hg by release of a valve on a connecting air storage tank. The voltage change across the gauge is traced out on a 250 mm. strip chart recorder moving at 300 mm. per minute. After about two or three minutes of recording, during which the chart speed may be decreased to 10 mm. per minute, the cuff is deflated and there is a 5 to 10 minute rest period before this procedure is repeated twice more.

For tonic finger exercise the patient is instructed to grasp a partially inflated, self-locked blood pressure cuff "as hard as possible," and the pressure is recorded. In the absence of severely debilitating illness, most patients can grip a cuff to a pressure of 120 to 250 mm.Hg. One third of the patient's maximum is calculated, and the patient is instructed to grip the cuff so that an aneroid barometer, which he can see, stays on the assigned value. Over the 90 seconds of exercise, another curve is run with a standard blood pressure measurement made before and after each run. This procedure is repeated once. In preliminary studies, we were unsuccessful at having patients perform tonic exercise at an arbitrarily assigned pressure level and, therefore, selected one third of the patient's maximal ability as a reproducible testing criterion. It should be kept in mind that the actual amount of work done in the tonic exercise varies from patient to patient.

After a five-minute rest the patient is requested to grasp the blood pressure cuff as tightly as possible and then release it at a rate of about once a second for 90 seconds or until he is too fatigued to continue. About 99 per cent of the patients are able to complete the 90-second exercise. Immediately after this exercise, the patient allows the arm to rest, and a final curve is run. This is called the interrupted repetitive exercise run. Blood pressure is simultaneously taken in the other arm.

After these procedures, the strain gauge is disconnected and calibrated by stretching it to known lengths and marking the chart in equivalent lengths of arm circumference. In general, magnification of arm changes is about 60 to 70 times. With trained assistants giving the tests, the entire procedure can be carried out in less than 20 minutes.

Calculations and Error Sources

These have been discussed in detail elsewhere.[7,8] Mean arterial pressure (MAP) is calculated as diastolic plus one-third pulse pressure and is calculated for each plethysmographic determination. The principal formulas used for computation are (refer to figure 1):

FBF (forearm blood flow in ml./min./100 gm. forearm) = (2 × early slope × calibration constant × chart speed × 100)/baseline strain gauge length,

FVR (forearm vascular resistance in mm. Hg/ml./min./100 gm. forearm) = MAP/FBF,

CFC (capillary filtration coefficient in ml./min./mm. Hg/100 gm. forearm) = (2 × late slope × calibration constant × chart speed × 100)/[(1/1.25) × 40 × baseline strain gauge length],

VC_{40} (venous capacity at 40 mm. Hg cuff pressure in ml./100 gm. forearm) = (2 × h × calibration

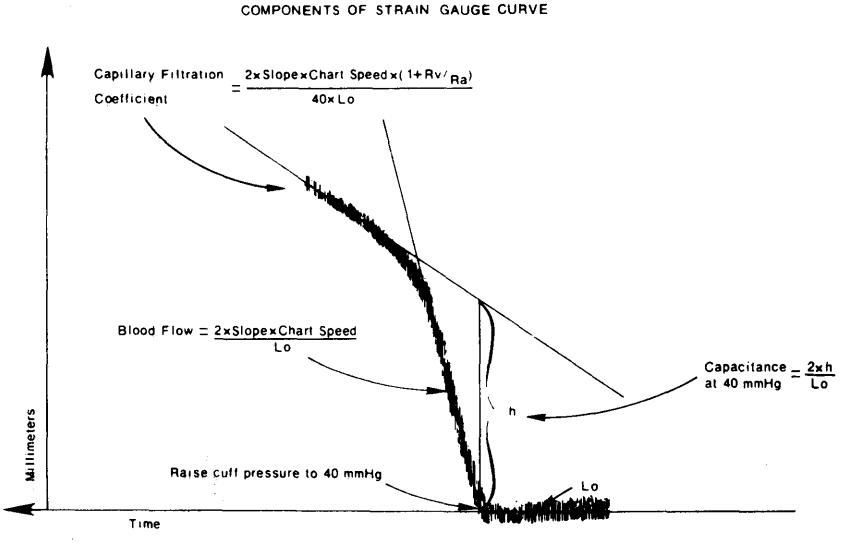

FIGURE 1

Plot of voltage drop across the mercury-in-rubber strain gauge as a function of time after an instantaneous inflation to 40 mmHg of a blood pressure cuff around the upper arm. Time axis reads from right to left. See text for details. (Reprinted with permission from *Cardiovascular Medicine*, Academic Press, 1978.

constant × 100)/baseline strain gauge length.

The factor 2 is utilized to convert a small fractional increase in arm circumference to a fractional volume increase.[8] The calculation assumes the density of the total forearm to be unity.[8] The early slope is used for forearm blood-flow calculation, because during this time the veins are "rounding up" as they receive the full amount of forearm blood flow into their storage or capacitance reservoirs. The late slope is interpreted as pure vascular filtration for reasons reviewed elsewhere.[8,10] By previous convention—one which in retrospect perhaps should be changed—the term "capillary filtration coefficient" has been used to characterize the parameter derived from the late slope, although "capillary" does not exactly correspond to the anatomic term, since some fluid flux also exists across the first order venules. It is suggested that future communications might refer to this number as vascular filtration coefficient (VFC).

Although there is no universally agreed upon method to measure venous capacity, we have selected a means that is reproducible and independent of time. The altitude h is erected from the baseline at time 0 and intersects the extrapolated filtration slope. Previous reports have used altitudes dropped from the filtration curve at arbitrary times after inflation of the cuff. We believe a time-independent capacity index is more easily reproducible than one dependent on time.

Errors in these calculations have been extensively discussed in an earlier report from this laboratory,[8] and systematic errors in the measurement of CFC are, in general, much smaller than systematic errors in most physiologic tests, amounting to about −1 per cent as the most likely error and −14 per cent as an outside limit. The tonic exercise test introduces an additional systematic error, since the baseline circumference of the forearm changes slightly, causing an error in forearm blood flow and CFC amounting to, at most, less than 1 per cent. Accordingly, the mercury-in-rubber strain gauge technique produces highly reliable and accurate results with an easily performed technique carried out with relatively inexpensive equipment.

Population Studied

Fifteen normotensive diabetic patients from the Tucson V.A. Hospital Diabetes Clinic were tested after giving their informed consent. They were all male, were not on insulin, had a mean fasting blood sugar of 190 ± 62 S.D. mg. per deciliter, and had a mean duration of diabetes of 13.0 ± 5.4 S.D. years. Three patients were being treated for hypertension but were normotensive at the time of the study. Mean serum creatinine was 1.0 ± 0.15 S.D. mg. per deciliter. One had a CO_2 content of 19 mmoles per liter, but the rest were within normal limits. Eight patients had nocturia at least once a night, five patients had mild to moderate nonproliferative diabetic retinopahy, and none had proliferative retinopathy. None had heart disease or heart failure. Ten had macrovascular peripheral disease, and two were diagnosed as having diabetic neuropathy. Four had 1 to 2+ proteinuria not quantitated further. These patients were studied plethysmographically at rest, during tonic exercise, and during interrupted repetitive exercise. Comparisons of measured values of these periods were made by two-way analysis of variance and Duncan's new multiple range test.[11]

To provide some comparison with a group of patients who might serve as a control group, we selected a previously reported series of normal elder volunteers whose characteristics are shown in table 1.[9] The groups are not strictly comparable in that sex distribution is different, and age, weight, and blood pressure are all slightly higher in the diabetic group. Upon subjecting the older group to one-way analysis of variance comparing males with females, we found no significant differences in any demographic variable except that the males were heavier than the females ($p = 0.030$). We therefore pooled the male and female population into a single group to compare with the diabetics. It should be noted that the differences arising between normal middle-aged volunteers and the diabetic groups cannot necessarily be attributed to the diabetes itself or to anatomic rather than functional changes. Results between groups were compared by use of one-way analysis of variance and Duncan's new multiple range test.

RESULTS

Table 2 is a summary of the results of the diabetic group and a comparison of the responses with the previously reported normal volunteer group of a simi-

TABLE 1

	Diabetic patients	Normal older volunteers
N	15	17
Age (yr.)	56 ± 1.1	58 ± 2.3
Weight (kg.)	70.3 ± 2.9	79.6 ± 2.8
Mean blood pressure (mm. Hg)	89 ± 2.0	96 ± 2.1

Values are means ± standard error of mean.

TABLE 2

	Diabetics n = 15	Normal volunteers n = 17	P
FVR control (mm. Hg·ml.$^{-1}$·min.·100 gm.$^{-1}$)	13.4 ± 1.9	9.2 ± 2.8	~0.05
TE	11.0 ± 1.2	8.3 ± 0.8	~0.05
IRE	3.3 ± 0.4	2.5 ± 0.2	~0.05
CFC control (ml.·min.$^{-1}$·mm.Hg^{-1}·100 gm.$^{-1}$·10^4)	56 ± 9	107 ± 15	<0.05
TE	63 ± 13	141 ± 28	<0.05
IRE	29 ± 7	32 ± 8	NS
VC_{40} control (ml.·100 gm.$^{-1}$)	1.5 ± 0.1	2.0 ± 0.2	~0.05
TE	1.6 ± 0.4	2.5 ± 0.2	~0.05
IRE	2.0 ± 0.3	2.9 ± 0.4	~0.05

TE = tonic exercise, IRE = interrupted repetitive exercise, ~ = approximately.

lar age but with a lower mean weight and a 7 mm.Hg lower mean arterial pressure.

Effects of Tonic Exercise

Tonic exercise produces no significant change in FVR, although mean FVR is slightly reduced. Variations in blood pressure were small under these conditions. Although mean CFC rises with tonic exercise in both groups, the scatter is large enough that no significant increase can be detected in these groups. Thus, the diabetic and similar age nondiabetic patients share the feature that tonic exercise under these conditions produces no striking change in FVR and CFC, or, it produces a change of such small magnitude that larger collections of patients would be necessary to demonstrate the change. This is in marked contrast to young normal patients and to similar age patients with hypertension who have been reported to show a marked reduction in FVR and a rise in CFC with tonic exercise.[9]

It is unusual in our experience for tonic exercise to produce a rise in VC_{40}, and the diabetic patients are no exception. As reported previously,[9] however, capacitance does increase in normal control patients of similar age. In summary, tonic exercise produces little alteration in plethsymographic responses of the forearm in diabetic patients or in normal, similar age volunteers.

Effects of Interrupted Repetitive Exercise

Forearm vascular resistance is dramatically reduced to about 30 per cent of its control value in both patient groups. As noted for other groups studied, not only does interrupted repetitive exercise produce no increase in CFC, but it may actually produce a decrease in CFC to one third to one half of the resting value. Finally, although there is a rise in mean VC_{40} with interrupted repetitive exercise, this is significant only for the normal group ($p < 0.01$).

Differences in Forearm Values Between Diabetic and Normal Patients

At rest the diabetic group has a higher mean FVR than the normal group, and at each level of exercise the values are slightly greater; but these differences are only of borderline significance ($p \sim 0.05$). The diabetic CFCs are considerably lower than those of the normal group during rest and tonic exercise periods, but they fall to the same mean value during interrupted repetitive exercise. Venous capacitance at 40 mmHg cuff pressure is slightly lower in the diabetic group than in the normal group at each level of exercise, but this is also of only borderline significance ($p \sim 0.05$). In general, the diabetic group is more constricted than the normals at all levels of exercise and at each anatomic level of the circulation tested including arteriolar resistance (mostly reflected in FVR), precapillary resistance (mostly reflected in CFC), and venous capacity (mostly reflected in VC_{40}).

Correlations Between Individual Values Within the Same Test

To test whether FVR, CFC, and VC_{40} are independent measures of forearm vascular function, correlation coefficients were calculated for all tests within groups. We report only those significant correlations common to both groups. Forearm vascular resistance during rest and during tonic exercise were weakly correlated (r for normals = 0.49, p = 0.023; r for diabetics = 0.58, p = 0.012). In addition, FVR during interrupted repetitive exercise negatively correlated with CFC during tonic exercise for both groups (r for normals = −0.49, p = 0.22; r for diabetics = −0.51, p = 0.026). All other correlation

coefficients either were not significantly different from zero or showed weak correlation in only one patient group. It is thus apparent that the three different values extracted from each curve are independent measures.

DISCUSSION

These studies clearly demonstrate that in adult-onset diabetes of approximately 13 years' duration, there is a large reduction in the peripheral vascular filtering area—perhaps up to 50 per cent below normal. In addition the evidence of increased resting FVR is consistent with the view that such patients have a pathologic increase in peripheral arteriolar resistance. A third reasonable deduction from the data is that, despite the frequent clinical finding of venodilation in diabetics throughout the vascular tree,[12] the functional venous capacity of the diabetic is less than that of age-matched controls. Both diabetics and nondiabetics in these middle-aged groups respond little to one-third maximum tonic exercise, which is in striking contrast to normal patients in their third decade.[9] Perhaps this indicates that at rest these older patients are already vasodilated in compensation for vascular disease in parallel vessels to the forearm. Finally, when the diabetics do repetitive exercise, it produces marked vasodilation of arteriolar vessels as in the normal group, but the vascular filtering surface does not rise. It actually decreases—a finding previously reported by us in all patient groups thus far studied.[9]

The reason that CFC and FVR become dissociated during interrupted repetitive exercise is unknown and awaits elucidation through other types of investigation. We can, however, speculate on the possibilities that might explain how FVR can decrease so drastically while CFC either does not change or may even go to zero. The first consideration is that the arteriolar dilation that causes the reduced FVR during interrupted repetitive exercise does not include the precapillary sphincter-like arterioles that control access to the capillary beds. The theory that shunt arterioles and "nutrient" arterioles are under different and independent control systems is an old one,[13,14] and recent evidence from this laboratory supports the concept that these two arteriolar systems are sensitive to different stimuli.[15] However, if this explanation is adopted for the phenomenon of dissociation of FVR from CFC by interrupted repetitive exercise, it is incompatible with the widespread belief that exercise-induced hyperemia is associated with a rise in CFC.[16,17] To date, however, all evidence that indicates CFC and FVR vary together in exercise comes from experiments in anesthetized animals during nerve stimulation without the use of standardized venous pressure to induce capillary filtration. Moreover, it is assumed in these studies that the measured increase in CFC is caused by the exercise rather than by the nerve stimulation itself—a thesis that has not been proved. In addition, the hyperbolic relationship presumed to exist between CFC and FVR in exercise[16] is one derived by visual inspection of a number of animal experiments that have not been subjected to statistical analysis. Hence, there are numerous problems in stating that the animal studies are equivalent to events occurring in interrupted repetitive exercise of the forearm of an unanesthetized human subject.

Even though the relationship between CFC and FVR after interrupted repetitive exercise is open to serious question, it may also be the current studies fail to demonstrate such an inverse relationship through some artifact or error in experimental design or theory. For example, it may be that with the decrease in FVR there is actually a rise in CFC, but the strain gauge technique cannot detect a rise because the new capillaries opened may have a lower mean pressure than the neighboring capillaries and thus produce a short circuit shunt pathway that falsely appears as a reduced CFC. A variant of this type of physiologic shunt has been suggested by Renkin in the form of recruitment of short capillaries with a high flow/permeability-surface product.[18] Other artifacts of the technique may also account for the failure to document a relationship between FVR and CFC. For example, it is possible that repetitive exercise produces such an amount of filtration that the resulting interstitial pressure rise is so high that a venous pressure elevation to 40 mm.Hg is not enough to cause further filtration. Indirect evidence from these studies mitigates against this thesis, since if this were the case, a steady baseline arm circumference would not be expected. In all our studies, there is at least a 30-second period during which a stable baseline is measured before inflating the blood pressure cuff. It is clear that further studies are necessary to determine the physiologic significance, if any, of the dissociation between FVR and CFC during interrupted repetitive exercise.

The current studies offer additional information besides the direct physiologic implications of the results. Until now, quantitative studies on diabetic angiopathy have usually been difficult to perform and

have necessitated large expenditures on equipment and trained personnel.[4-7,19] This means that, for the majority of diabetic patients being managed by clinicians who have no access to such techniques, their angiopathic disease cannot be followed except by the grossest of grading systems. The mercury-in-rubber strain gauge technique provides a simple method available to any clinician at a capital investment of about $400. The tests require about 20 minutes to execute by a trained technician and about that time to compute results with a pocket calculator. Any clinician can thus catalogue the FVR, CFC, and VC_{40} with responses to tonic exercise and interrupted repetitive exercise for each diabetic patient as a function of time and therapy. Each patient serves as his own control, with serial measurements used to follow and possibly influence the progression of this incapacitating disease.

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REFERENCES

[1]de Calvi, M.: Recherches sur les accidents diabétiques et essai d'une théorie générale du diabète. Paris, P. Asselin, Successeur de Bechet Jne et Labe, 1864, p. 108.

[2]Wells, R.: The microcirculation in diabetes mellitus. *In* The Microcirculation in Clinical Medicine. Roe Wells, Ed. New York, Academic Press, 1973, pp. 47-59.

[3]Wayland, H.: Intravital microscopy. Advances in optical and electron microscopy. Vol. 6. R. Barer and V. E. Cosslett, Eds. New York, Academic Press, 1975, pp. 1-47.

[4]Lassen, N. A., Lindbjerg, J., and Munck, O.: Measurement of blood-flow through skeletal muscle by intramuscular injection of xenon-133. Lancet *1*:686-89, 1964.

[5]Gosselin, R. E., and Stibitz, G. R.: Rates of absorption from tissue depots. Pflügers Arch. Eur. J. Physiol. *318*:85-98, 1970.

[6]Trap-Jensen, J., and Lassen, N. A.: Increased capillary diffusion capacity for small ions in skeletal muscle in long-term diabetics. Scand. J. Clin. Lab. Invest. *21*:116-22, 1968.

[7]Alpert, J. S., Coffman, J. D., Balodimos, M. C., Koncz, L., and Soeldner, J. S.: Capillary permeability and blood flow in skeletal muscle of patients with diabetes mellitus and genetic prediabetes. N. Engl. J. Med. *286*:454-60, 1972.

[8]Katz, M. A.: Capillary filtration measurement by strain gauge. Analysis of methods. Am. J. Physiol. *232*:H354-60, 1977.

[9]Katz, M. A., and Janjan, N.: Forearm hemodynamics in normal, young, and elder volunteers, untreated and treated hypertensives. Cardiovascular Medicine *3*:317-27, 1978.

[10]Johnson, P. C., and Hanson, K. M.: Capillary filtration in the small intestine of the dog. Circ. Res. *19*:766-73, 1966.

[11]Steele, R. G. D., and Torrie, J. H.: Principles and Procedures of Statistics. New York, McGraw, 1960, pp. 107-09.

[12]McMillan, D. E.: Deterioration of the microcirculation in diabetes. Diabetes *24*:944-57, 1975.

[13]Krogh, A.: Anatomy and Physiology of Capillaries. New Haven, Yale University Press, 1930, pp. 252-54.

[14]Hyman, C.: Independent control of nutritional and shunt circulation. Microvasc. Res. *3*:87-94, 1971.

[15]Katz, M. A.: Dissociation of acetylcholine induced responses of arteriolar resistance vessels and precapillary sphincter-like arterioles. Microvasc. Res. 1978, in press.

[16]Kjellmer, I.: The effect of exercise on the vascular bed of skeletal muscle. Acta Physiol. Scand. *62*:18-30, 1964.

[17]Folkow, B., and Halicka, H. D.: A comparison between "red" and "white" muscle with respect to blood supply, capillary surface area and oxygen uptake during rest and exercise. Microvasc. Res. *1*:1-14, 1968.

[18]Renkin, E.: Transcapillary exchange in relation to capillary circulation. J. Gen. Physiol. *52* (Pt. 2):96s-108s, 1968.

[19]Spetz, D.: Peripheral circulation in pregnancy complicated by diabetes mellitus. Acta Obstet. Gynecol. Scand. *44* (Suppl. 1):1-20, 1965.