

Low bilirubin levels are associated with coronary slow flow phenomenon

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Abstract

Background and aim: Increasing evidence suggests an inverse relationship between bilirubin levels and cardiovascular disease. The present study evaluated the effect of bilirubin level on the slow coronary flow (SCF) phenomenon.

Methods: This study was cross-sectional and observational. We enrolled 222 consecutive patients who underwent coronary angiography for suspected ischaemic heart disease and were found to have normal or near-normal coronary arteries. Then, bilirubin levels were measured and coronary flow rate was assessed using the thrombolysis in myocardial infarction (TIMI) frame count. SCF was defined as a TIMI frame count > 27 frames.

Results: SCF was observed in at least one coronary vessel in 22 of the 222 subjects, indicating a prevalence of 10%. Serum bilirubin levels were significantly decreased in the SCF group. In multivariate logistic regression analysis, total bilirubin and diabetes mellitus were independent risk factors for SCF. Furthermore, after adjusting for age, sex, and cardiovascular disease risk factors, serum bilirubin level ($B = -0.34$, $p < 0.001$) was independently associated with TIMI frame count.

Conclusions: These findings suggest that serum total bilirubin levels may be a useful marker for patients with the SCF phenomenon. We believe that further studies are needed to clarify the role of bilirubin in patients with SCF.

Key words: bilirubin, endothelial dysfunction, slow coronary flow, TIMI frame count, atherosclerosis

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INTRODUCTION

Reactive oxygen species play an important role in body events such as inflammation, apoptosis, and atherosclerosis [1]. Bilirubin, the end product of heme catabolism, has antioxidant properties, as indicated by its ability to scavenge peroxy radicals and inhibit oxidation of low-density lipoprotein (LDL) [2]. Epidemiologic studies have shown that the serum total bilirubin (TB) concentration is inversely related to coronary artery disease (CAD), diabetes mellitus (DM), hypertension, and metabolic syndrome [3–6].

The slow coronary flow (SCF) phenomenon is characterised by delayed opacification of the epicardial coronary vessels in a normal or near-normal coronary artery [7, 8]. The majority

of patients with SCF experience recurrent chest pain, and most are referred for coronary angiography. Several mechanisms have been proposed as causing SCF, including inflammation, oxidative stress, endothelial dysfunction, and diffuse atherosclerosis [9–11]. Although there have been numerous studies on the association between serum bilirubin level and cardiovascular disease (CVD), there is a lack of direct investigation into the relevance of TB level to the SCF phenomenon. Given the protective effect of bilirubin on the cardiovascular system, we hypothesised that TB is associated with the SCF phenomenon. To test this hypothesis, we investigated the relationship between TB level and coronary flow rate using the thrombolysis in myocardial infarction (TIMI) frame count (TFC) method.

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METHODS

This observational cross-sectional study screened 2,123 patients who underwent coronary angiography for suspected stable ischaemic heart disease between November 2011 and November 2012. All patients had stable angina and a myocardial perfusion defect (stress imaging test) or ST segment changes on cardiac stress test. Stable angina was defined as discomfort in the chest, jaw, shoulder, back, or typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. 222 patients who were found to have normal or near-normal coronary arteries were included in the study. Age, sex, body mass index, and information on the following CAD risk factors were recorded: hypertension (self-report, blood pressure > 140/90 mm Hg, or use of an antihypertensive drug), DM (self-report, fasting glucose > 126 mg/dL, or use of oral hypoglycaemic agents or insulin), dyslipidaemia (self-report, LDL > 130 ng/dL, total cholesterol > 200 ng/dL), and nicotine use (within one year). The use at admission of cardioprotective drugs such as angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers, statins, beta-blockers, and calcium channel blockers was recorded. All patients underwent echocardiography to assess left ventricular systolic function and dimensions. The study was approved by the local ethics committee. All patients provided informed consent.

Exclusion criteria were previous myocardial infarction (MI), cardiomyopathy, ejection fraction < 50%, severe valvular disease, chronic renal and liver disease, active malignancy, sustained supraventricular or ventricular arrhythmia during angiography, and nitrates used within 24 h.

Laboratory methods

Fasting blood samples were collected one day before coronary angiography for the evaluation of full blood count, glucose, creatinine level, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and serum bilirubin level. Complete blood counts were performed using a Beckman Coulter LH 780 analyser (Miami, FL, USA). Serum bilirubin levels were determined by the colorimetric diazo method on the Aeroset System (Abbott Laboratories, Abbott Park, IL, USA).

Coronary angiography

Patients underwent elective coronary angiography using the standard Judkins technique. Iohexol (Omnipaque, Nycomed Ireland Ltd., Cork, Ireland) was used as the contrast agent during angiography in all patients. The coronary arteries were visualised in the left and right oblique planes using cranial and caudal angulation. Cineangiography was performed by hand injection through a 6 F Judkins diagnostic catheter. The coronary angiography was recorded at 30 frames/s. Two independent observers evaluated the coronary angiograms. Normal and near-normal coronary arteries were defined as having < 40% stenosis.

TIMI frame count measurement

The TFC was determined for each major coronary artery in each patient by two independent observers using a previously reported technique [12]. Any disagreement was resolved by a third observer. Frame counts in the left anterior descending coronary artery (LAD) were divided by a factor of 1.7 to correct for its longer length. Mean TFC for each subject was calculated by dividing the sum of the corrected LAD, left circumflex coronary artery (LCx), and right coronary artery (RCA) values by three. Any frame count exceeding 27 was considered abnormal and indicative of SCF according to Gibson et al. [12]. The interobserver variability of the TFC measurement was 3.9%.

Statistical analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyse normality of the data. Continuous data was expressed as mean \pm standard deviation (SD), and categorical data was expressed as percentages. Chi-square test was used to assess differences in categorical variables between groups. The relationships among parameters were assessed using Pearson's or Spearman's correlation analysis according to the normality of the data. Student's t-test or Mann Whitney U test was used to compare unpaired samples as needed. Multivariate logistic regression analysis was used to identify independent predictors of SCF. The results are expressed as relative risk (RR) and 95% confidence interval (CI). Significance was assumed at a two-sided $p < 0.05$.

RESULTS

Baseline characteristics of the 222 patients divided into a SCF group and a normal coronary flow (NCF) group are shown in Table 1. Hyperlipidaemia, active nicotine use, and DM were more common in the SCF group. No differences in other variables, including hypertension, age, or sex were present. Blood pressure measurements, lipid levels, glucose and creatinine were similar between the groups. The usage rates of aspirin, statins, and ACEI, calcium channel blockers, and beta-blockers were similar between the groups.

TFCs of the LAD, LCx, and RCA were significantly higher in the SCF group than in the NCF group (Table 1). Of our study population, SCF was observed in at least one coronary vessel in 22 subjects, indicating a prevalence of 10%. The TB levels and indirect (unconjugated) bilirubin in the NCF group were significantly higher than those of the SCF group, and direct (conjugated) bilirubin levels were not significantly different between the groups (Table 1). In a receiver operating characteristics curve analysis, a TB value > 0.88 was identified as the optimal cutoff for SCF (area under the curve 0.68, 95% CI 0.58–0.76, sensitivity 71.6%, specificities 64.4%, $p = 0.005$).

Table 1. Baseline characteristics of the study population

	NCF (n = 200)	SCF (n = 22)	P
Age [years]	59.7 ± 7.54	61 ± 9.16	0.34
Female	38%	35%	0.09
Hypertension	32%	31.8%	0.57
Diabetes mellitus	17%	36.3%	< 0.005
Smoking	10%	36.3%	< 0.005
Dyslipidaemia	18%	40%	0.008
Body mass index	25.1 ± 4.52	27.1 ± 4.13	0.21
GFR [mL/min]	89.6 ± 17.2	81.7 ± 14.9	0.08
Total cholesterol [mg/dL]	179 ± 43	187 ± 41	0.6
Triglyceride [mg/dL]	111 ± 32	129 ± 41	0.41
LDL cholesterol [mg/dL]	113 ± 35	124 ± 37	0.18
HDL cholesterol [mg/dL]	39 ± 12	37 ± 12	0.83
Total bilirubin [mg/dL]	0.97 ± 0.51	0.74 ± 0.42	0.005
Direct bilirubin [mg/dL]	0.34 ± 0.18	0.30 ± 0.16	0.27
Indirect bilirubin [mg/dL]	0.62 ± 0.36	0.43 ± 0.32	0.005
Haemodynamic data on coronary angiography			
Systolic BP [mm Hg]	130.89 ± 9.99	133.56 ± 11.6	0.45
Diastolic BP [mm Hg]	78.68 ± 10.24	79.49 ± 10.83	0.7
Heart rate [bpm]	74.53 ± 9.88	73.81 ± 7.98	0.82
Drug usage			
Acetylsalicylic acid	21%	22.7%	0.54
ACE inhibitor	12%	9%	0.22
Angiotensin receptor blocker	15%	13.6%	0.3
Beta-blocker	18%	22.7%	0.12
Calcium channel blocker	10%	9%	0.65
Statin	16%	13.6%	0.27
TIMI frame count			
LAD corrected	20.46 ± 1.36	28.39 ± 2.53	< 0.001
LCx	20.34 ± 2.49	33.38 ± 3.68	< 0.001
RCA	21.1 ± 2.64	31.64 ± 3.38	< 0.001
Mean	20.54 ± 1.97	31.56 ± 3.12	< 0.001

ACE — angiotensin converting enzyme; BP — blood pressure (during angiography); HDL — high lipoprotein density; LDL — low lipoprotein density; LCx — left circumflex coronary artery; GFR — glomerular filtration rate according to Cockcroft-Gault formula; LAD — left anterior descending coronary artery; NCF — normal coronary flow; RCA — right coronary artery; SCF — slow coronary flow; TIMI — thrombolysis in myocardial infarction

Table 2. The relevant analysis between mean thrombolysis in myocardial infarction frame count and clinical parameters

Variables	Correlation coefficient (r values)	P
Age	0.49	0.013
Smoking	0.12	0.12
Diabetes mellitus	0.58	0.008
Hypertension	0.28	0.08
Triglyceride	0.13	0.3
Low lipoprotein density cholesterol	0.31	0.034
High lipoprotein density cholesterol	0.1	0.41
Body mass index	0.08	0.58
Total bilirubin	−0.64	0.002

Table 3. Predictors of slow coronary flow in univariate and multivariate logistic regression analysis

	Odds ratio	95% confidence interval	P
Univariate analysis (variables)			
Diabetes mellitus	0.78	0.47–0.83	< 0.005
Hypertension	1.41	0.83–2.34	0.13
Hyperlipidaemia	1.58	1.21–2.18	0.023
Smoking	0.615	0.38–0.75	0.01
Total bilirubin	0.86	0.80–0.91	< 0.005
Multivariate logistic regression analysis (variables)			
Diabetes mellitus	0.84	0.7–0.89	0.008
Hypertension	1.06	0.85–1.85	0.45
Hyperlipidaemia	1.47	0.91–2.25	0.089
Smoking	0.76	0.42–1.37	0.09
Total bilirubin	0.93	0.66–0.98	0.006

Relationship between bilirubin levels and TFC

Among the study variables, TFC was found to be correlated with age, DM, LDL cholesterol, and TB levels (Table 2). Linear regression analysis revealed that DM ($B = 0.23$, $p = 0.036$), and TB levels ($B = -0.34$, $p < 0.001$) were independently correlated with the mean TFC.

Univariate and multivariate analyses for SCF

Individuals with SCF were likely to have DM, hyperlipidaemia, active nicotine use, and decreased TB levels. In multivariate logistic regression analysis, TB and DM were independent risk factors for SCF (Table 3).

DISCUSSION

Our observational study revealed an association between the prevalence of SCF and TB levels independent of age, sex, and several other potential confounding factors. Furthermore, TB level was independently correlated with mean TFC.

Recent prospective studies have determined that serum TB levels are inversely correlated with the presence and severity of CAD [13, 14]. Furthermore, TB levels independently predict adverse cardiac effects in MI patients who undergo primary percutaneous coronary interventions [15]. Additionally, there is evidence that serum bilirubin level is a potential biochemical marker for the preclinical development of atherosclerosis [16]. Gullu et al. [17] showed that the highest serum bilirubin tertile had a protective effect against impaired coronary flow reserve and coronary microvascular dysfunction. In another study, Yoshino et al. [18] showed that greater bilirubin levels were associated with improved coronary endothelial function.

The mechanisms underlying bilirubin's prevention of CAD are not known; however, a possible mechanism is the antioxidant effect of bilirubin. The oxidation of LDL cholesterol has a detrimental role in the pathogenesis of atherosclerosis. The uptake of oxidised LDL cholesterol by macrophages results in the formation of oxygen and peroxy radicals. Those radicals cause the atherosclerotic process and inflammation. In several studies, all forms of bilirubin were found to be effective in protecting LDL cholesterol against peroxidation [19]. Heme oxygenase is an important enzyme for bilirubin production. Increased activity of this enzyme may account for the antiatherogenic effect through increased elimination of heme and reducing tissue iron. Increased tissue iron because of decreased heme oxygenase activity can trigger inflammation [20].

The SCF phenomenon is an angiographic entity characterised by delayed progression of the contrast medium during coronary angiography. The SCF phenomenon is associated with angina pectoris, acute MI, hypertension, and sudden cardiac death [21, 22]. Although the factors underlying this phenomenon are not fully understood, several mechanisms have been suggested to play a role in the development of SCF. Recently, inflammation, platelet function disorders, and imbalance of vasoactive substrates have also been implicated in the pathogenesis of the SCF phenomenon [23, 24]. Additionally, the slow-flow pattern in coronary arteries has been associated with diffuse atherosclerotic disease resulting from endothelial injury [8–17]; thus, SCF may be an early manifestation of diffuse atherosclerosis involving the microvascular system and epicardial coronary arteries. Yucel et al. [25] showed increased plasma levels of plasma total oxidative status and oxidative stress index in SCF, and these findings suggest that atherosclerosis caused by the increased oxidative stress may play a role in the pathogenesis of SCF.

Although it is well known that there is a prominent relationship between CAD and serum bilirubin concentration, to the best of our knowledge there has been no study published to date investigating the effects of serum bilirubin concentrations on normal coronary arteries with SCF. Given its relationship with CVD and inflammation, serum bilirubin may be associated with the SCF phenomenon. We found that serum TB level was independently associated with SCF. From the findings of the present study, we suggest that TB is widely available to clinicians as a biochemistry parameter and a predictive factor for SCF in patients undergoing coronary angiography. It can be used for risk stratification in this patient population. Furthermore, this protective effect of TB for SCF can be used for new treatment options. In the future, bilirubin levels can be selected as a therapeutic target for SCF. Additionally we found that unconjugated bilirubin levels were significantly decreased in the SCF group. Unconjugated hyperbilirubinemia may also be observed in haemolysis and Gilbert's syndrome in which disordered glucuronyl-transferase leads to increased unconjugated bilirubin levels and is associated with lower cardiovascular mortality [26]. In light of these facts, further studies to investigate the effects of the inhibition of glucuronyl-transferase and mild haemolysis on SCF are warranted.

Limitations of the study

Our study has several limitations, including a relatively small sample size limited to patients with a stable condition and a single centre experience. Additionally, there is no established cutoff value available from large-scale clinical trials. Furthermore, the cross-sectional and observational nature of our study does not allow us to determine cause-and-effect relationships.

CONCLUSIONS

Our study indicates an independent association between serum TB levels and SCF. Bilirubin may have preventive effects on the development of the SCF phenomenon. Further large-scale studies to investigate the effects of serum bilirubin on the SCF phenomenon are warranted.

Conflict of interest: none declared

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Związek między niskimi stężeniami bilirubiny a zjawiskiem zwolnionego przepływu wieńcowego

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Streszczenie

Wstęp i cel: Coraz większa liczba dowodów naukowych wskazuje, że istnieje odwrotna zależność między stężeniem bilirubiny a chorobami sercowo-naczyniowymi. W niniejszym badaniu oceniono wpływ stężenia bilirubiny na zjawisko zwolnionego przepływu wieńcowego (SCF).

Metody: Do tego przekrojowego badania obserwacyjnego włączono 222 kolejnych pacjentów, u których wykonano koronarografię z powodu podejrzenia choroby niedokrwiennej serca i stwierdzono prawidłowe lub prawie prawidłowe tętnice wieńcowe. Następnie zmierzono stężenie bilirubiny i oceniono szybkość przepływu wieńcowego, stosując metodę określania liczby klatek do pojawienia się środka cieniującego, użytą w badaniu *Thrombolysis in Myocardial Infarction* (TIMI). Zwolniony przepływ wieńcowy zdefiniowano jako liczbę klatek TIMI wynoszącą > 27.

Wyniki: W badanej populacji SCF w co najmniej 1 tętnicy wieńcowej stwierdzono u 22 chorych, co oznacza chorobowość wynoszącą 10%. Stężenia bilirubiny w surowicy były istotnie mniejsze w grupie osób z SCF. W wieloczynnikowej analizie regresji logistycznej całkowite stężenie bilirubiny i cukruzy stanowiły niezależne czynniki ryzyka SCF. Ponadto po skorygowaniu względem wieku, płci i czynników ryzyka chorób sercowo-naczyniowych stężenie bilirubiny w surowicy ($B = -0,34$; $p < 0,001$) było niezależnie związane z liczbą klatek TIMI.

Wnioski: Podsumowując, powyższe rezultaty wskazują, że całkowite stężenie bilirubiny w surowicy może być użytecznym wskaźnikiem u chorych, u których występuje SCF. Autorzy uważają, że należy przeprowadzić dalsze badania w celu sprecyzowania znaczenia oznaczeń stężenia bilirubiny u chorych z SCF.

Słowa kluczowe: bilirubina, dysfunkcja śródbłónka, wolny przepływ wieńcowy, liczba klatek TIMI, miażdżycza

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