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Association of serum bilirubin with pulsatile arterial function in asymptomatic young adults: the Bogalusa Heart Study

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Abstract

The inverse association between serum bilirubin, a potent antioxidant, and oxidative stress–mediated diseases like cardiovascular disease is known. However, information is scant regarding the influence of bilirubin in relation to traditional cardiovascular risk factors on pulsatile arterial function in asymptomatic younger adults. The present study examines this aspect in 777 black and white subjects (71% white, 42% male) aged 18 to 44 years. Pulsatile arterial function was assessed in terms of large-artery (capacitive) and small-artery (oscillatory) compliances by radial artery pressure pulse contour analysis. In bivariate analysis adjusted for race and sex, bilirubin related significantly and positively to large- and small-artery compliances and high-density lipoprotein cholesterol, and inversely to age, body mass index, blood pressure variables, non–high-density lipoprotein cholesterol, triglycerides, and insulin resistance index. In multivariable analysis including race, sex, body surface area, and risk factor variables mentioned above, bilirubin did not relate to large-artery compliance, without or with smoking status in the model, whereas bilirubin associated beneficially with small-artery compliance ($P = .01$) in a model that excluded smoking status. When smoking status was included in the model, this association became less strong ($P = .04$); and smoking entered the model as an adverse predictor ($P = .003$). The observed beneficial association of serum bilirubin on pulsatile arterial function, albeit the attenuating effect of smoking on this relationship, in asymptomatic younger adults supports the antioxidant function of bilirubin in providing protection against oxidative stress–mediated vascular dysfunction.

1. Introduction

It is well recognized that oxidative stress involving oxygen and peroxy radicals and lipid oxidation is an initiating factor of vascular dysfunction and related cardiovascular (CV) diseases, whereas antioxidants are beneficial in attenuating this process [1,2]. Because bilirubin, the end product of heme catabolism, is a potent scavenger of reactive oxygen species, it has been suggested that bilirubin functions as an endogenous antioxidant of physiological significance [3-5]. Furthermore, studies have demonstrated an inverse relationship between serum bilirubin and oxidative stress–mediated diseases, in particular atherosclerosis [6-9]. However, information is lacking on the influence of serum bilirubin levels in physiologic ranges on pulsatile arterial function.

Impaired arterial compliance, a measure of pulsatile arterial function, is an independent predictor of CV risk and mortality [10-12]. Risk factors for CV disease mediate their effects by adversely altering the structure, endothelial function, and hemodynamic properties of the vasculature [13]. Recent studies have shown that alterations in the pulsatile behavior of the vasculature may be a sensitive marker to detect vascular dysfunction related to CV risk factors [14-16]. Thus, studies of pulsatile behavior can help examine the beneficial role of bilirubin in relation to CV risk factors that induce oxidative stress.

As part of the Bogalusa Heart Study, a community-based investigation of early natural history of CV disease [17], the present study examines the influence of serum bilirubin in relation to other CV risk factor variables on pulsatile behavior in terms of large-artery (capacitive) compliance and small-artery (oscillatory or reflective) compliance in asymptomatic younger adults.

2. Materials and methods

2.1. Study population

The Bogalusa Heart Study is conducted in the biracial (65% white and 35% black), semirural community of

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Table 1
Mean ± SD of age, serum bilirubin, and large- and small-artery compliances in the study cohort by race and sex

	White		Black		Comparison [a]	
	Male (n = 244)	Female (n = 308)	Male (n = 85)	Female (n = 140)	Race	Sex
Age (y)	36.8 ± 4.4	36.5 ± 5.0	35.1 ± 6.3	36.3 ± 4.9	.01	NS
Bilirubin (mg/dL)	0.60 ± 0.27	0.49 ± 0.20	0.63 ± 0.27	0.47 ± 0.23	NS	<.0001
Large-artery compliance (mL/mm Hg × 10)	16.93 ± 4.09	14.25 ± 3.74	14.89 ± 3.50	13.76 ± 4.22	<.001 [b]	<.0001 [c]
Small-artery compliance (mL/mm Hg × 100)	7.80 ± 2.42	5.60 ± 2.24	6.58 ± 2.44	4.93 ± 2.06	<.0001	<.0001

NS indicates not significant.
[a] Analysis of covariance (*P* value adjusted for age).
[b] Male subjects only.
[c] White subjects only.

Bogalusa, LA. Young adults (n = 777; 71% white, 42% male) aged 18 to 44 years were examined from 2000 to 2002 for arterial compliance, serum bilirubin, and other CV risk factor variables as part of the longitudinal cohort study. Participants whose level of bilirubin was within the physiological range were included. Tulane University Medical Center Institutional Review Board approved the study. Informed consent was obtained from all participants.

2.2. General examination

Standardized techniques and protocols were used by trained field observers. Height and weight were measured twice to 0.1 cm and 0.1 kg, respectively; and the mean values were used. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and used as a measure of overall adiposity. Body surface area was calculated as square root of weight in kilograms times height in centimeters divided by 3600. Information on smoking status was obtained by questionnaires. Those who smoked at least one cigarette per week during the past 1 year or more were identified as current smokers; the rest, as nonsmokers.

2.3. Laboratory analysis

Subjects were instructed to fast for 12 hours before screening, and the compliance was determined by interview on the morning of examination. Serum cholesterol and triglycerides were assayed using an enzymatic procedure on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum lipoprotein cholesterols were analyzed using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures [18]. The laboratory has been monitored for precision and accuracy of lipid measurements by the surveillance program of the Centers for Disease Control and Prevention (Atlanta, GA). Serum total bilirubin levels were determined by the diazo method as part of multiple chemistry profile (SMA20) by the multichannel Olympus Au-5000 Analyzer (Olympus, Lake Success, NY); glucose levels, by a glucose oxidase method as part of SMA20. A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin levels (Pharmacia Diagnostics, Piscataway, NJ). An index of insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]) was calculated according to the homeostasis model assessment formula [19]: fasting insulin (in microunits per milliliter) × fasting glucose (in millimoles per liter) ÷ 22.5.

2.4. Arterial compliance measurements

Radial arterial pulse pressure waveforms were recorded by an acoustic transducer using the HDI/Pulse Wave CR-2000 Research Cardiovascular Profiling System (Hypertension Diagnostics, Eagan, MN) [20]. A wrist stabilizer was used to gently immobilize the right wrist and stabilize the radial artery during measurements. For each subject in the supine position, pressure waveforms were recorded for 30 seconds, digitized at 200 samples per second, and stored in a computer. A modified Windkessel model of the circulation was used to match the diastolic pressure decay of the waveforms and to quantify changes in arterial waveform morphology in terms of large-artery (capacitive) compliance, representative of the aorta and major branches, and small-artery (oscillatory) compliance, representative of the distal part of the circulation including the arteriolar bed [20,21]. In addition, systolic, diastolic, and mean arterial blood pressure levels were obtained from the HDI instrument.

Four measurements were taken for each subject: 2 repeated measurements followed by separation of sensor from the tonometer for a 5-minute rest of subjects and then an additional 2 repeated measurements. The means of 4 values were used in the analyses. The reproducibility of measurements was valid and described in an earlier study [22].

2.5. Statistical analyses

All analyses were conducted using SAS software, version 9.1 (SAS, Cary, NC). Descriptive statistics for the compliances were calculated for each race-sex group. Analysis of covariance was used to measure race-sex differences in risk factor variables after adjusting for age. Serum bilirubin, triglycerides, and HOMA-IR were not normally distributed; thus, log transformation was used. All analyses were performed on transformed data where appropriate. Partial Pearson correlation was used for the relationship of arterial compliance and serum bilirubin with risk factor variables. Stepwise multiple regression analysis was used to determine the independent association of bilirubin in relation to measured CV risk factor variables with arterial compliance;

Table 2
Correlation coefficients between serum bilirubin, large- and small-artery compliances, and risk factor variables

Variables	Serum bilirubin [a]
Large-artery compliance	0.11 †
Small-artery compliance	0.15 §
Age	−0.09 *
BMI	−0.14 §
Systolic BP	−0.09 *
Diastolic BP	−0.09 *
Mean arterial pressure	−0.09 *
Non-HDL cholesterol	−0.13 ‡
HDL cholesterol	0.07 *
Triglycerides	−0.16 §
HOMA-IR	−0.17 §

[a] Adjusted for race and sex.
* $P < .05$.
† $P < .01$.
‡ $P < .001$.
§ $P < .0001$.

Table 3
Multivariable predictors of small-artery compliance in young adults

Predictor variables	Small-artery compliance			
	Model 1		Model 2	
	Standardized estimate	*P* value	Standardized estimate	*P* value
Female sex	−0.277	<.001	−0.281	<.001
Mean arterial pressure	−0.437	<.001	−0.432	<.001
Body surface area	0.503	<.001	0.506	<.001
Age	−0.136	<.001	−0.132	<.001
Triglycerides	−0.119	<.001	−0.113	<.001
Black race	−0.077	.003	−0.076	.009
Smoking	–	–	−0.079	.003
Bilirubin	0.063	.01	0.056	.04
BMI	−0.126	.03	−0.140	.01
	Total $R^2 = 0.515$ ($P < .001$)		Total $R^2 = 0.521$ ($P < .001$)	

Model 1 included race, sex, age, body surface area, BMI, mean arterial pressure, non-HDL cholesterol, HDL cholesterol, triglycerides, HOMA-IR, and bilirubin. Model 2: model 1 + smoking status (yes/no).

because cigarette smoking, which contains substantial amounts of free radicals and prooxidants to produce oxidative stress [23], may confound the results, 2 separate models without (model 1) and with (model 2) smoking status were used. To examine the arterial compliance by bilirubin status, subjects (n = 327) who had bilirubin (0.40 mg/dL) below the 25th percentile were categorized as the low-bilirubin group; those (n = 152) with bilirubin (0.40-0.60 mg/dL) between the 25th and 75th percentile, as the intermediate group; and those (n = 298) with bilirubin (>0.60 mg/dL) above the 75th percentile, as the high-bilirubin group.

3. Results

Mean ± SD of age, serum bilirubin, and large- and small-artery compliances in the study cohort is presented in Table 1

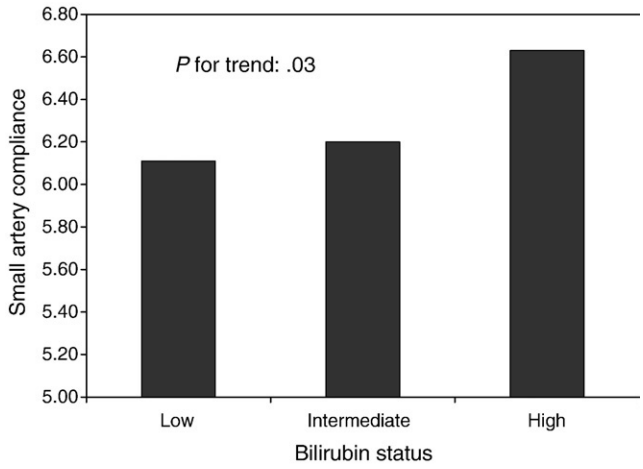

Fig. 1. Small-artery compliance by bilirubin status after adjusting for race and sex.

by race and sex. With respect to race difference, black vs white subjects were significantly younger and had lower small-artery compliance; and black men vs white men had lower large-artery compliance. Regarding sex difference, men vs women had higher serum bilirubin and higher small-artery compliance; and white men vs white women had higher large-artery compliance.

As a continuous variable, bilirubin correlated significantly and positively to large- and small-artery compliances and high-density lipoprotein (HDL) cholesterol, and inversely to age, BMI, blood pressure variables, non-HDL cholesterol, triglycerides, and HOMA-IR after adjusting for race and sex (Table 2). As a categorical variable, the high-bilirubin group significantly and positively associated with small-artery compliance after adjusting for race and sex (Fig. 1).

In multivariable analysis that included bilirubin along with race, sex, BMI, body surface area, BMI, mean arterial pressure, non-HDL cholesterol, HDL cholesterol, triglycerides, and HOMA-IR, bilirubin did not relate to large-artery compliance, with or without smoking status in the model (data not shown), whereas, as shown in Table 3, bilirubin associated beneficially with small-artery compliance ($P = .01$) in a model that did not include smoking status. With the inclusion of smoking status in the model, this association became slightly attenuated but remained significant ($P = .04$); and smoking entered the model as an adverse predictor ($P = .003$). It should be noted that because colinearity was present among different blood pressure variables, we included only mean arterial blood pressure in the multiple regression model. Substitution of other blood pressure parameters for mean arterial pressure in the model did not change the outcome (data not shown).

4. Discussion

Oxidative stress, an imbalance between reactive oxygen species–generating and –scavenging systems, is intimately involved in the pathogenesis of endothelial dysfunction and related diseases [24]. As a scavenger of reactive oxygen species, serum bilirubin is considered to protect the CV system against oxidative stress [3-5]. In the present study, elevated levels of serum bilirubin within the reference range associated beneficially and independently with pulsatile arterial function measured as small-artery compliance; and cigarette smoking attenuated this relationship, with smokers vs nonsmokers showing lower bilirubin values. These findings on a community-based asymptomatic younger adults, free of selection bias, are noteworthy in that they underscore the potential value of bilirubin as an inverse risk factor for CV risk. Furthermore, no comparable data linking elevated serum bilirubin levels favorably to arterial pulsatile function in younger population are available.

The observed positive association between bilirubin and small-artery compliance, independent of traditional CV risk factors including smoking, is consistent with previous studies showing salutary effects of bilirubin on preserving coronary flow reserve and microvascular function [25,26], preventing intimal hyperplasia [27], attenuating vascular endothelial activation and dysfunction [28], and preventing the development of ischemic heart disease among Gilbert syndrome patients [29]. The present observational study, however, cannot address the issue of causality or mechanisms by which bilirubin protects the vasculature against oxidative stress and inflammation. Based on research findings in this area [27-32], the possible mechanisms include, among others, activation of endothelial nitric oxide synthase expression and suppression of proinflammatory genes like vascular cell adhesion molecule 1, monocyte chemoattractant protein 1, and macrophage colony-stimulating factor; inhibition of superoxide producing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; protein phosphorylation; protein kinase C activity; and p38 mitogen-activated protein kinase signal transduction pathways.

In this study, cigarette smoking attenuated the strength of the positive association between bilirubin and small-artery compliance and reduced the bilirubin level. That smoking is a major risk factor for CV disease and relates adversely to vascular compliance is known [33,34]. Furthermore, consistent with the present findings, an earlier study found that cigarette smoking decreased serum bilirubin level [35] and attenuated the beneficial association of bilirubin on risk of early coronary artery disease [7]. Lower bilirubin level among smokers may be due to oxidation of bilirubin by reactive oxygen species generated by cigarette smoke. In fact, smokers are known to have reduced levels of endogenous antioxidants such as vitamins C and E in serum [23].

It is of interest that in this study cohort, adiposity, blood pressure, non-HDL cholesterol, triglycerides, and insulin resistance index were associated inversely and HDL cholesterol was associated positively with bilirubin. Obesity, dyslipidemia, hypertension, and insulin resistance, by promoting oxidative stress [36-38], may deplete bilirubin levels; HDL, with its antioxidant property, in part through the enzyme paraoxanase [39], may enrich bilirubin levels.

With respect to large-artery compliance in the study cohort, bilirubin showed positive association in bivariate analysis, but not in multivariable analysis. The reason for this is not clear. Of note, regarding the influence of excess oxidative stress on pulsatile arterial function, previous studies including ours showed independent adverse effect of smoking on small-artery but not on large-artery compliance [34,40]. Alterations in large-artery compliance generally reflect structural (sclerotic) changes over time with aging and hypertensive medial degeneration and as such a late marker of CV disease [41]. Furthermore, any reduction in compliance of large arteries, unlike small arteries, might be counterbalanced by caliber increase, thereby to a certain extent maintaining their compliance [41]. On the other hand, because small arteries are sensitive to endothelial dysfunction, the loss of the oscillatory diastolic waveform is considered as an early feature of impaired arterial function [42]. Furthermore, a decrease in small-artery compliance with no change in large-artery compliance in response to endothelial nitric oxide synthase inhibition implicated nitric oxide–mediated alteration in smooth muscle tone [42]. Therefore, it is likely that the beneficial effect of bilirubin can be readily seen in small-artery rather than large-artery compliance.

In summary, higher serum bilirubin levels in physiological ranges beneficially associated with small-artery compliance; and cigarette smoking attenuated this relationship in asymptomatic younger adults. These findings in conjunction with other studies on this subject support the antioxidant function of bilirubin in improving vascular function. These cross-sectional findings need to be confirmed in a prospective study or in an independent database.

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