Original Research

Hypertension and Triglyceride Catabolism: Implications for the Hemodynamic Model of the Metabolic Syndrome

Robert D. Brook, MD, Lynn Glazewski, RD, Sanjay Rajagopalan, MD, and Robert L. Bard, MA

Division of Hypertension, University of Michigan, Ann Arbor, Michigan

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Objective: We sought to determine if hypertensive adults have a blunted triglyceride catabolic rate (TG K_2) and if related hemodynamic and vascular alterations are determinants of TG K_2.

Methods: Fasting levels of insulin, glucose, lipoproteins and plasma catecholamines were measured in 10 normotensive and 10 hypertensive adults. TG K_2 was determined by an intravenous fat tolerance test. Forearm blood flow, maximum forearm blood flow and minimal forearm vascular resistance were determined by strain gauge plethysmography. Vascular compliance and systemic hemodynamics were measured by computerized arterial pulse waveform analysis.

Results: Compared to normotensives, hypertensives had a significantly elevated blood pressure (145 ± 8/94 ± 11 *versus* 111 ± 15/74 ± 14 mm Hg, $p < 0.001$), systemic vascular resistance (1695 ± 441 *versus* 1172 ± 430 dynes × sec × cm^{-5}, $p = 0.02$) and reduced large vessel compliance (11.7 ± 3.6 *versus* 15.1 ± 3.1 ml/mm Hg × 100, $p = 0.04$). There were no significant group differences in TG K_2 (3.07 ± 2.01 *versus* 2.88 ± 2.12 mg/dL/min, $p = 0.85$) or other metabolic and anthropometric variables. TG K_2 was not predicted by the forearm vascular measures or the hemodynamic variables, but was correlated to waist/hip ratio ($r = -0.71$, $p = 0.001$), fasting triglycerides ($r = -0.64$, $p = 0.003$), and male gender ($r = 0.56$, $p = 0.012$). An enhanced TG K_2 was independently predicted by a reduced small vessel compliance ($r = -0.61$, $p = 0.006$).

Conclusions: Elevated blood pressure *per se* and hypertension-related hemodynamic and vascular alterations are not associated with reduced TG K_2 or other metabolic abnormalities. Rather, aspects of the insulin resistance syndrome are closely related to abdominal adiposity. The independent association between small vessel compliance and TG K_2 deserves further investigation.

INTRODUCTION

Essential hypertension is often associated with multiple metabolic abnormalities including glucose intolerance, hypertriglyceridemia and enhanced postprandial lipemia [1,2]. A hemodynamic model linking insulin resistance and hypertension has been proposed as a mechanism explaining this relationship [3]. While some experiments support this hypothesis [4–6], others do not [7–9]. Recently the hemodynamic model was challenged by the demonstration of a disassociation between insulin-mediated vasodilatation and glucose disposal [10]. Furthermore, the majority of the metabolic abnormalities may be produced by the prevalence of abdominal adiposity [11]. Subtle and often unrecognized differences in body fat distribution impact insulin sensitivity and lipoproteins, even at identical levels of body mass index [11].

We sought to test the hypothesis that hypertension-related hemodynamic and vascular alterations play a direct pathophysiologic role in producing the dyslipidemia associated with hypertension. While previous experiments have focused on impaired glucose uptake, we hypothesized that the hemodynamic model may also apply to lipoprotein metabolism.

Triglycerides (TG) are catabolized in the circulation at both muscle cells and adipocytes by endothelial-bound lipoprotein

Address correspondence to: Robert D. Brook, M.D., 3918 Taubman Center, 1500 East Medical Center Dr., Ann Arbor, MI 48104. E-mail: Robdbrok@groupwise.umich.edu

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Abbreviations: CAPWA = computerized arterial compliance waveform analyzer, IVFTT = intravenous fat tolerance test, TG = triglycerides, TG K_2 = triglyceride catabolic rate.

lipase. Lipoprotein lipase activity is an important determinant of triglyceride catabolic rate (TG K_2), postprandial lipemia and, ultimately, fasting TG level [12,13]. As lipoprotein lipase is expressed at the vascular lumen surface, its activity is diminished with decreased microvascular density [14]. Therefore, vascular rarefraction common to essential hypertension [15] may be directly responsible for impairing TG K_2 and producing the cardiovascular risk factors of hypertriglyceridemia and enhanced postprandial lipemia [16,17]. This concept is supported by the improvement in both insulin sensitivity and TG K_2 following treatment with vasodilators such as α-blockers [18]. We sought to determine if hypertensive adults, with similar levels of obesity and fat distribution, have a reduced TG K_2 compared to normotensive control subjects. In this manner, the indirect and direct effect of high blood pressure *per se* on TG K_2 was evaluated. The independent impacts of hemodynamic and vascular alterations on TG K_2 were analyzed.

MATERIALS AND METHODS

Ten hypertensive and ten normotensive adults were studied in the General Clinical Research Center at the University of Michigan. The University of Michigan Institutional Review Board approved the protocol and written informed consent was obtained from each subject.

All subjects were without known cardiovascular disease and had no history of diabetes mellitus, dyslipidemia, current tobacco smoking or family history of premature heart disease. Subjects were excluded if they had abnormal laboratory values of thyroid stimulating hormone, fasting glucose $\geq$ 126 mg/dL, TG $\geq$ 400 mg/dL or total cholesterol $\geq$ 240 mg/dL. No subject was taking medications known to alter TG K_2, such as oral hypoglycemics, decongestants, sympathomimetics or lipid-lowering medications. Hypertensive subjects had a prior history of essential hypertension and discontinued all blood pressure medications for at least two weeks prior to the experiment. Control subjects were without previous history of hypertension and were otherwise healthy.

A brief history and physical exam were conducted, including exercise and dietary history, determination of body mass index, waist/hip ratio and body composition by bioelectrical impedance. All subjects were fasting $\geq$10 hours prior to undergoing an intravenous fat tolerance test (IVFTT), brachial plethysmography, and computerized arterial pulse waveform analysis (CAPWA).

IVFTT

TG K_2 was determined by a similar technique to that described by Rosser [19]. An intravenous catheter was placed in each brachial vein. After 30 minutes of supine rest, blood was drawn via one catheter for fasting insulin, glucose, lipoproteins, catecholamines and a baseline glycerol-blanked TG value. One mL of 10% Liposyn® (Abbott Laboratories, Abbot Park, IL) intravenous dietary fat solution was given per kg of body weight as a 1 mL/second bolus via one of the catheters. Blood was drawn for glycerol-blanked TG from the opposite catheter every five minutes for a total of 40 minutes. A glycerol-blanked TG determination was used for the IVFTT because Liposyn contains free glycerol.

Plethysmography

Forearm blood flow was measured by venous occlusion plethysmography using a mercury-in-silastic strain gauge (D.E. Hokanson Incorporated, Bellevue, WA). Each patient rested in a supine position for 10 minutes in a temperature controlled room. A pediatric cuff was placed on the wrist of the non-dominant arm, and the strain gauge was placed around the largest diameter of the same forearm. A blood pressure cuff connected to a rapid cuff inflator was placed around the ipsilateral upper arm. The forearm was held stable in a support device at a 45 degree angle from supine. The wrist cuff was inflated to 200 mm Hg for 60 seconds to isolate the forearm vasculature. Afterward, the upper arm cuff was rapidly inflated to 50 mm Hg to prevent the return of venous blood. As arterial blood continues to flow into the forearm, the increase in forearm diameter was recorded graphically by the plethysmograph as an increase in diameter *versus* time. The upper cuff was rapidly deflated and the process was repeated three times. Baseline forearm blood flow was calculated as the average slope of the three graphs and expressed in mm flow/(100 mL tissue) (min).

Maximum forearm blood flow was measured as above immediately following 10 minutes of forearm ischemia, produced by upper arm cuff occlusion at 200 mm Hg. The wrist cuff was inflated to 200 mm Hg at the ninth minute of upper cuff occlusion. Maximum forearm blood flow was calculated by the same method as baseline forearm blood flow. Minimum forearm vascular resistance was calculated as mean arterial pressure/maximum forearm blood flow. Blood pressure was measured on the contralateral arm after the 10 minutes of ischemia.

Systemic hemodynamics and arterial compliance were determined as previously described [20] using a CAPWA device (Hypertension Diagnostics Incorporated, Eagan, MN). Subjects rested in a supine position in a temperature-controlled room for 10 minutes. Signal-averaged arterial pulse waveform recordings were obtained for 30 seconds using applanation plethysmography by a surface-residing transducer over the radial pulse of the non-dominant arm. Blood pressure was measured in the opposite arm by oscillometric technique. Diastolic decay of the arterial waveform was analyzed by the CAPWA device, and two components of arterial compliance were calculated based upon a modified Windkessel model of the circulation (capacitive compliance = large conduit arteries, oscillatory compliance = small, peripheral arteries and arterioles). Cardiac output, cardiac index and systemic vascular resistance were also calculated by the CAPWA device.

Statistical Analysis

Glycerol-blanked TG values were log-normalized and TG K_2 was calculated as the slope of the regression line determined by the least square technique and the equation log Y = bX + a. TG K_2 was expressed as $-b \pm$ standard deviation of b (in mg/dL/min).

All calculations and descriptive statistics were performed using SPSS 9.0 software for windows (SPSS Incorporated, Chicago, IL). Univariate analyses were performed by Pearson correlation coefficients. Multivariate models were constructed using general linear regression analyses. Group differences in characteristics were analyzed by 2-tailed independent samples *t* tests. Significance was defined as a *p* value <0.05.

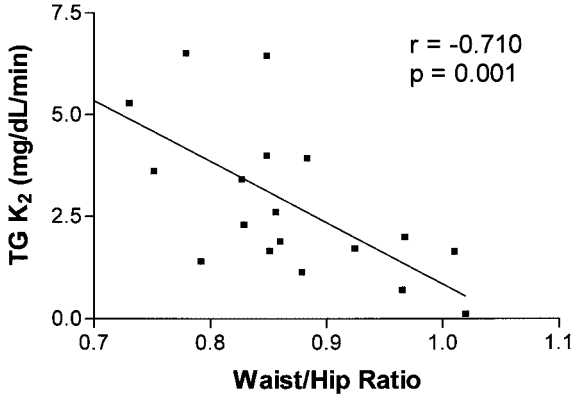
RESULTS

The hypertensive and normotensive groups were well matched by body size and age, as displayed in Table 1. There were very few differences noted between hypertensive subjects and controls. Hypertensive subjects had significantly greater blood pressure and systemic vascular resistance and a significantly smaller large and small vessel compliance. There were no differences in any of the forearm blood flow variables (baseline and maximum blood flow, vascular resistance), laboratory analyses (catecholamines, lipoproteins, fasting glucose and insulin) or TG K_2.

Predictors of TG K_2

TG K_2 was not significantly related to hemodynamic variables (blood pressure, systemic vascular resistance, cardiac output, cardiac index) or to any vascular alteration measured by plethysmography.

In all 20 subjects, TG K_2 was only significantly predicted by small blood vessel compliance ($r = -0.61$) and waist/hip ratio ($r = -0.71$) as depicted in Fig. 1. TG K_2 was also predicted by fasting TG ($r = -0.64$) and male gender ($r = 0.56$).



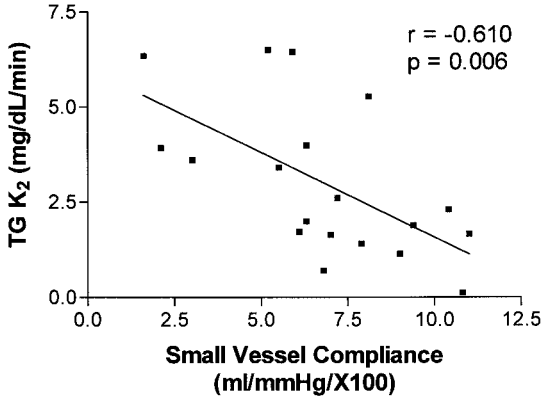


Fig. 1. Triglyceride catabolic rate (TG K_2) displays an inversely significant correlation with both waist/hip ratio and small vessel compliance.

Predictors of Other Metabolic Parameters

In all 20 subjects, insulin level was significantly related to age ($r = -0.48$), body mass index ($r = 0.86$), waist/hip ratio ($r = 0.54$), baseline forearm blood flow ($r = 0.47$) and cardiac

Table 1. Comparisons between the Hypertensive and Control Subjects

	Hypertensives	Controls	*p*
Demographics/Anthropometrics			
n (males)	10 (6)	10 (6)	
Age (years)	39 ± 11	35 ± 3	0.25
Weight (kg)	81 ± 21	76 ± 13	0.57
Height (m)	1.72 ± 0.12	1.69 ± 0.10	0.63
Waist/Hip ratio	0.86 ± 0.09	0.86 ± 0.10	0.87
Hemodynamics			
Systolic blood pressure (mm Hg)	145 ± 8	111 ± 15	<0.00*
Diastolic blood pressure (mm Hg)	94 ± 11	74 ± 14	<0.00*
Systemic vascular resistance (dynes · sec · cm^{-5})	1695 ± 441	1172 ± 430	0.02*
Large vessel compliance ((ml/mm Hg) × 10)	11.7 ± 3.6	15.1 ± 3.1	0.04*
Small vessel compliance ((ml/mm Hg) × 100)	6.1 ± 2.7	7.6 ± 2.6	0.22
Metabolics			
Triglyceride catabolic rate (mg/dL/min)	3.1 ± 2.0	2.9 ± 2.1	0.85

* $p < 0.05$ by independent samples *t* test.

output (r = 0.61). Insulin level was not significantly related to blood pressure or other hemodynamic/vascular parameters.

Fasting lipoproteins and glucose were also unrelated to blood pressure, hemodynamics or vascular alterations. However, TG were predicted significantly by body mass index (r = 0.48) and waist/hip ratio (r = 0.59) while high-density lipoproteins were predicted by body mass index (r = −0.57) and insulin (r = −0.50). Fasting glucose was related to weight (r = 0.55) and insulin (r = 0.49).

Multivariate general linear models were constructed to test the independence of the inverse relationship between small vessel compliance and TG K_2. Since small vessel compliance was predicted by waist/hip ratio and inversely related to age and gender (variables which were also related to TG K_2), these variables were entered into several different models. The model with the highest predictive value (adjusted $r^2 = 0.59$, $p < 0.001$) included only small vessel compliance ($p = 0.03$) and waist/hip ratio ($p = 0.004$). The addition of any other variable, including fasting TG, failed to improve this model. Small vessel compliance remained a significant determinant of TG K_2 even after waist/hip ratio, age, gender and TG were included as covariates.

DISCUSSION

Essential hypertension is part of the insulin resistance syndrome, which also includes dyslipidemia, glucose intolerance and abdominal adiposity [1–3]. One experiment has linked enhanced postprandial lipemia with high blood pressure in adults [2], so we tested the role of hemodynamic and vascular alterations as the mechanism behind the elevated TG and postprandial lipemia in hypertensive adults. The hemodynamic model of the metabolic syndrome suggests that vascular alterations cause insulin resistance via a pre-receptor defect in glucose disposal [3]. Essential hypertension may directly lead to impaired insulin sensitivity by under-perfusion of insulin-sensitive muscle fibers resulting from systemic vasoconstriction, loss of small blood vessel density and surface area (rarefraction) and capillary shunting. If this model were of physiologic relevance, TG K_2 would be similarly affected, because the enzyme responsible for TG catabolism is expressed on the endothelium at the vascular lumen surface. Indeed, this hypothesis is supported by diminished lipoprotein lipase activity associated with decreased microvascular density [14]. Therefore, non-invasive markers of hypertension-related vascular changes and rarefraction (decreased maximum forearm blood flow, minimum forearm vascular resistance, arterial compliance and increased systemic vascular resistance) should be determinants of TG K_2.

The primary finding of our study does not support the physiological relevance of the hemodynamic model, in relation to TG catabolism. There were no group differences between hypertensives and normotensives in the rate of TG catabolism. Furthermore, blood pressure *per se*, hemodynamic and vascular alterations were not significant predictors of TG K_2. TG K_2 is an important determinant of both fasting TG and the degree of postprandial lipemia; our results suggest that essential hypertension is not directly linked to these metabolic abnormalities.

Our findings support the notion that reduced TG K_2 (dyslipidemia) and possibly insulin resistance are related to increased abdominal adiposity, rather than hypertension *per se*. All metabolic parameters were similar between hypertensives and normotensives. As with TG K_2, fasting levels of insulin, glucose and lipoproteins were not related to hemodynamic alterations, but were highly correlated with the degree of abdominal adiposity (Fig. 1). This finding holds true in both normotensives and hypertensives.

These observations agree with other reports [4–6]. The lack of metabolic abnormalities in our hypertensive group, and therefore the normal TG K_2, are most likely a result of our study design. Our control subjects had similar levels of obesity and body fat distribution as the hypertensive subjects, thus explaining the similar metabolic profiles. The elevated blood pressure and vascular-hemodynamic alterations cannot account for any differences in TG K_2 or other metabolic abnormalities in our patients. Rather, these findings suggest that increased abdominal adiposity is the primary mechanism behind the dyslipidemia associated with hypertension.

In agreement with our findings, Toft *et al.* [11] found that insulin resistance in hypertension is associated with body fat distribution rather than blood pressure. All metabolic abnormalities present in hypertensive subjects became insignificant after controlling for the waist/hip ratio. Our results confirm and extend their conclusions to include TG K_2. Previous reports of insulin resistance and dyslipidemia associated with hypertension may be the result of a failure to completely account for abdominal or visceral fat [4–6].

An increased waist/hip ratio may be linked to the metabolic abnormalities and a reduced TG K_2 because of excess visceral fat [21]. Visceral fat can produce insulin resistance by multiple mechanisms. Possible explanations include elevations in free fatty acid levels via poor suppression of adipocyte lipolysis, lipotoxicity, alterations in skeletal muscle membrane properties and secretion of molecules such as TNF-α, leptin and angiotensinogen [22]. It is important to note that genetic and environmental factors may also influence this relationship, as this finding is not always found in different population groups [23].

Small Vessel Compliance and TG K_2

A novel finding in our study is the strong, independent, inverse relationship between small blood vessel compliance and TG K_2. Although the vast majority of hypertension-related hemodynamic and vascular alterations were unrelated to TG K_2, we found that a reduction in small vessel compliance independently predicted an increased rate of TG catabolism.

This finding is contrary to the hemodynamic model of the metabolic syndrome, which would predict that reduced arterial compliance would be associated with impaired TG K_2. In the present study, large vessel compliance did not predict TG K_2. There is no clear biological explanation for this finding. It is possible that reduced arterial compliance serves as a marker for other determinants of TG K_2. For example, we found that age predicted TG K_2, and we also saw a significant correlation between age and small vessel compliance. However, small vessel compliance decreases with age, and we found increasing age to be associated with reduced TG K_2, making age an unlikely link between vascular compliance and TG catabolism.

Small vessel compliance tended to increase with higher waist/hip ratio, which may explain the relationship between small vessel compliance and reduced TG K_2. However, after controlling for other covariates, small vessel compliance remained a significant predictor of TG K_2. The most powerful multivariate model explaining the greatest degree of TG K_2 variability included both waist/hip ratio and small vessel compliance as independent significant determinants. Additionally, the lack of correlation between small vessel compliance and other aspects of the insulin-resistance syndrome supports the notion that there may be an undiscovered direct relationship between arterial compliance and TG K_2. Perhaps the activity of lipoprotein lipase is more effective on a stiffer, less compliant blood vessel. It is doubtful that this represents an inadequate measurement technique of vascular compliance because the CAPWA device has recently been independently validated [24].

In conclusion, essential hypertension *per se* and the related hemodynamic and vascular alterations are not associated with an impaired rate of TG catabolism. This finding does not support a pathophysiological relevance of the hemodynamic model of the metabolic syndrome, at least pertaining to TG catabolism. Increased visceral fat is the likely mechanism linking essential hypertension to aspects of the metabolic insulin resistance syndrome. The finding of an independent association between reduced small vessel compliance and increased TG K_2 deserves further investigation.

Limitations

The major limitation of this study is the small number of subjects ($n = 20$). The group differences in the primary outcome (TG K_2) and the relationship between blood pressure, hemodynamic and vascular alterations with TG K_2 were highly insignificant and the inclusion of more subjects is unlikely to alter the results. Although our results suggest that visceral fat is the major determinant of TG K_2, we cannot exclude the possibility that essential hypertension (blood pressure) has a small impact on TG K_2 not found in our subjects. Even if that is the case, the pathophysiological relevance would be minor compared to the impact of visceral fat.

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