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Нарушения углеводного обмена и коллатеральный кровоток в миокарде у больных хронической ишемической болезнью сердца

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Цель. *Изучение связи между состоянием коллатерального кровотока и нарушениями углеводного обмена (НУО) у больных хронической ишемической болезнью сердца (ИБС).*

Материалы и методы. *В когортное исследование поперечного (одномоментного) типа были последовательно набраны 603 больных хронической ИБС. По результатам плановой коронароангиографии (КАГ) оценивали состояние коронарного русла и проводили количественную оценку коллатерального кровотока с расчетом модифицированного индекса Рентропа (МИР). Состояние углеводного обмена оценивали по стандартным критериям. Независимый характер связей между НУО и состоянием коллатерального кровотока проверяли в в многофакторных упорядоченных логит-регрессионных моделях, учитывающих ряд ключевых ангиографических и клинических параметров.*

Результаты. *Из 603 больных ИБС нарушения углеводного обмена выявлены у 47,4% больных, при этом у 24,2% больных был сахарный диабет 2 типа (СД2), у 3,5% – нарушение толерантности к глюкозе, у 2,8% – нарушение гликемии натощак, у 1,0% – сахарный диабет 1 типа (СД1) и 16,1% больных имели неуточненное НУО. В ходе многофакторного анализа установлено, что у больных с НУО состояние коллатерального кровотока хуже (отношение шансов [ОШ]=0,96, p=0,003). При наличии НУО связь между максимальной выраженностью стеноза и коллатеральным кровотоком ослабевает (ОШ=0,93, p=0,005). Независимых ассоциаций между коллатеральным кровотоком, с одной стороны, и видом сахароснижающей терапии, уровнем HbA_{1c}, инсулинорезистентностью (индекс HOMA) и компонентами метаболического синдрома (индексом массы тела, уровнем триглицеридов, уровнем гликемии натощак, уровнем ХС ЛПВП и артериальной гипертонией), с другой стороны, не выявлено.*

Заключение. *У больных хронической ИБС нарушения углеводного обмена независимо ассоциированы с худшим состоянием коллатерального кровотока. НУО ослабляют связь между максимальной выраженностью стеноза и коллатералями. Состояние коллатерального кровотока не зависит от ряда компонентов метаболического синдрома, компенсации углеводного обмена и вида сахароснижающей терапии.*

Ключевые слова: *коллатеральный кровоток; углеводный обмен; ишемическая болезнь сердца*

Carbohydrate metabolism disorders and coronary collateral circulation in patients with chronic coronary artery disease

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Aim. *To evaluate an association between coronary collateral circulation (CCC) and carbohydrate metabolism disorders (CMD) in patients with chronic ischemic heart disease (IHD).*

Materials and Methods. *Six hundred and three patients with chronic IHD were included into this cohort cross-sectional study. Coronary angiograms were used to quantify coronary circulation, including CCC evaluation, with a modified technique proposed by Rentrop. CMD were classified according to WHO criteria. Potential associations between CMD and CCC were evaluated using multiple linear models that included major angiographic, clinical and laboratory parameters.*

Results. *Among 603 patients with chronic IHD, 47.4% had CMD, including type 2 diabetes mellitus in 24.2% of the patients, impaired glucose tolerance in 2.8%, type 1 diabetes mellitus in 1.0% and unspecified CMD in 16.1%. CMD were independently associated with lower CCC (odds ratio [OR] 0.96, p = 0.003) and with a decrease in the association between maximal stenosis and CCC (OR = 0.93, p = 0.005). No associations were found between CCC and type of anti-diabetic treatment, HbA1c levels, insulin resistance (HOMA index), or metabolic syndrome components (body mass index, triglycerides, fasting glucose levels, LDLP cholesterol and arterial hypertension).*

Conclusion. *CMD in patients with chronic IHD are independently associated with worse CCC. The presence of CMD weakens the association between maximal stenosis and CCC. Metabolic syndrome components, blood glucose control and anti-diabetic treatment were not found to influence CCC.*

Key words: *collateral circulation, carbohydrate metabolism, ischemic heart disease.*

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Collateral blood flow is a natural compensatory mechanism allowing blood flow to bypass regions of injury or blockage. It is associated with significantly better survival in patients with ischaemic heart disease (IHD). [1] The efficiency of collateral blood flow in ischaemic myocardial regions is highly patient-specific; [2,3,4] however, the underlying causes of this variability remain incompletely understood.

It is assumed that carbohydrate metabolism disorders (CMD) is a major contributing factor to poor collateral blood flow in patients with IHD. In a study of 596 patients with coronary occlusion, the prevalence of diabetes mellitus (DM) in a subgroup with well-developed collaterals was substantially lower than in a subgroup with poorly-developed collaterals (27.1% vs 44%; $p < 0.001$). [5] A higher incidence of metabolic syndrome (MS), with dysregulation of carbohydrate metabolism being one of its components, has been reported in patients with a poor collateral circulation than in those with well-developed collaterals (78.4% vs 49.2%; $p < 0.001$). [5] In a regression analysis, DM and MS were shown to be independent predictors of insufficient collateral blood flow. The intensity of collateral circulation in the presence of occlusions is inversely proportional to the number of MS components [6], with hyperglycaemia having the largest effect on collateral circulation development, hypertension a somewhat smaller effect and insulin resistance the smallest effect. [7] An inverse correlation between CMD and collateral circulation has also been demonstrated in rat and dog experiments . [8, 9]

However, limitations of these studies, such as small numbers of participants, inclusion of patients with occlusions or stenoses above 95% and failure to evaluate concomitant factors, including severity and type of coronary bed lesions, have prevented the full elucidation of an association between CMD and collateral blood flow.

Aim

The aim of the study was to examine collateral circulation in the myocardium of IHD patients with coronary bed lesions of varying severity and various forms of CMD with consideration of concomitant clinical, angiographic and biochemical parameters.

Materials and methods

This cohort cross-sectional study included 603 IDH patients, with coronary angiography data (KAG) demonstrating at least one stenosis ≥50% of one coronary artery ≥1.5 mm in diameter, recruited in the inpatient departments of the Cardiology Research and Production Complex, Moscow, Russia. Exclusion criteria were a history of coronary artery bypass grafting, coronary artery angioplasty in the preceding 3 months or acute coronary syndrome in the preceding month. The study was approved by the local ethics committee. All patients gave written informed consent to participate in this study.

The localization and degree of stenoses were determined for each coronary artery visualised on coronary angiograms. The preservation of antegrade blood flow in each stenotic region was assessed by the modified Thrombosis In Myocardial Infarction (TIMI) risk score [10].

Collateral circulation was quantitatively measured by the modified Rentrop method, the modified Rentrop index (MIR) [7,10,11] as follows: 0-no visible collaterals; 1- collaterals are visualized, and contrast fills only branches of the stenotic /occluded artery; 2 – collaterals are visualized, contrast does not fully fill the coronary artery segment distal to the stenosis/occlusion, absence of the contrast in the coronary artery branches due to collateral flow; 3- collaterals are visualized, contrast tightly fills the coronary artery segment distal to the stenosis/occlusion, branches of the affected coronary artery are filled with contrast due to collateral flow.

A source of collateral circulation, either the artery itself or two adjacent coronary arteries, was found for each coronary artery. For each patient, only one value of MIR (the largest) was considered in the analysis.

CMD were diagnosed according to standard criteria [12]. In cases where analysis results were insufficient to conclusively identify the type of CMD, diagnoses were obtained from discharge summaries or medical records. Those patients, for whom no history of CMD was known and no current CMD diagnosis was mentioned in their medical records, but whose glucose values fell outside the normal range, were assigned to the 'unspecified carbohydrate metabolism disorder' subgroup.

Insulin resistance was measured by HOMA2, [13] which was calculated only in patients not receiving antidiabetic medications (n = 156). Insulin levels were determined using an electrochemiluminescence analyser Elecsys 2010 (Roche, Switzerland) and commercial kits (Roche, Switzerland). Glycated haemoglobin (HbA1c) levels were determined in 233 patients using ion exchange chromatography (normal range up to 6.2%).

Statistical analysis

Summary statistics for categorical variables were calculated using absolute and relative frequencies (percentages). For quantitative variables, descriptive statistics were used with normally distributed data presented as average ± standard deviation and non-normally distributed data presented as medians, 1st and 3rd quartiles.

Differences in normally distributed continuous variables between two independent groups were compared by Student's t-test for independent samples and simple linear regression methods. In cases of non-normally distributed data, the Mann–Whitney test was used to compare two groups and Kruskal–Wallis test was used to compare three or more groups. Categorical variables were compared by χ^2 test and ordered logistic regression analyses. The Bonferroni correction was applied to multiple comparisons.

Statistical analyses were performed in two stages, with a univariate analysis and a subsequent multivari-

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Table 1

Main demographic data of included patients		
Characteristics	Number of observations (n = 603)	Value (% or average ± CO)
Age, years	603	61.6 ± 9.8
Men:women	443:160	73.5%:26.5%
Body mass index, kg/m^2	535	29.2 ± 4.5
Smoking at the time of study	141	23.4%
AH	529	87.7%
Left ventricular ejection fraction, %	579	57.5 ± 8.5
Family history SVR	523	31.5%
Any CMD	286	47.4%
IFG	17	2.8%
T1DM	6	1.0%
IGT	21	3.5%
T2DM	146	24.2%
unspecified CMD	95	15.8%
IHD duration	590	5.1 ± 6.0
Myocardial infarction history	364	60.4%
Effort angina	517	85.7%
Angina FC		
I	23	3.8%
II	228	37.8%
III	139	23.1%
IV	126	20.9%
Painless myocardial ischaemia	66	11.0%
Drug intake		
Acetylsalicylic acid	379	63.2
Clopidogrel	150	24.9%
Beta blockers	375	62.2
Nitrates	266	44.1%
Statins	323	53.6%
ACE inhibitors	280	46.4%
Calcium antagonists	139	23.1%
Diuretics	107	17.8%
Insulin	34	5.6%
Biguanides	55	9.1%
Sulphonylureas	38	6.3%

ate analysis. In the univariate analysis, we analysed an association between the presence of CMD, type of CMD, collateral circulation and various external and internal factors. These factors included two demographic, three anthropometric, nine angiographic and up to 30 medical (use of different drug groups) characteristics, laboratory parameters, including haematology and clinical chemistry parameters, C-reactive protein, HbA1c, vascular endothelial growth factor levels (in total, 61 laboratory parameters) and concomitant diseases (22 factors). Parameters found to be significantly associated with CMD and/or collateral circulation were introduced in multivariate models. Multivariate ordered logistic regression analysis was used because of the qualitative (categorical) and ordered nature of the dependent variables, 'carbohydrate metabolism disorder type' and 'collateral circulation condition'. The results of the multivariate ordered logistic regression analyses are presented as odds ratio (OR) for improved collateral circulation. Parallel regression assumptions were checked by the Brant test.

In univariate analyses, statistical significance was set at $\alpha = 5\%$ ($p < 0.05$). Because of the exploratory nature of multivariate models, factors with statistical significance values of $p < 0.1$ were considered to have a significant and independent association [14].

Independent variables in all models were checked for potential linear and nonlinear interactions ('modification effect' phenomenon). The analyses were performed using the computer statistics package Stata, version 12 (Stata Corporation, USA) [15]..

Results

General description of the studied population

Patient demographics are shown in Table 1.

A total of 603 patients with IHD were included into this study. Their mean age was 61.6 ± 9.8 years; mean IHD duration, 3 years (1; 7) and mean body mass index

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Table 2

Factors found to significantly differ between IHD patients with and without carbohydrate metabolism disorders

Characteristics	Patients without CMD n = 317	Patients with CMD n = 286	Comparisons between groups
Clinical			
Gender	77% men	70% men	0.04*
BMI, kg/m^2	28.2 ± 4.3	30.4 ± 4.5	0.00005**
Arterial hypertension, %	41.3	51.4	0.01*
IHD duration, years	2 (0.8; 6)	3.5 (1; 9)	0.01***
Factors associated with drug use			
Use of any nitrates, %	38.5	51.4	0.0005*
Use of ACE inhibitors/ARB, %	53.0	60.8	0.03*
Angiographic			
Maximum stenosis severity, %	91 (78; 100)	97 (84; 100)	0.0002***
Stenosis >95%, %	38.8	55.6	0.0005*
Number of occluded arteries	0.4 ± 0.6 0 (0; 1)	0.5 ± 0.6 0 (0; 1)	0.001***
Laboratory findings			
Urea, mmol/L	5.7 (4.9; 6.9)	6.3 (5.2; 7.4)	0.0009***
Triglycerides, mmol/L	1.45 (1.14; 1.95)	1.7 (1.3; 2.43)	0.00005***
Monocytes, %	7.8 (6.5; 9.0)	7.1 (5.91; 8.6)	0.002***

* χ^2; ** t-test; *** Mann–Whitney test; ACE inhibitor–angiotensin-converting enzyme inhibitor; ARB–angiotensin II receptor blocker

(BMI), 29.2 ± 4.5 kg/m2. The majority (73.5%) of patients were male. At the time of the study, 23.4% of the patients were smokers, 31.5% had a family history of cardiovascular diseases, 87.7% had arterial hypertension, 60.4% had a history of myocardial infarction, 85.7% had exertional angina, 11.0% had silent ischaemia and 24.8% had a history of percutaneous coronary intervention. Regarding the number of affected coronary vessels, 42.3% of the patients had a single-vessel lesion, 30.5% had two-vessel disease and 17.9% had three-vessel disease.

52.6% of the patients (n = 317) had no evidence of CMD, 24.2% (n = 146) had type 2 diabetes mellitus (T2DM), 3.5% (n = 21), impaired glucose tolerance (IGT), 2.8% (n = 17), impaired fasting glucose (IFG), 1.0% (n = 6), type 1 diabetes mellitus (T1DM) and 16.1% (n = 97), unspecified CMD. Therefore, a total of 47.4% of patients (n = 286) had CMD. The patients with CMD differed from those without CMD at a number of clinical, demographic, angiographic and laboratory parameters ((Table 2) that were subsequently tested as potential confounders and modifiers of the association between CMD and collateral flow. There were no differences of other parameters depending on the presence of CMD.

CMD and collateral circulation

According to the univariate analysis results, collateral blood flow was unexpectedly better in the patients with CMD than in those without (MIR value 2 [0–3] vs 1 [0–2]; p = 0.002, Mann–Whitney test0. However, this association completely disappeared when the patients were divided into subgroups according to stenoses ≤95% or >95% (H3, Mann–Whitney test) indicating that the result of the univariate analysis of the whole group was false. Pairwise comparisons of MIR in the groups with various types CMD demonstrated that the patients with IHD and T2DM had better collateral blood flow than IHD patients without CMD (2 [0; 3] vs 1 [0; 2]; p = 0.004). However, when comparisons were made separately in the subgroups with 'moderate' (≤95%) or 'critical' (>95%) stenosis, this association was again lost. Thus, no association between collateral flow and CMD, including various types of CMD, was found in the univariate analysis.

A multivariate ordered logistic regression model was constructed to assess the association between CMD and coronary collateral blood flow. The model included factors that have been found to significantly differ between the IHD patients with and without CMD (Table 1) and also some key angiographic, clinical and biochemical factors. . This model showed that gender, BMI, use of nitrates, ACE-inhibitors and angiotensin II receptor blockers and biochemical factors listed in Table 1 were not statistically significant independent predictors of collateral blood flow and that they did not modify the association between CMD and collateral blood flow. Arterial hypertension, IHD duration, maximal stenosis severity and number of occluded arteries were all found to be statistically significant independent predictors of collateral blood flow and were retained in the model.

In the multivariate analysis, it was found that CMD were independently associated with decreased collateral blood flow (OR = 0.96; p = 0.003). Although this association was found to be statistically significant, collateral blood flow was reduced by just 2% in the patients with CMD.

Differences in the collateral blood according to the presence of CMD presence are shown in Fig. 1.

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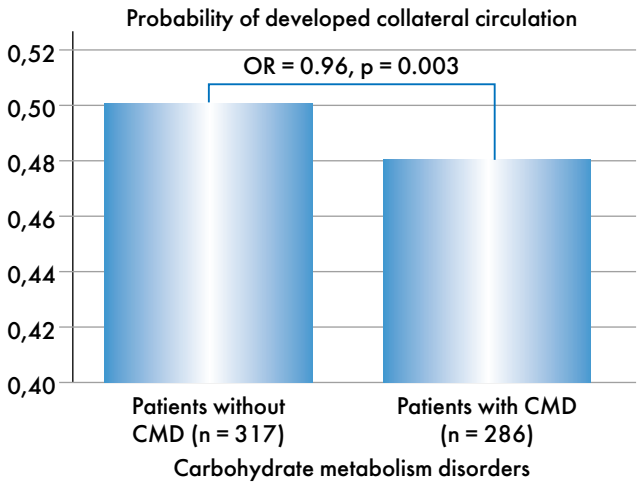

Fig 1. Collateral flow and carbohydrate metabolism disorders, taking into account the effect of other factors effect.

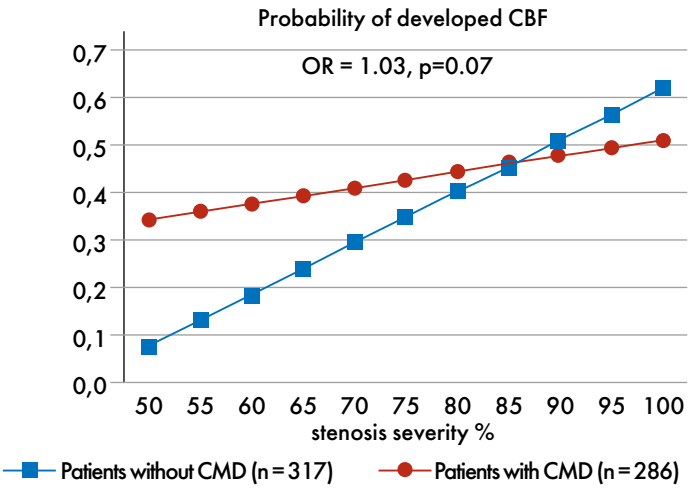

Fig. 2. Association between collateral blood flow and maximum stenosis severity according to the presence or absence of CMD and adjusted for confounding factors.

Both the univariate and multivariate analyses found that maximum stenosis severity was associated with collateral blood flow (ρ = 0.79, p < 0.00005 by the univariate analysis; OR = 1.07, p = 0.001 by the multivariate analysis).

In-depth analysis revealed that the strength of the independent association between index stenosis severity and collateral blood flow differed according to the presence of CMD. In the patients without CMD, the increase in maximum stenosis severity was found to be independently associated with increased collateral blood flow (OR = 1.11; p = 0.0005). In the patients with CMD, the association was significantly weaker (OR = 0.93; p = 0.005); however, there was a trend towards increased collateral blood flow with increased maximum stenosis severity (OR = 1.03; p = 0.07).

The associations between collateral blood flow and increased maximum stenosis severity in the patients with and without CMD are shown in Fig. 2.

The resultant association between collateral blood flow and maximum stenosis severity indicated that an increase in stenosis severity from 50% to 100% is accompanied by increased collateral blood flow; however, this increase is less marked in the presence of CMD.

Effect of aetiology of CMD

In the general group, MIR was considerably higher in the patients with T2DM than in those without CMD (OR = 1.7; p = 0.06 with the Bonferroni correction) or with IFG (OR = 3.3; p = 0.09), whereas IFG was found to be associated with decreased collateral blood flow compared to patients with IGT (OR = 3.3; p = 0.09). In subgroups divided according to 'moderate' and 'critical' stenosis, no difference in collateral blood flow according to the aetiology of CMD was observed, i.e. the previously determined association turned out to be false. Further, there was no apparent difference in collateral blood flow according to the aetiology of CMD in the final multivariate model.

Collateral blood flow and biochemical values related to carbohydrate metabolism

Overall, no difference in fasting glucose levels was observed between the subgroups divided according to collateral blood flow and the groups divided according to stenosis severity (H3, Kruskall–Wallis test). The ordered logistic regression model demonstrated that increased glucose levels were associated with increased collateral blood flow condition per MIR score in the general group (OR = 1.1; p = 0.03); however, this association was lost when the patients were divided into subgroups according to stenosis severity.

HbA_{1c} levels were measured in 233 patients with an average value of 6.5% ± 1.2%. No association between HbA_{1c} levels and collateral blood flow was observed in the general group, in the subgroup analyses according to stenosis severity or in the multivariate analysis.

HOMA insulin resistance index

HOMA insulin resistance indices were measured in 156 patients with IHD (73 without CMD, 9 with CMD, 9 with IGT, 20 with T2DM and 45 with unspecified CMD; HOMA indices were not determined in the patients with T1DM). The mean HOMA insulin resistance index was 3.7 ± 2.8 and was found to be higher in the patients with CMD than in those without CMD [median 3.3 (2.3–5.7) vs 2.4 (1.8–3.4); p = 0.0005, Mann–Whitney test) reflecting increased insulin resistance in the patients with CMD. No association between the HOMA index and collateral blood flow (MIR) was observed, including the subgroup analyses according to 'moderate' or 'critical' stenosis.

The introduction of HOMA indices as an independent variable or substitution for the 'CMD' variable in multivariate models did not demonstrate an independent effect of HOMA index on collateral blood flow.

Anti-hyperglycaemic medications

No differences in collateral blood flow were observed with the use of insulin or metformin in the general group or in the 'moderate' and 'critical' stenosis subgroups.

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Table 3

Collateral blood flow (MIR) according to the use of oral anti-hyperglycaemic medications				
IHD patient groups	Patients receiving two OAM	Patients receiving two OAM	Patients not receiving OAM	P-values
General group	2 (1; 3)	2 (0; 3)	1 (0; 2)	p = 0.05*
Stenosis ≤95%	1 (1; 1.5)	0 (0; 0)	0 (0; 1)	p = 0.01*
Stenosis >95%	2 (2; 3)	3 (2; 3)	2 (2; 3)	H3*

*Kruskal–Wallis test; OAM–oral anti-hyperglycaemic medications

In the general group, the patients receiving sulphonylureas (SU, n = 37) had significantly increased collateral blood flow compared with the patients not receiving SU (MIR 2 [1; 3] и 1 [0; 2]; p = 0.02, Mann–Whitney test). Subgroup analysis according to 'moderate' or 'critical' stenosis demonstrated that this association was inaccurate. In the multivariate analysis, an effect of SU on collateral blood flow was not demonstrated.

In the general group and subgroup IHD patients with moderate stenosis of coronary arteries, the patients receiving a large number of oral anti-hyperglycaemic medications (OAM) were found to have increased collateral blood flow (Table 3).

However, an independent association between the use of anti-hyperglycaemic mediations and collateral blood flow was not demonstrated.

MS components

To analyse the association between the number of MS components and collateral blood flow, the following criteria were evaluated from the data obtained from medical records (n = 535): triglyceride level ≥ 1.7 mmol/L; high-density lipoprotein cholesterol (HDLPC) level < 1.03 mmol/L in men and <1.29 in women; arterial hypertension; fasting blood glucose ≥ 5.6 mmol/L and T2DM.

We found that 12.3% of the patients (n = 66) had no MS component, 20.9% (n = 112) had one MS component, 27.1% (n = 145) had two MS components, 21.6% (n = 115) had three, 13.5% (n = 72) had four and 4.7% (n = 25) had all five. No association between the number of MS components and collateral blood flow was found by the univariate or multivariate analyses, including the subgroup analyses according to 'moderate' and 'critical' stenosis.

Discussion

CMD are known risk factors for the development of cardiovascular diseases and their adverse outcomes (16). Thus, there is a higher incidence of myocardial infarction, higher post-infarction mortality, larger infarction zones and higher incidence of post-infarction congestive heart failure (CHF) in DM (17).

Accordingly, prior to the study initiation we anticipated an adverse effect of CMD on collateral blood flow. However, the findings of this study revealed a more complex interaction between CMD and collateral blood flow. The univariate analyses showed a positive association between collateral blood flow (MIR) and CMD, i.e. better collateral blood flow was observed in the patients with CMD. However, a separate analysis in IHD patient subgroups formed according to 'moderate' (≤95%) and 'critical' (>95%) stenosis of coronary arteries failed to confirm this association. The multivariate logistic regression model, after adjustment for confounders, demonstrated significantly decreased collateral blood flow in the patients with CMD.

This result seems logical as there are many known CMD-related abnormalities of arteriogenesis mechanisms, with studies in patients with occlusions confirming this relationship (5, 18). However, this is the first study to demonstrate that this association is independent of concomitant factors. Also, it is the first one to extend this finding to patients without occlusions.

As CMD comprise conditions with various degrees of pathophysiological abnormalities, we propose that the types CMD may differently affect collateral blood flow. Indeed, in the whole group MIR was found to be lower in the patients with impaired fasting glucose levels compared to those with impaired glucose tolerance (OR = 3.3; p = 0.09), T2DM (OR = 3.3; p = 0.09) and those without CMD (OR = 2.72; p = 140). However, these associations were not confirmed by the multivariate analysis, which could be related to a small number of observations in some subgroups.

According to the univariate analysis, the use of SU was found to be associated with increased collateral blood flow in the > 95% stenosis subgroup and consequently, in the whole group. These results are particularly interesting in the light of findings demonstrating a potentially negative effect of SU on nitric oxide meditated vasodilation (19). Although the multivariate model used in this study found neither a positive nor a negative association between collateral blood flow and the use of SU, both in the whole group and in the subgroups with 'moderate' and 'critical' stenosis, the pathophysiological effect of SU on myocardial blood flow requires further investigation.

According to the results of the univariate analysis, there was no significant effect of HbA1c levels on collateral blood flow. The HbA1c levels were found to not have an independent effect on collateral blood flow in the multivariate models. These results may seem conflicting with the above mentioned differences in collateral blood flow differs depending on the presence of CMD; however, this discrepancy can have some explanation. Firstly, the number of patients with measured HbA1c levels was more than 2-fold less than the whole study population. Besides, the HbA1c

levels reflect carbohydrate metabolism over 3 months prior to the measurement, while process of collateral blood flow formation can take substantially longer and therefore may not correlate with the HbA1c levels.

Previous concepts of an association between the insulin resistance index (HOMA) and collateral blood flow were not confirmed by our multivariate model built for assessment of an association between CMD and collateral blood flow.

In the present study, an effect of CMD on collateral blood flow relating to the severity of coronary artery stenosis was demonstrated. The presence of CMD was found to be associated with a less marked physiological response (collateral blood flow formation) to increasing maximum stenosis severity. Further, as shown in Fig. 2, the prevalence of good collateral blood flow in patients with stenoses ≤95% was found to be lower than in those without CMD. Stenosis duration, not measured in this study, may serve as the most probable explanation for this phenomenon. The standard limitations of 'cross-sectional' study designs, in addition to insufficient numbers of patients with some aetiologies of CMD, apply to this study.

A role of MS components in collateral blood flow, reported in previous studies, was not found in this study. This discrepancy may be explained by differences in the sampling and statistical modelling methods.

Conclusions

1. CMD in patients with chronic IHD are independently associated with decreased collateral blood flow (OR = 0.96; p = 0.003).
2. CMD in patients with chronic IHD weaken the association between maximum stenosis severity and collateral blood flow (OR = 0.93; p = 0.005).
3. Associations between collateral blood flow and the use of anti-hyperglycaemic medications, HbA_{1c} levels and MS components (insulin resistance, BMI, triglyceride levels, fasting glucose levels, HDLPC levels and arterial hypertension) were not found.

Funding and conflict of interest

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