Blood Pressure and Hematocrit in Diabetes and the Role of Endothelial Responses in the Variability of Blood Viscosity

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OBJECTIVE — To investigate the relationship between mean arterial blood pressure and hematocrit in a population of treated diabetic patients and a control population of healthy individuals.

RESEARCH DESIGN AND METHODS — Data on hematocrit and blood pressure were obtained from 129 diabetic subjects (87 women and 42 men) and 103 healthy subjects (76 women and 27 men) enrolled in a cross-sectional study. Alcohol consumption, ischemic heart disease, stroke, neoplasia, renal, hepatic, and chronic inflammatory disease were exclusion criteria.

RESULTS — The hematocrit of diabetic patients ranged from 0.35 to 0.52, and blood pressure had a bimodal distribution described by a second-order polynomial ($P < 0.001$), whereby elevated pressures correlated with low and high hematocrit, while the minimum average pressure was at hematocrit 0.43. Hematocrit of normal control subjects (range 0.28–0.55) was uncorrelated to blood pressure (averaged 99.7 ± 9.7 mmHg). High blood pressure, low hematocrit diabetic subjects up to the minimum average hematocrit of 0.43 had a negative correlation ($P < 0.0001$) between these variables.

CONCLUSIONS — Our findings are compatible with the hypothesis that diabetic patients present normal responses to hematocrit variation and therefore blood viscosity and shear stress in mediating the release of vasodilators and lack the ability to autoregulate blood pressure relative to differences in hematocrit by comparison to nondiabetic subjects. These findings also suggest that the treatment of diabetes should target maintaining an optimal hematocrit in order to lower cardiovascular risk.

Diabetes Care 29:1523–1528, 2006

Diabetes is a multifactorial disease that affects cardiovascular regulation via metabolic dysfunctions. The cellular bases of these processes resides in the inability of pancreatic cells to produce insulin and/or by defects in insulin action, processes that per se do not necessarily compromise cardiovascular regulation. However, hypertension is a usual outcome of diabetes. The causes for hypertension are also multifactorial, with its functional basis residing in the increase in peripheral vascular resistance, primarily determined by arterial vessel tone and secondarily by blood viscosity. Blood viscosity takes second place in the analysis of factors leading to hypertension when compared with the effect of vessel tone, since changes in vessel diameter affect peripheral vascular resistance according to Poiseuille's law in proportion to the fourth power of the diameter change, while changes due to blood viscosity are linearly related.

Clinical findings support the contention that pathologically high hematocrit causes complications and indicates the existence of a direct relationship between hypertension and high hematocrit and blood viscosity in normal and hypertensive individuals (1,2), being generally indicated that hypertensive patients have higher hematocrit than normotensive control individuals (3). Increasing blood viscosity by increasing hematocrit or other mechanisms is considered to be potentially pathological as shown by the study of Danesh et al. (4), who found that high hematocrit increases cardiovascular risk. It should be noted that the Framingham Heart Study (5) found that anemia may also be an independent risk factor for cardiovascular disease.

Systemic changes in hematocrit should be a common occurrence in the treatment of hypertension by diuretics since they reduce plasma volume, leading to hemoconcentration and increased whole-blood viscosity (6); thus, increasing hematocrit is not universally associated with pathological outcomes. As an example, the study of De Simone et al. (7) showed that systolic blood pressure and whole-blood viscosity had a negative relationship in Indian Americans participating in the Strong Heart Study who presented higher pulse pressure in combination with lower whole-blood viscosity and hematocrit ($P < 0.01$). Martini et al. (8) produced small acute increases in systemic hematocrit in awake hamsters and found that mean arterial blood pressure (MAP) was lowered.

A critical issue is that variations in hematocrit and therefore blood viscosity change shear stress on the endothelium and, therefore, the production of vasoactive materials such as nitric oxide (NO), prostacyclin, and endothelin, which have a direct effect on microvascular diameter. Therefore, changes in blood viscosity are potentially powerful mediators of peripheral vascular resistance. The relationship between blood viscosity and MAP was shown to be mediated by NO production by Martini et al. (8), who found significantly elevated plasma NO concentrations in animals pretreated with the NO synthase inhibitor L-N^G-nitro-L-arginine methyl ester compared with untreated an-

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Received for publication 8 February 2006 and accepted in revised form 14 April 2006.

Abbreviations: MAP, mean arterial blood pressure; SNP, sodium nitropruside.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0323

imals. In the same study, hematocrit augmentation in endothelial NO synthase knockout mice that do not produce NO via endothelial NO synthase did not cause vasodilatation; thus, the link between hematocrit, blood viscosity, shear stress, and the regulation of MAP is well established. Hemoglobin is a scavenger of NO; therefore, increased hematocrit should in principle compete with vasodilation due to increased shear stress, but this effect did not appear to be significant in the experiments of Martini et al. (8).

The healthy population presents a range of hematocrit due to environmental adaptation, diet, and genetic predisposition; therefore, endothelial responses to the potentially changed shear stress should be a factor in autoregulating MAP with the result that in healthy individuals MAP should be essentially independent of moderate changes in hematocrit. Conversely, Natali et al. (9) showed that hematocrit is inversely related to small-vessel endothelial-dependent dilatation (and therefore to endothelial viability) by comparing the responses to the injection of acethylcholine and sodium nitroprusside (SNP) in the forearm of a diabetic and a control nondiabetic population. Given these precedents, we hypothesize that a population that presents endothelial dysfunction should be less capable of compensating for the natural variability in hematocrit and therefore show a correlation between MAP and hematocrit. To test this hypothesis, we studied MAP and hematocrit in diabetic patients and compared this population with healthy control subjects.

RESEARCH DESIGN AND METHODS

— A cross-sectional study was performed to compare the relationship between hematocrit and MAP in 129 subjects (87 women and 42 men) with previous diagnosis of type 2 diabetes and a control group of 103 healthy subjects (76 women and 27 men). Protocol approval was obtained from the Mexican Social Security Institute research committee, and informed consent was provided by each individual.

Exclusion criteria included alcohol consumption ≥30 g/week (10), smoking, ischemic heart disease, stroke, neoplasia, and renal, hepatic, and chronic inflammatory disease. Blood pressure was measured in subsequent days, in accordance with the Sixth Joint National Committee recommendation (11).

Previously diagnosed diabetic patients that had undergone treatment for a minimum period of 8 years were enrolled from the First Medical Care Level Offices of the Mexican Social Security Institute in Durango, Mexico. The average glycemia for these patients was 213 ± 99 mg/dl. Diabetic patients ($n = 187$) were screened for hypertension and were included in the study if systolic blood pressure was ≤130 mmHg and/or diastolic blood pressure was ≤85 mmHg. Fifty-eight patients (31.0%) were not included because they did not fulfill the inclusion-exclusion criteria, and a total of 129 diabetic patients were enrolled.

Healthy subjects randomly selected from a middle-income neighborhood in Durango, Mexico, who were aged ≥35 years and not hypertensive (MAP <130/85 mmHg), without exclusion due to height or weight, were allocated to the control group ($n = 103$). All participants in the control group were required to be in good health. For this purpose, detailed medical history and complete physical examinations were obtained. Patients were considered to have diabetes if glucose levels were >126 mg/dl when fasting and were excluded from the control group. Blood samples (3 ml) were drawn from the antecubital vein 8–10 h after fasting and collected in EDTA anticoagulated tubes for hematocrit measurements. Hematocrit was measured using a microhematocrit centrifuge (13,000*g* for 3 min at 20°C, Sol-Bat Centrifuge M-600; Readacrit, Mexico City, Mexico). Three-milliliter blood samples were taken in tubes without anticoagulants for glucose measurements. Systolic and diastolic blood pressure were recorded and MAP was determined using the following relationship: $MAP = P_{diastolic} + 1/3(P_{systolic} - P_{diastolic})$.

Statistical analysis

Differences between groups were assessed using unpaired Student's *t* test or χ^2 test. Pearson's analysis was performed to examine the correlation between blood pressure and hematocrit. For the purpose of statistical analysis, all the skewed numerical data were transformed by log *n* to obtain a symmetrical distribution. Data were analyzed using the statistical package SPSS 12.0 (SPSS, Chicago, IL). A 95% CI was considered, and a *P* value <0.05 defined the level of statistical significance.

RESULTS

— The study comprised 103 healthy control subjects. This population had average hematocrit of 0.425 ± 0.050 (range 0.28–0.55). MAP presented a random Gaussian distribution characterized by 99.4 ± 9.7 mmHg (average ± SD) (range 2–120). The plot of pressure versus hematocrit for this population shown in Fig. 1*A* was fitted to a second-order polynomial curve whose lowest MAP was 86 mmHg at hematocrit 0.32–0.34 and which increased to 97 mmHg at hematocrit 0.55. The correlation coefficient for this trend was $R^2 = 0.04$ and was not statistically significant ($P > 0.5$).

Analysis of the results using data obtained in 129 diabetic patients were fitted to a second-order polynomial and showed a similar trend as control subjects; however, the effects were more pronounced and had statistical significance ($R^2 = 0.44$, $P < 0.001$). Figure 1*B* shows that diabetic patients presented a somewhat smaller range (0.35–0.52) in hematocrit than control subjects. MAP had the lowest average value at hematocrit 0.42, where it was 81 mmHg, and it increased to 140 mmHg at hematocrit 0.52, the difference with control subjects being statistically significant.

Diabetic individuals were older than healthy control individuals (52.3 ± 6.6 vs. 44.1 ± 10.5 years, $P < 0.001$). Duration of diabetes and HbA_{1c} was 12.4 ± 5.2 years and 9.3 ± 2.5%, respectively. Thirty-seven (28.7%) diabetic subjects had hypertension and a duration of 1.4 ± 3.7 years of hypertensive disease. As expected, diabetic individuals showed higher systolic and diastolic blood pressure (125.5 ± 19.3/76.4 ± 13.1 vs. 121.1 ± 12.9/73.2 ± 7.4 mmHg, $P = 0.03$), fasting glucose (213.7 ± 99.7 vs. 98.8 ± 16.2 mg/dl, $P < 0.0001$), total cholesterol (248.7 ± 57.0 vs. 195.1 ± 56.2 mg/dl, $P < 0.0001$), LDL cholesterol (162.1 ± 52.9 vs. 128.4 ± 50.0 mg/dl, $P < 0.0001$), and triglycerides (222.9 ± 139.6 vs. 174.9 ± 109.1 mg/dl, $P = 0.01$) and lower HDL cholesterol (42.4 ± 10.4 vs. 37.5 ± 11.2, $P = 0.008$) than healthy control subjects. There were no significant differences in hematocrit (0.43 ± 0.04 vs. 0.43 ± 0.05, $P = 0.33$) or creatinine levels (1.2 ± 0.4 vs. 1.1 ± 0.4 mg/dl, $P = 0.06$) between diabetic and control groups, respectively.

CONCLUSIONS

— The principal finding of this study is that while the distribution of MAP in healthy control subjects appears to be essentially independent from hematocrit, treated diabetic patients present a bimodal distribution, with a minimum blood pressure at a he-

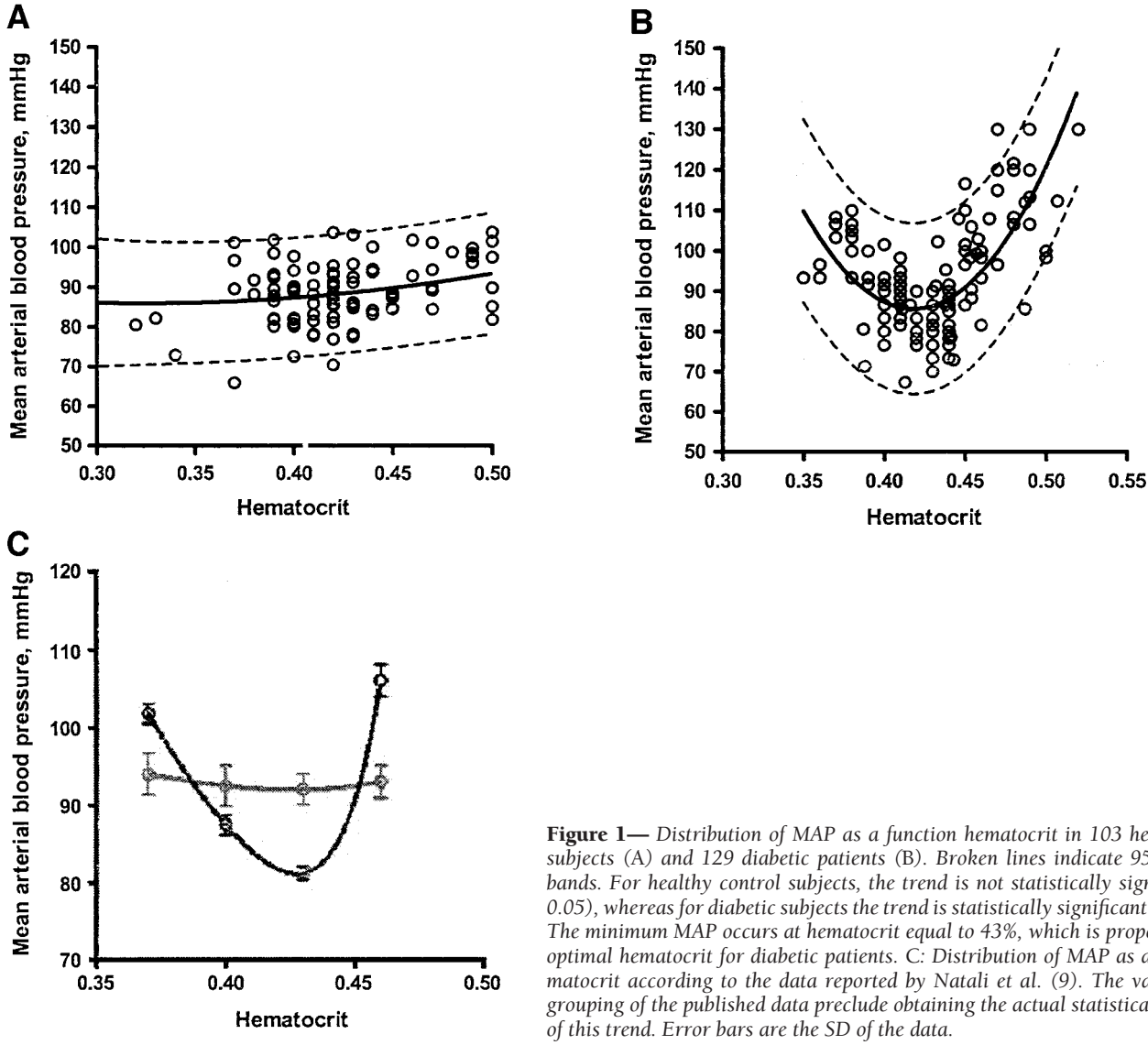

Figure 1— *Distribution of MAP as a function hematocrit in 103 healthy control subjects* (A) *and 129 diabetic patients* (B). *Broken lines indicate 95% prediction bands. For healthy control subjects, the trend is not statistically significant* ($P < 0.05$), *whereas for diabetic subjects the trend is statistically significant* ($P < 0.001$). *The minimum MAP occurs at hematocrit equal to 43%, which is proposed to be the optimal hematocrit for diabetic patients. C: Distribution of MAP as a function hematocrit according to the data reported by Natali et al. (9). The variability and grouping of the published data preclude obtaining the actual statistical significance of this trend. Error bars are the SD of the data.*

matocrit between the minimum and maximum found in the population (Fig. 1*B*), a trend that is statistically significant. A similar but weaker trend can be seen in the data of Natali et al. (9), although these authors did not analyze the correlation between blood pressure and hematocrit for their dataset (Fig. 1*C*).

The control population showed a weak trend, whereby MAP slightly increased with hematocrit as found in previous studies by Smith et al. (12) and Fowkes et al. (13). The lack of pronounced effects on blood pressure due the variation of hematocrit in normal individuals should be attributable to the ability of circulation to compensate for the changes in blood viscosity consequent to the variability of hematocrit and therefore shear stress by varying the production of NO, thus modulating vasodilatation. Presumably, when hematocrit is below normal, shear stress is decreased, lowering NO production and causing vasoconstriction, which is compensated by the lowered blood viscosity. Considering that these effects would be superposed to those of baroreceptors and other mechanisms that regulate blood pressure, it is not surprising that normal individuals do not show a relationship between blood pressure and hematocrit.

Diabetic subjects present pronounced changes in MAP as a function of hematocrit when compared with control subjects. MAP lowers significantly as hematocrit increases in the low hematocrit range, a trend also found by Martini et al. (8), when hematocrit was changed acutely in experimental animals. In the case of Martini et al., the blood pressure response could be directly linked to the production of NO by the endothelium and therefore presumably the changes in shear stress in the circulation. The present study is cross sectional and does not represent the response to a change in hematocrit but rather how blood pressure correlates with the hematocrit in individuals; thus, it is a condition frozen in time for individuals who present a given hematocrit. Conversely, Martini et al. (8) found statistical significance comparing changes in MAP versus changes in hematocrit induced by exchange transfusion or erythrocytes. However, in both the Martini et al. study and the present study, independent and dependent variables are the same; thus, the similarity of responses suggests that the same NO-based mechanisms are involved.

It is generally accepted that diabetes presents decreased formation of vasodila-

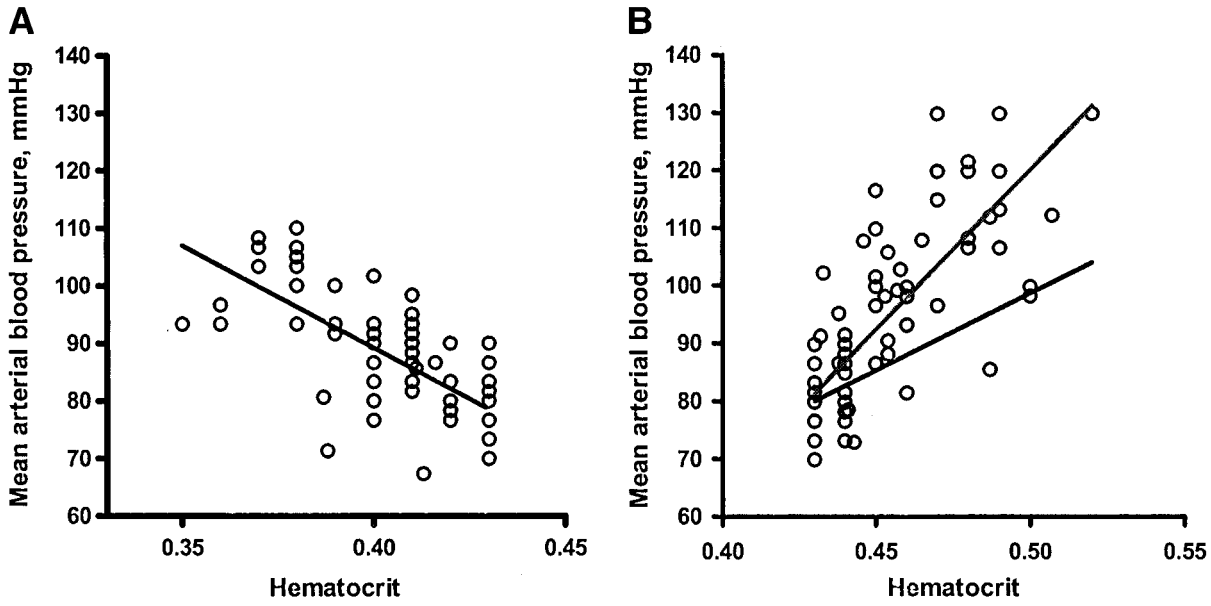

Figure 2—A: *Distribution of MAP as a function of hematocrit for patients with low hematocrit up to optimal hematocrit shown in Fig. 1*B. *The correlation of the data are statistically significant* (n = *56,* P < *0.0001).* B: *Distribution of MAP as a function of hematocrit for patients with hematocrit in the optimal hematocrit range and higher (upper line). The correlation of the data are statistically significant* (n = *69,* P < *0.0001). The black solid line shows the trend of MAP if blood viscosity changes due to the hematocrit increase were the only factor affecting MAP. Blood viscosity data are approximately linear in this range of hematocrit according to Simchon et al. (18).*

tors such as NO and prostacyclin and increased formation of vasoconstrictor eicosanoids (14). This concept is well established in the literature since the study of Calver et al. (15), who found that diabetic patients presented reduced forearm blood flow responses to locally infused N^G-monomethyl-L-arginine and SNP. Natali et al. (9) recently confirmed these findings. However, this interpretation may not be unequivocally certain since these responses can also be due to increased NO synthesis, requiring increased dosages of N^G-monomethyl-L-arginine to cause the expected reductions in responses, a concept that was acknowledged by Calver et al. (15). Although some studies indicate that diabetes implicates a lowering of NO availability, there is evidence to the contrary. As an example, Cosentino et al. (16) showed that high glucose levels increase NO synthase expression and superoxide anion generation in human aortic endothelial cells, and Chiarelli et al. (17) implicated increased NO availability in young patients with type 1 diabetes.

Our results suggest that endothelial responses to shear stress remain unaltered in diabetic patients and that the lack of regulation of blood pressure versus hematocrit is unrelated to the inhibition of NO production, and therefore it is due to nonendothelial mechanisms of blood pressure autoregulation. We propose this hypothesis in view that normal individuals regulate blood pressure independently of hematocrit, while diabetic patients present a steep reduction in blood pressure in the hematocrit range of 0.35–0.43. As in the study of Martini et al. (8), this highly significant reduction of blood pressure corresponding to increased hematocrit (Fig. 2*A*) can be explained by a reduction in peripheral vascular resistance due to increased viscosity-dependant vasodilation mediated by the release of vasodilators and principally NO by the endothelium.

The low hematocrit associated with hypertension found in the present study may also be related to the impairment of renal function in diabetic patients, leading to decreased stimuli for the production of erythrocytes and anemia. This conjecture is in part supported by the finding that five patients (9%) in the low-hematocrit group (Fig. 2*A*) had creatinine levels ≥1.5 mg/dl, the threshold for renal insufficiency.

The results found for the increase in blood pressure in patients whose hematocrit is >0.43 should reflect the condition in which vasodilation is no longer able to counteract the increase in vascular resistance due to increased blood viscosity. Figure 2*B* shows the increase in blood pressure as function of hematocrit, starting from the hematocrit corresponding to the minimum blood pressure. These data can be fitted by a straight line, and the correlation is statistically significant. Assuming that the change in MAP reflects the increase in peripheral vascular resistance due to increased blood viscosity, we can estimate the corresponding change in blood pressure from existing data relating hematocrit and blood viscosity (18). This relationship is approximately linear for the range of hematocrit under consideration and is shown in Fig. 2*B*. It is notable that the blood pressure increase is greater than that attributable to blood viscosity only, indicating that there may be additional hematocrit-related parameters influencing blood pressure in diabetic patients.

These findings raise the broader question whether acethylcholine and SNP tests of endothelial function do in fact expose the ability of the endothelium to respond to mechano transduction and the shear stress environment of the endothelium. An alternative explanation is that these patients present an inherently smaller capacity to vasodilate in response to NO-related stimuli.

Our study and those of Martini et al. (8) show that the concept that hematocrit is related to small–blood vessel endothelial-dependent dilatation is applicable to a specific range of hematocrit. Outside of

this range, the increase in hematocrit increases blood pressure, suggesting that there may be an "optimal hematocrit" particularly in the case of diabetic patients. In general, hematocrit has a strong influence on the efficiency of cardiovascular function. Anemia impairs oxygen delivery, and chronic anemia can cause increased cardiac output and severe cardiac pathology (19). Conversely, polycythemia hinders oxygen transport because of the increase in whole-blood viscosity. Conditions associated with high hematocrits such as polycythemia vera or adaptation to high altitudes are reported to increase MAP and to decrease cardiac output due to a viscosity-dependant increase in vascular resistance (20,21). In conditions of a compromised circulatory system, where vessel walls have lost their elasticity due to atherosclerotic lesions and their response to vasoactive mediators is reduced, high hematocrit values may further impair organ perfusion. Many studies show that high hematocrits are related to coronary heart disease (22). The concept of optimal hematocrit also relates to cardiovascular morbidity and mortality. Gagnon et al. (23) analyzed 5,209 men and women who were followed for 34 years for the development of cardiovascular diseases and found J- or U-shaped relationships between hematocrit and cardiovascular disease, whereby the optimal hematocrit for women was 0.42–0.43 and for men 0.45–0.46, where lower and higher hematocrit groups showed increased occurrence of cardiovascular disease.

Diabetic patients present increased plasma and blood viscosity, which most reports on the normal population show to be related to the increase of blood pressure. In our study, we measured hematocrit, which is closely correlated to blood viscosity but gives no indication of the changes in plasma viscosity. This was shown by Koenig et al. (24) to be positively correlated to blood pressure, whereby an increase of 0.1 cp corresponds to an uncorrected increase of systolic blood pressure of 6.5 mmHg in men (plasma viscosity range 1.16–1.37 cp) and 7.5 mmHg in women (plasma viscosity range 1.15–1.35 cp). Correction of these results for confounding factors such as cholesterol levels, age, BMI, and total serum protein reduced this effect to the range of 1.37–1.79 mmHg of blood pressure increase per 0.1-cp plasma viscosity increase. Similarly, Junker et al. (25) found that the severity of coronary heart disease is associated to a difference between 1.141 and 1.162 cp or a 1.8% increase in plasma viscosity, a finding that does not appear to be a hemodynamically significant cause in determining risk.

The elevation of plasma viscosity found to be a risk factor in diabetes and cardiovascular disease is small in absolute value when compared with the changes in blood viscosity determined by the variation of hematocrit found in the present study, which is of the order of 1 cp for both the increase of hematocrit up from the optimal hematocrit (proposed in this study) and an additional 1.0 cp for the low hematocrit range. These changes, when related to the actual blood viscosity, are of the order of 25% and should affect peripheral vascular resistance and blood pressure accordingly, as found for increased hematocrit beyond the optimal hematocrit. Surprisingly, blood pressure and peripheral vascular resistance fall in the range up to the optimal hematocrit, suggesting that a mechanism that overwhelms the viscosity component in setting vascular resistance is operational. By comparison, the changes in plasma viscosity related to increased risk are globally ~5% of blood viscosity or 2.5% for hematocrit up to and from the optimal 1, thus an order of magnitude smaller effect. These considerations suggest that the increase of plasma viscosity associated with the incidence of diabetes as well as hypertension may be a consequence of the disease process rather than a cause.

Our findings suggest that the diabetic patient population has an optimal hematocrit that is associated with a minimal blood pressure. Since hypertension is a risk factor in diabetes, these findings suggest that the control of hematocrit may be an additional factor in the treatment of diabetes, since this could lead to a decrease in the development of hypertension-related complications.

In conclusion, in the present study we related blood pressure to hematocrit in normal control subjects and diabetic patients and found that the latter presents a U-shaped correlation between these variables that is significant. We suppose that the variability in hematocrit is independent from the underlying disease condition. Therefore, naturally occurring changes in hematocrit allow the determination of whether diabetic patients present changes in the endothelial responses to shear stress, a determining factor for the production of endothelial-derived materials. Given the strong negative correlation between MAP and hematocrit up to a specific hematocrit value, we propose that an explanation of this finding is the presence of normal endothelial responses to differences in the shear stress environment of the circulation determined by the different hematocrits. Alternately or concomitantly, anemia may be the result of impaired kidney function, which is a factor associated with hypertension. Therefore, while diabetes may be associated with endothelial dysfuction in terms of the vascular responses to acethylcholine and SNP, the responses to the mechanotransduction environment appear to be unaltered. Consequently, we propose that the trend shows that diabetic patients lack the regulatory mechanism that renders MAP independent of hematocrit in normal subjects. Finally, our findings suggest that diabetic patients should strive to attain an optimal hematocrit in order to diminish cardiovascular risk factors.

Acknowledgments— This research was conducted with the financial support from U.S. Public Health Service Commissioned Corps Grants R01-HL62354 and R01-HL62318 (to M.I). M.I. is a member of the Board of Directors of La Jolla Bioengineering Institute. Also, this work was supported by grants from the Research Fund of Durango's State-National Science and Technology Council of Mexico (FOMIX Dgo-2002-C01-3760), the Research Promotion Fund of the Mexican Social Security Institute (FP 2002/366), and the Mexican Social Security Institute Foundation Civil Association.

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