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Endotypes of angina with non-obstructive coronary arteries: a prospective multicentre study

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Abstract

Background and Aims Angina with non-obstructive coronary arteries (ANOCA) is a prevalent myocardial ischaemic syndrome, and women are disproportionately affected. Mechanisms of ischaemia are challenging to diagnose and treatment is empirical.

Methods Consecutive patients with angina (or equivalent symptoms), no angiographically severe stenosis and fractional flow reserve > 0.80 undergoing coronary functional testing were prospectively enrolled in nine centres in Europe and North America. Haemodynamic endotypes were assessed measuring coronary flow reserve and resistance using an intracoronary pressure- and temperature-sensitive sensor and bolus thermodilution. Measurements were obtained during resting conditions and following adenosine and acetylcholine. Chest pain and electrocardiographic ischaemic changes were recorded. The participant characteristics of each haemodynamic endotype were investigated using regression analysis. A three-step Delphi consensus method was applied to identify endotype-specific therapies.

Results Overall, 1001 participants (mean age 62 ± 11years, 56% female) were enrolled and eight distinct endotypes were defined by adenosine testing ($n = 3$) and acetylcholine testing ($n = 5$), respectively: high resting coronary blood flow ($n = 195$, 19%); high resistance ($n = 125$, 13%); compensated high resistance ($n = 112$, 11%); epicardial coronary spasm ($n = 162$, 17%); microvascular spasm ($n = 75$, 8%); endothelial dysfunction ($n = 96$, 10%); ischaemia w/o haemodynamic changes ($n = 68$, 7%); and enhanced cardiac nociception ($n = 79$, 8%). More than one endotype occurred in 119 (12%) individuals and normal responses occurred in 234 (23%) individuals. Each endotype was associated with distinct clinical correlates. The Delphi consensus (100% 'agree' or 'strongly agree') identified endotype-specific medical therapy with a Likert scale score ≥ 6 for all endotypes.

Conclusions In patients with suspected ANOCA, assessment of the symptomatic, electrocardiographic, and haemodynamic responses to adenosine and acetylcholine identifies distinct endotypes and enables mechanism-guided stratified medicine.

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Structured Graphical Abstract

Key Question

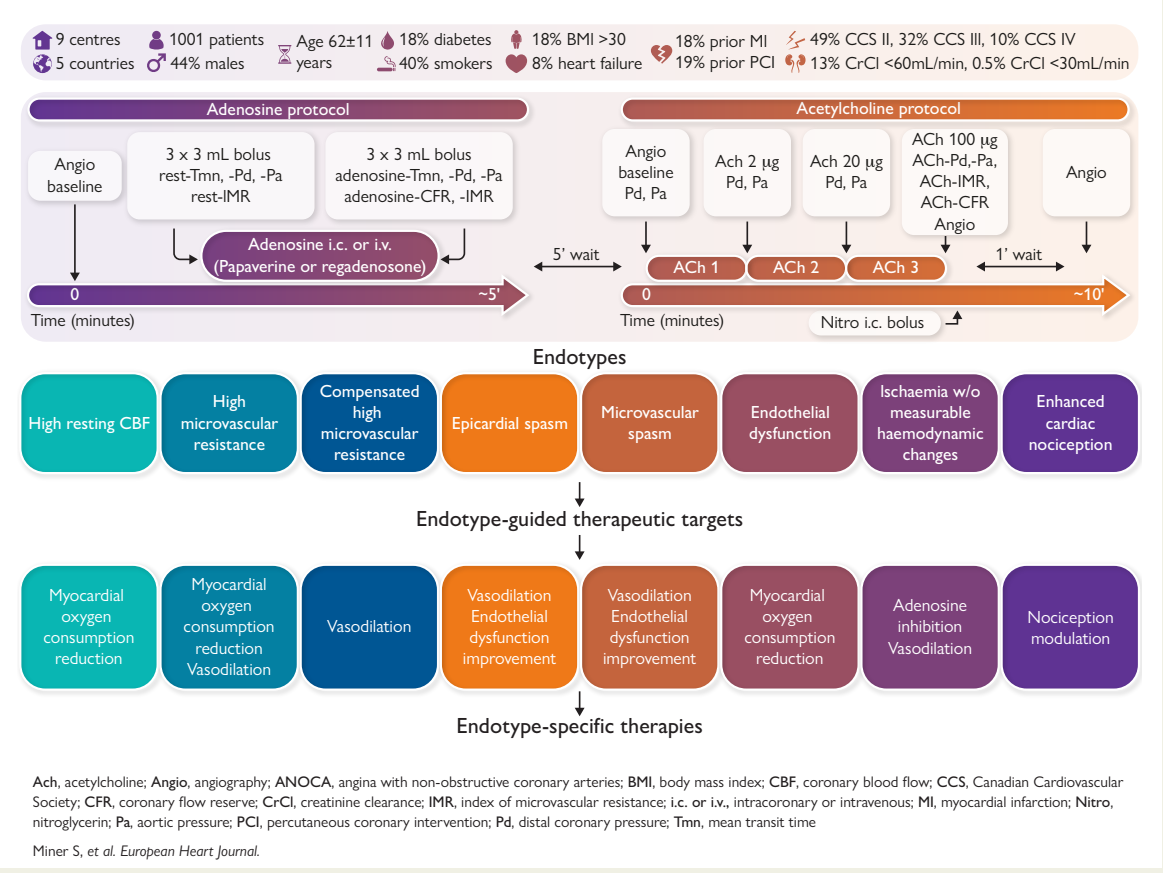
What are the endotypes of angina with non-obstructive coronary arteries (ANOCA) as defined by quantitative assessments of coronary vasomotor function? What is the prevalence of these endotypes in ANOCA? What are the clinical correlates of these endotypes and what are endotype-specific therapies?

Key Finding

Assessment of the symptomatic, electrocardiographic, and haemodynamic responses to adenosine and acetylcholine using intracoronary bolus thermodilution in 1001 ANOCA patients (56% women) identified eight distinct endotypes amenable to consensus-based medical therapy. An abnormal finding was detected in 77% of the patients, 12% showed more than one endotype.

Take Home Message

Stratified medicine involving quantitative assessments of coronary vasomotor function identifies endotypes of ANOCA amenable to mechanism-guided therapy.



Ach, acetylcholine; **Angio**, angiography; **ANOCA**, angina with non-obstructive coronary arteries; **BMI**, body mass index; **CBF**, coronary blood flow; **CCS**, Canadian Cardiovascular Society; **CFR**, coronary flow reserve; **CrCl**, creatinine clearance; **IMR**, index of microvascular resistance; **i.c. or i.v.**, intracoronary or intravenous; **MI**, myocardial infarction; **Nitro**, nitroglycerin; **Pa**, aortic pressure; **PCI**, percutaneous coronary intervention; **Pd**, distal coronary pressure; **Tmn**, mean transit time

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Keywords Angina • Coronary artery disease • Microvascular disease • Coronary spasm

Introduction

Angina and/or myocardial ischaemia with non-obstructive coronary arteries (ANOCA/INOCA) affects more than one in three individuals with stable ischaemic heart disease, and women are more often affected.[1,2] This high prevalence of ANOCA, its impact on health-related quality of life[3] and prognosis,[4] and evidence supporting the role of invasive coronary function tests in persistently symptomatic patients[5] have led to a class I recommendation in international practice guidelines[6] and a call for further research into the diagnosis of this condition.[6] As underlined in these guidelines, ANOCA/INOCA is 'rarely correctly diagnosed and no tailored therapy is prescribed for these patients.'[6]

The introduction of invasive diagnostic measures of coronary flow reserve (CFR) and microvascular resistance,[7,8] typically only applied to adenosine responses, has been instrumental to hypothesize how abnormalities in these parameters may be associated with structural (capillary rarefaction, arteriolar remodelling, fibrosis) and/or functional alterations (impaired vasodilation) and/or myocardial metabolic dysfunction.[9–11] Dysregulation of multiple, distinct pathways that control coronary blood flow is implicated in the pathogenesis of ANOCA[12] and may be diagnosed invasively. This diverse pathophysiology presents a diagnostic and therapeutic challenge for clinical decisions in individual patients. A stratified medical approach guided by invasive evidence of coronary vasomotor dysfunction improves angina and health-related

quality of life.[5,13,14] Thus, a clinical algorithm to objectively classify patients with ANOCA, applied to both adenosine and acetylcholine responses, during routine care is needed to guide individualized therapy based on the mechanism of ischaemia (endotype).

The objectives of this study were (i) to prospectively implement a protocol to quantify responses to adenosine and acetylcholine and identify ANOCA endotypes in patients undergoing clinically indicated invasive management in multiple international centres; (ii) to determine the prevalence of each endotype and their overlap; (iii) to establish clinical correlates; and (iv) to produce, through a structure Delphi consensus process, a concept for endotype-specific therapies.

Methods

Study population

The Microvascular Dysfunction-Searching for a New Acetylcholine Spasm Definition (MICRO-SNAPE) is an international study of patients undergoing invasive angiography for suspected coronary artery disease (NCT06125392). The study has a cross-sectional design. Patients were not included if they were ≤18 years, had no angina or angina-equivalent symptoms, or had obstructive coronary artery disease [fractional flow reserve (FFR) ≤ 0.80), haemodynamic instability, coronary artery bypass grafts, decompensated congestive heart failure, acute renal failure, severe valvular heart disease, or comorbidities limiting (<1 year) life expectancy. All participants gave written informed consent.

The study involved nine cardiovascular centres in five countries (Germany, Italy, UK, Spain, Canada).

Invasive endotyping

Following coronary angiography, vasomotor function was assessed in all patients in the left anterior descending coronary artery using a standardized protocol (*Figure 1*). Haemodynamic responses were acquired using a combined pressure/temperature diagnostic guidewire (PressureWire X, Abbott Vascular, Irvine, CA, USA) with linked software (CoroFlow, CoroVentis, Uppsala, Sweden). Haemodynamic measurements were performed at rest, in response to adenosine (intravenous, 140 μg/kg/min or intracoronary, 140–200 μg bolus) and then intracoronary bolus doses of acetylcholine (2 μg, 20 μg, 100 μg). Symptoms, e.g. chest pain, and electrocardiography (ECG), e.g. ST-segment deviation, were simultaneously recorded.

Patients were recommended to avoid vasoactive medications on the day of the test. All tests were performed during continuous 12-lead ECG monitoring. The occurrence of chest pain was assessed during intracoronary acetylcholine infusion but not during adenosine infusion as adenosine can cause chest pain through the stimulation of A1 receptors in the absence of ischaemia.[15]

Vasomotor responses

In line with practice guidelines,[6,16–18] thresholds for normal responses were defined as follows:

Adenosine-CFR > 2.5
Adenosine-IMR < 25
Acetylcholine-CFR > 1.5

As quantitative confirmation of the absence of acetylcholine-induced spasm:

Acetylcholine-Pd/Pa > 0.80
Acetylcholine-IMR < rest-IMR

Endotype classification

Abnormal responses were classified in three groups ('abnormal adenosine responses,' 'abnormal acetylcholine responses', 'altered nociception') resulting in eight endotypes.

Abnormal adenosine responses

(1) Adenosine-CFR < 2.5 with adenosine-IMR < 25 (later described as 'high resting coronary blood flow')
(2) Adenosine-CFR < 2.5 with adenosine-IMR > 25 (later described as 'high resistance')
(3) Adenosine-CFR > 2.5 with adenosine-IMR > 25 in which compensation mechanisms are recruited to maintain CFR (later defined as 'compensated high resistance)

Abnormal acetylcholine responses

(1) Acetylcholine-Pd/Pa < 0.80 and/or >90% coronary diameter reduction with ECG changes and angina during acetylcholine (later defined as 'epicardial spasm')
(2) Acetylcholine-IMR > rest-IMR (i.e. measurable evidence of increased microvascular resistance during acetylcholine) with ECG changes and angina during acetylcholine (later defined as microvascular spasm)
(3) Acetylcholine-CFR < 1.5 with preserved Adenosine-CFR and no microvascular spasm (later defined as 'impaired endothelium-dependent vasodilation')
(4) Angina AND ischaemic ECG changes during acetylcholine without measurable haemodynamic abnormalities

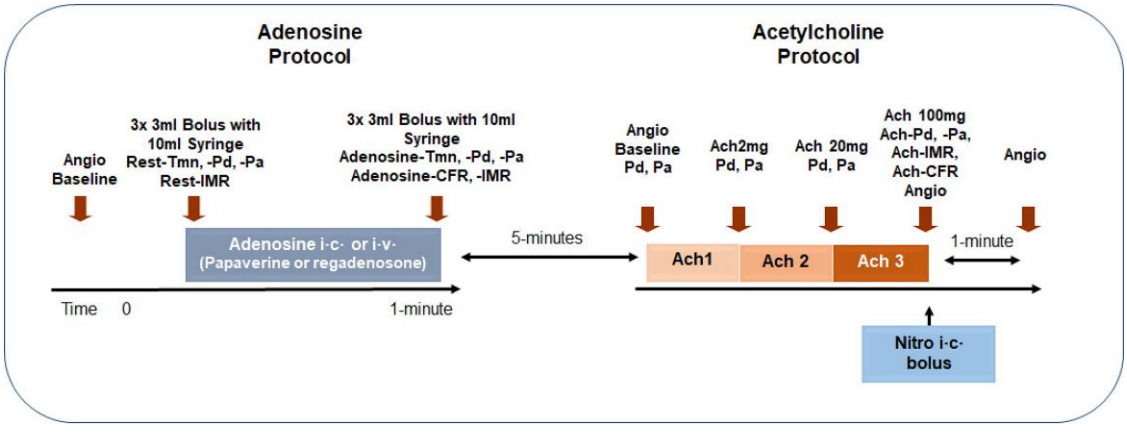

Figure 1 Protocol for the haemodynamic assessment. The protocol duration was approximately 9 min

Altered nociception

Angina without ischaemic ECG changes or haemodynamic abnormalities during acetylcholine infusion (later defined as enhanced nociception).

Bias

Bias was minimized by prospective enrolment, simultaneously followed by data lock after the sample size had been achieved. The data were archived centrally, and the analysis was undertaken independent of the site clinical investigators who remained blind until the statistical analysis was reported.

Data management

Anonymized routine data were collected via a standardized electronic case report form (see Supplementary data).

Statistics

Sample size

For the analysis of differences in the diagnosis of microvascular spasm using haemodynamic and clinical criteria, 946 patients would be required to have a 90% chance of detecting, as significant at the 5% level, a decrease in the prevalence of the diagnosis from 40% (using clinical criteria) to 30% (using haemodynamic criteria).

Statistics

Univariate logistic regression for binary categorical and linear regression for continuous data was performed using 'statsmodels' to assess the association of individual predictors with the outcome variable. Continuous data were standardized prior to analysis. Predictors with missing values were managed by excluding cases with missing data from the respective analysis. Comparisons involved analysis of variance, the Mann–Whitney test for non-paired samples, and the Fisher's exact and χ^2 for contingency tables. Individuals with normal haemodynamic responses and no angina or ECG changes during acetylcholine tests were classified as a reference group.

Statistics were undertaken by researchers (R.S., C.B.) at the University of Glasgow, independent of the sites. The analysis was performed using MedCalc and a custom Python function (Python version 3.11.0) (see Supplementary Methods).

Structured consensus on endotype-specific therapies

The Delphi method was used to achieve consensus among thirteen interventional cardiologists on endotype mechanisms (round 1) and suggested therapies (rounds 2–4; Supplement data).

Results

Population characteristics

Overall, 1001 consecutive patients with ANOCA were included. Comprehensive invasive assessments of coronary pressure and flow measured initially during infusion of adenosine and then acetylcholine were performed in each individual (*Figure 1*).

The cohort characteristics are presented in *Table 1*. The population was balanced in terms of sex/gender (56% female), and 81% of individuals reported chronic chest pain classified as Canadian Cardiovascular Society angina Class II or III severity.

In 234 (23%) patients, administration of adenosine followed by acetylcholine was associated with normal haemodynamics and no symptoms or ECG changes. These individuals were defined as reference group.

Endotype prevalence

The prevalence of each endotype is reported in *Figure 2*. Eight distinct endotypes (three identified by adenosine testing and five by acetylcholine testing) were defined: high resting coronary blood flow ($n = 195$, 19%); high resistance ($n = 125$, 13%); compensated high resistance ($n = 112$, 11%); epicardial coronary spasm ($n = 162$, 17%); microvascular spasm ($n = 75$, 8%); endothelial dysfunction ($n = 96$, 10%); ischaemia w/o haemodynamic changes ($n = 68$, 7%); and enhanced cardiac nociception ($n = 79$, 8%). More than one endotype occurred in 119 (12%) individuals (11 had 3 endotypes), indicating minimal overlap between groups (see Supplementary data online, *Figure S1*). Normal responses occurred in 234 (23%) individuals.

Endotypes and clinical associations

The associations of each endotype with comorbidities, clinical characteristics and haemodynamic responses are described in *Figure 3* and the Supplement data (Supplementary data online, *Tables S1–S8*).

Abnormal adenosine responses

High resting blood flow

The group with low adenosine-CFR (<2.5) but normal adenosine-IMR (<25) represented the most prevalent endotype ($n = 195$, 19%) (see Supplementary data online, *Tables S1* and *S2*). They were more often female ($P = .036$), and hypertension was less common ($P = .039$). Individuals in this category exhibited higher cardiac work (rate pressure product) and an increased resting coronary blood flow (both $P < .0001$) (*Figure 4*). The increase in resting coronary blood flow (+43% compared with controls) exceeded the increased cardiac work (+11%), resulting in markedly lower rate pressure product/flow compared with controls ($P < .0001$; *Figure 4*).

High resistance

The endotype of low adenosine-CFR (<2.5) and concurrent high adenosine-IMR (>25) affected 13% of the patients ($n = 125$) (see Supplementary data online, *Tables S1* and *S3*). Compared with controls, this group was defined by higher IMR ($P < .001$) compatible with their older age ($P = .001$) and higher prevalence of prior MI ($P = .01$). Left ventricular ejection fraction and creatinine clearance were lower in this group ($P = .03$ and $P < .001$).

Compensated high resistance

The group with increased adenosine-IMR (>25) and preserved adenosine-CFR (>2.5) ($n = 112$, 11%) had the highest adenosine-IMR (see Supplementary data online, *Tables S1* and *S4*). Compared with controls, the rest-IMR was higher ($P < .001$), and left ventricular ejection fraction ($P = .023$), heart rate ($P = .027$), and resting coronary blood flow ($P < .001$) were lower. Consequently, the rate pressure product/coronary flow in this group was higher than in controls ($P < .0001$). These patients were more often smokers ($P = .02$).

Abnormal acetylcholine responses

Epicardial spasm

The group with epicardial coronary artery spasm ($n = 162$, 17%) had a higher prevalence of prior myocardial infarction and percutaneous coronary intervention (PCI) ($P = .030$ and $P = .010$) (see Supplementary data online, *Tables S1* and *S5*). The prevalence of subclinical atherosclerosis was higher in patients with epicardial spasm ($P = .001$, Supplementary data online, *Figure S1*) than in other endotypes; in

Table 1 Population characteristics ($n = 1001$)

	n	Mean	SD
Patients, *n*	1001		
Age, years		62	11
Male sex	437 (44%)		
Body mass index, kg/m^2	975	28	5
Creatinine clearance, mL/min	909	82	30
Left ventricular ejection fraction, %	963	58	5
White ethnicity	926 (93%)		
Risk factors			
Family history	271 (27%)		
Insulin-dependent diabetes	88 (9%)		
Non-insulin dependent	94 (9%)		
Smoking			
Current	115 (12%)		
Former	275 (28%)		
Hyperlipidaemia	616 (62%)		
Hypertension	623 (62%)		
Clinical presentation			
Chronic angina	884 (88%)		
Effort dyspnoea	38 (4%)		
Unstable angina	66 (7%)		
Non-ST-elevation myocardial infarction	12 (1%)		
Canadian Cardiovascular Society class			
I	60 (8%)		
II	350 (49%)		
III	230 (32%)		
IV	72 (10%)		
Timing of symptoms			
Rest only	145 (17%)		
Effort only	351 (42%)		
Both	348 (41%)		
Type of symptoms			
Typical	427 (68%)		
Atypical	198 (32%)		
New York Heart Association functional class			
I	149 (26%)		
II	157 (27%)		
III	66 (11%)		
IV	4 (1%)		
Heart failure			
None	919 (92%)		
Preserved ejection fraction	42 (4%)		
Reduced ejection fraction	7 (<1%)		
Mildly reduced ejection fraction	30 (3%)		
Peripheral artery disease	43 (4%)		
Prior percutaneous coronary intervention	191 (19%)		
Prior myocardial infarction	183 (18%)		
Prior stroke	46 (5%)		
Vasoactive therapies			
Angiotensin-converting enzyme inhibitor	258 (27%)		
Beta-blocker	428 (45%)		
Long-acting nitrate	96 (10%)		
Verapamil/diltiazem	35 (4%)		
Dihydropyridine calcium antagonist	282 (30%)		
Myocardial bridge	80 (11%)		
Haemodynamic variables			
Resting heart rate, b.p.m.	940	73	13
Pd/Pa rest	999	93	4
Rest-IMR	998	71	38
Adenosine-IMR	998	20	13
Fractional flow reserve	998	0.90	0.04
Coronary flow reserve	1000	3.5	1.9
Acetylcholine-Pd/Pa	895	0.89	0.08
Acetylcholine-IMR	930	32	22
Acetylcholine coronary flow reserve	944	2.6	1.6

CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microvascular resistance; M-W, Mann–Whitney; Pa, mean aortic pressure; Pd, mean pressure in the distal left anterior descending coronary artery; Tmn, transit time.

addition, patients with epicardial spasm and atherosclerosis had more cardiovascular risk factors than other groups (mean ± standard deviation 3.3 ± 0.1 vs 2.7 ± 0.1, $P = .004$). Acetylcholine-IMR ($P = .124$) was not different in this group, indicating distinct mechanisms for impaired acetylcholine responses in the epicardial and microvascular circulation. Acetylcholine-induced epicardial spasm was significantly more prevalent in patients with myocardial bridges (19.7% vs 10.2%, $P = .022$) compared with those without.

Microvascular spasm

In the group with microvascular spasm ($n = 75$, 8%), individuals were older ($P = .022$) and had lower creatinine clearance and higher resting

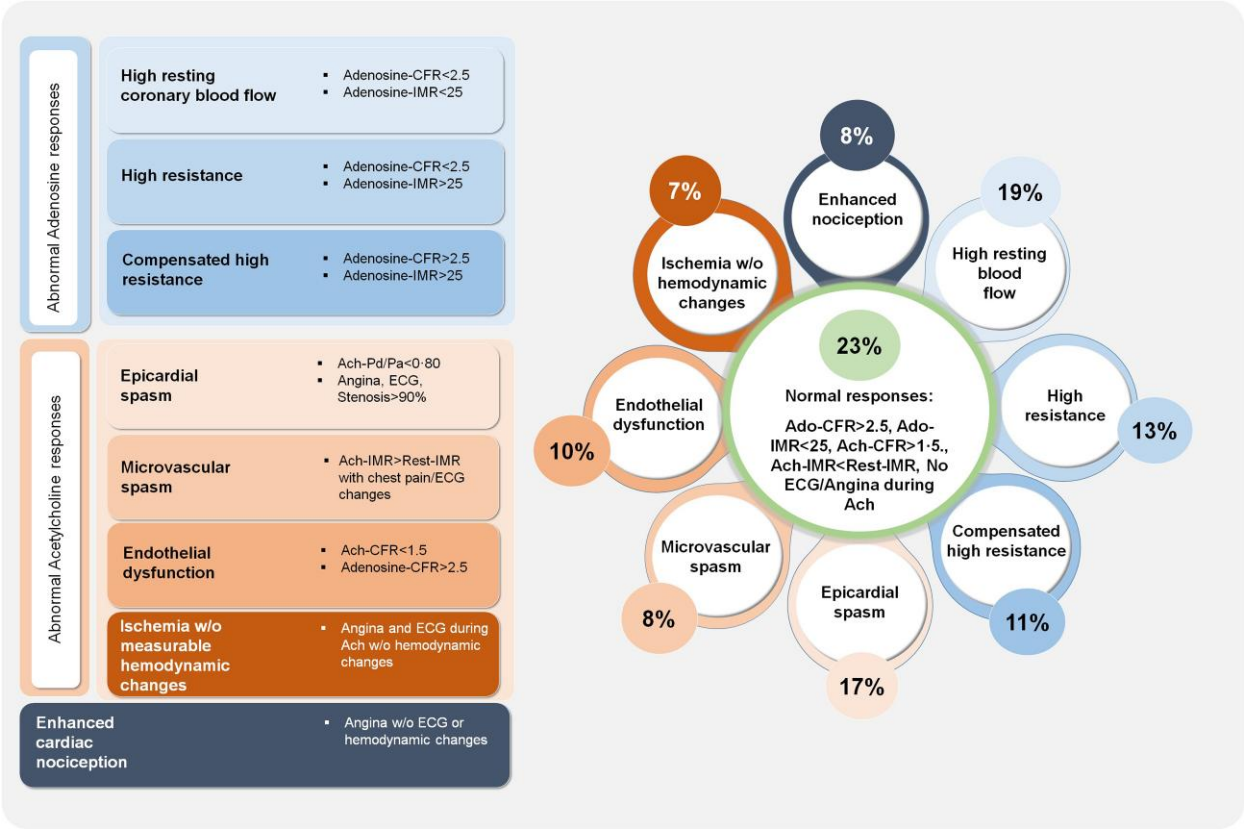

Figure 2 Definitions and prevalence of each endotype

heart rate (both $P < .0001$) (see Supplementary data online, *Tables S1* and *S6*). While a correlation (R^2=0.13, $P < .0001$) between acetylcholine- and adenosine-induced IMR occurred in the whole cohort, this correlation was absent (R^2=0.03, $P = .14$) in the microvascular spasm group (see Supplementary data online, *Figure S2*). Acetylcholine-Pd/Pa (expressing the epicardial effect of acetylcholine) was not different from controls ($P = .085$).

Impaired endothelium-dependent vasodilation

In the group with impaired endothelium-dependent vasodilation (endothelial dysfunction) ($n = 96$, 10%), male sex ($P = .039$) and prior PCI ($P = .030$) were more prevalent (see Supplementary data online, *Tables S1* and *S7*). Patients in this group had a lower left ventricular ejection fraction ($P = .047$) and hyperaemic flow ($P < .001$) in response to adenosine and to acetylcholine, respectively. Furthermore, 48% of the patients with the endothelial dysfunction endotype reported angina during acetylcholine infusion, 33% had evidence of ECG changes, and 27.5% had both.

Ischaemia without measured haemodynamic changes

The group with acetylcholine-induced angina and ECG signs of ischaemia and no haemodynamic abnormalities ($n = 68$, 7%) had a higher resting ($P = .006$) and hyperaemic heart rate ($P = .003$) (see Supplementary data online, *Table S8*). Acetylcholine-CFR and acetylcholine-IMR were not different from the reference group ($P = .208$ and $P = .143$). Based on COVADIS criteria, these patients would have qualified for the clinical diagnosis of microvascular spasm. If haemodynamic criteria for spasm are used instead of angiographic criteria, then the percentage of patients with microvascular spasm reduced from 15% to 7%.

Enhanced nociception

The participants ($n = 79$, 8%) reporting angina during intracoronary infusion of acetylcholine in the absence of haemodynamic or ECG abnormalities did not differ from controls in any characteristic.

Medical therapy—Delphi structured consensus

The consensus on endotype-specific medical therapy of 13 cardiologists is provided in *Table 2*. A median consensus above 6 on the Likert scale (agree) occurred for all endotypes.

Discussion

This international study addressed the gap in clinical practice for a comprehensive classification of ANOCA endotypes, based on measurable coronary haemodynamic parameters, and stratified medical therapy linked to the mechanisms of disease (*Structured Graphical Abstract*). The results are relevant to clinical guidelines[6] and transferable to daily practice. Consistent with known associations between female sex and ANOCA,[1,2] most of the individuals in this population were female.

The protocol provided quantitative assessments of coronary pressure, flow and microvascular resistance, and adenosine- and

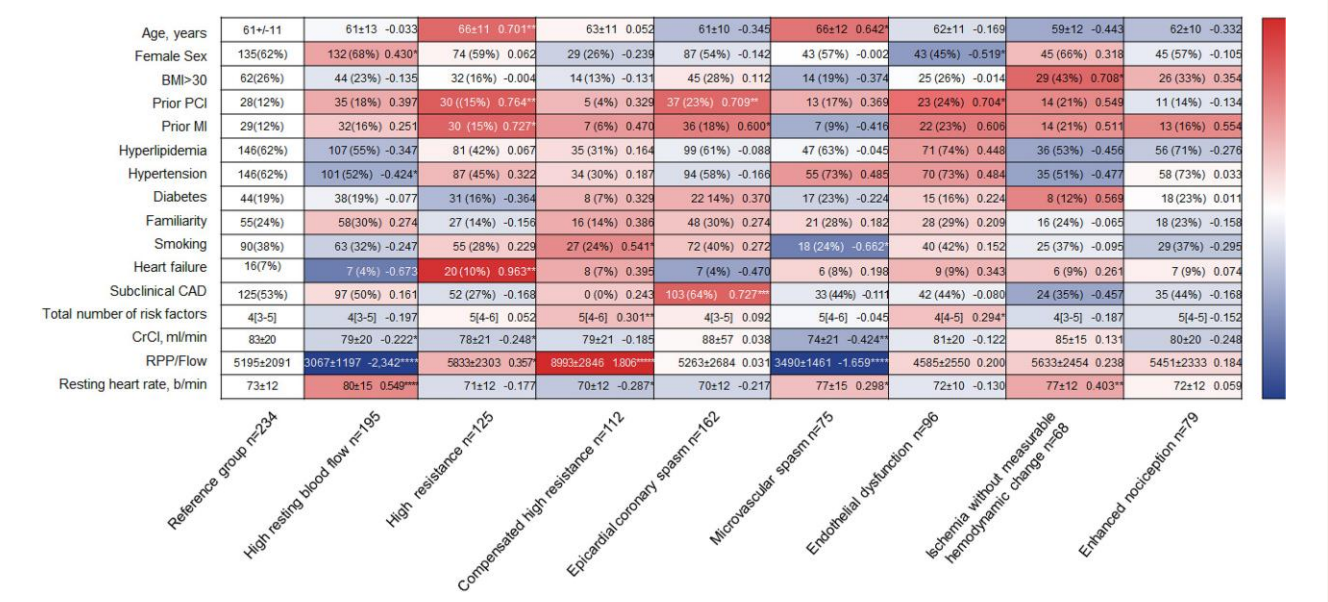

Figure 3 Heat map describing the phenotypic associations of each endotype (univariable logistic regression). Data in Supplementary data online, *Table S1*, categorical variables are presented as number (% in the endotype). Continuous variables are standardized prior to analysis (mean = 0, SD = 1). Beta coefficients are coloured from blue (−1) to red (1), with white representing 0. Statistical significance is indicated by asterisks: *<.05, **<.01, ***<.001, and ****<.0001. Missing data for each variable: age > 65: 48 missing; female sex: 48 missing; body mass index > 30: 74 missing; prior percutaneous coronary intervention: 48 missing; prior myocardial infarction: 48 missing; hyperlipidaemia: 50 missing; hypertension: 52 missing; diabetes: 51 missing; familiarity: 52 missing; smoking: 54 missing; heart failure: 51 missing; subclinical coronary artery disease: 51 missing; total number of risk factors: 58 missing; CrCl: 140 missing; rate pressure product/coronary flow: 111 missing; resting heart rate: 109 missing

acetylcholine-induced vasomotor responses. Our protocol had a high diagnostic yield, with at least one abnormality in more than two-thirds of patients with suspected ANOCA. The overlap among the endotypes was limited, and clinical signatures of each endotype (clinical characteristics, comorbidities) differentiated patients with distinct underlying pathophysiology that would otherwise have passed undetected. The consensus-based stratified treatment of ANOCA determined using a Delphi process should be evaluated in prospective clinical trials enrolling patients with a similar endotype.

In 1959, coronary artery spasm was hypothesized by Prinzmetal *et al.*[19] as being a cause of angina and transient ST-segment elevation and this hypothesis was confirmed by Maseri *et al.*[20,21] In 1973, myocardial ischaemia during atrial pacing was described in 10 patients without obstructive coronary arteries by Arbogast and Bourassa; this condition was labelled 'syndrome X'. This contrasted with the paradigm of myocardial ischaemia being exclusively caused by flow-limiting coronary artery disease, and Camici and Crea[22] implicated functional alterations of the coronary circulation. The current data confirm that ANOCA represent a framework in which different forms of inefficient microvascular autoregulation and (micro)vascular spasm have a pathogenetic roles, in the presence or absence of atherosclerosis and altered cardiac workload.[20–22]

Endotype diagnosis and management

Adenosine-CFR has established prognostic significance,[23,24] whereas the added value of IMR in chronic coronary syndrome is debated.[5,25] When using these indices in combination, our findings identify three distinct endotypes that would not be diagnosed by a CFR-only approach.

In patients with low adenosine-CFR and preserved microvascular resistance, despite a resting cardiac workload that was on average higher, the ratio of workload/flow was lower, i.e. an unbalanced myocardial function/coronary blood flow relationship.[26] This points to a disorder characterized by impaired myocardial oxygen delivery and/or utilization compensated by an enhanced oxygen supply rather than a primary vascular alteration. Vasodilator drugs are unlikely to produce clinical benefit since the impaired CFR does not appear to depend on lack of vasodilation but rather on increased resting coronary flow. In these patients, cardiac workload and metabolic inefficiency, such as in diabetes,[27] inflammation with inducible nitric oxide synthase activation,[9] or other mechanisms which disturb normal metabolism/autoregulation,[28] may be causal[29,30] and amenable to targeted pharmacological therapy.[31] As a first line, drugs reducing resting coronary blood flow, such as beta-blockers, or drugs which improve myocardial metabolism, such as ranolazine, might be beneficial.

In patients with concurrent abnormal IMR ('high resistance'),[9] the increased prevalence of heart failure, prior myocardial infarction, and older age is compatible with vascular remodelling (structural problem), compression of the microcirculation, and/or systemic vascular disease. Strategies aimed at reducing myocardial wall tension, oxygen consumption, and peripheral resistance may be preferred.

Among patients with increased IMR, individuals with normal CFR have higher resting coronary microvascular resistance and a lower rate pressure product, as a compensatory mechanism aimed at reducing oxygen demand in resting conditions. Medical therapy should primarily address the increased coronary microvascular resistance.

Combined quantitative assessment of adenosine and acetylcholine haemodynamic responses resulted in the identification of five additional endotypes.

Epicardial spasm is associated with subclinical atherosclerosis. Whether this link is anatomic or other shared pathophysiology such

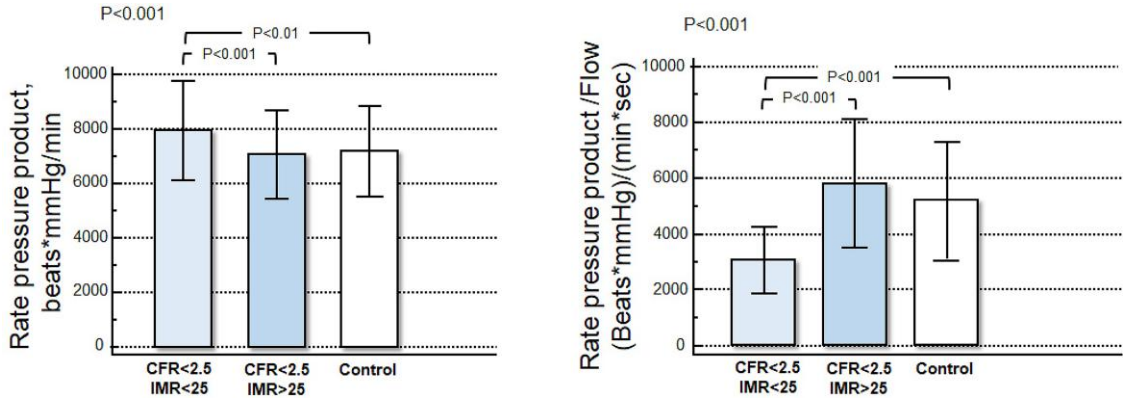

Figure 4 Rate pressure product and rate pressure product/flow. Patients with reduced coronary flow reserve and normal index of microvascular resistance had an increased resting rate pressure product (+11%) and an even larger increase in flow (+41%), resulting in a reduced rate pressure product/coronary blood flow. This observation suggests a state of resting activation and metabolic dysfunction

as inflammation or abnormal nitric oxide synthase activity is unclear. Nonetheless, in patients with coronary atherosclerosis, preventive therapy, including aspirin, angiotensin-converting enzyme inhibitors, and lipid-lowering drugs, is recommended in guidelines, and vasodilators improve symptoms and prognosis.[6,32]

Microvascular spasm exhibited different phenotypic associations. While epicardial vasomotion is modulated by a balance among smooth muscle cell reactivity, sympathetic input, and the bioavailability of nitric oxide, the contribution of nitric oxide is comparatively less in the microcirculation as compared with conduit arteries.[32,33] Use of non-nitric oxide-based peripheral vasodilators and rate-limiting beta-blockers or verapamil would seem appropriate in this group, especially if the resting heart rate is elevated.

Impaired acetylcholine-CFR is an independent predictor of prognosis.[25] We identified patients with suboptimal vasodilation resulting in a reduction of acetylcholine-CFR but no acetylcholine-induced increase of IMR (which would be classified under microvascular spasm). Vasodilators and drugs which improve endothelial function, along with adherence to recommendations to reduce cardiovascular risk factors, might be attempted in these patients.

Some patients did not exhibit any haemodynamic alteration in response to acetylcholine, yet they exhibited typical ischaemic ECG changes and typical angina. It has been hypothesized that heterogeneous microvascular dilation may lead to the 'steal phenomenon' from myocardial regions with higher vascular resistance to regions with lower resistance thus causing ischaemia.[20] In patients with adenosine-induced angina, adenosine antagonists, or vasodilators, might improve symptoms by limiting inappropriate adenosine-mediated vasodilation.[34]

The final endotype included patients with acetylcholine-induced chest pain but no ECG change nor haemodynamic abnormalities. For these patients, treatment of abnormal cardiac nociception, including behavioural therapy, stress management, and drugs reducing ischaemic pain generation or modulating pain perception, should be a priority.[35]

Most of the individuals enrolled in this study were female. Our findings advance the agenda of the Lancet Women and Cardiovascular Disease Commission.[36] Our study elucidates the feasibility and diagnostic value of quantitative coronary function tests enhancing diagnostic options for women (and men) with ANOCA. Our study adds evidence to support specific aims of this Commission, including reducing knowledge gaps, improving care, and enhancing global awareness about sex-specific disparities in ischaemic heart disease.

Generalizability

This study was undertaken during daily clinical practice in centres in Europe and North America. Our algorithm provides a quantitative readout to inform the diagnosis and treatment of ANOCA endotypes in daily practice. The study has potential to move the field forward in the following ways: first, the description of endotypes in ANOCA facilitating guideline recommendations[6]; second, the definition of specific treatment for each endotype based on mechanisms of disease; and third, an objective method to be used in clinical trials of medical therapy in ANOCA.

Limitations

The above classification was based on binary cut-off values (e.g. 25 for IMR) and mediators which, although widely applied and recommended to simplify decisions, do not necessarily reflect the complexity of vascular homeostasis. For instance, acetylcholine testing is an established method to assess vasomotor function, but this test does not distinguish between endothelial dysfunction and smooth muscle cell hyperreactivity and it does not necessarily reflects the physiological effects of endogenous acetylcholine which is rapidly degraded by the ubiquitous cholinesterase. As well, it is unclear whether adenosine (particularly in this single dose) can fully recruit flow reserve.[37] Further, a number of other cell types (for instance pericytes) are involved,[38] and testing with other vasoactive substances, including vasoconstrictors and vasodilators, may provide additional insight, for instance, alpha-adrenergic or serotonergic[39,40] vasoconstriction, which both have been implicated in myocardial ischaemia in patients. Additionally, testing multiple coronary arteries may provide additional insight. Also, there may be other endotypes not captured by our protocol. Invasive endotyping was based on vasomotor testing of the left anterior descending coronary artery since this artery subtends the largest amount of myocardium, its distribution territory is less variable among subjects, and since perfusion defects in patients with coronary dysfunction are not expected to reflect necessarily the distribution territory of the three major vessels like 'traditional' coronary artery disease. Since the diagnostic guidewire is necessary for adenosine testing, the wire-based algorithm for quantifying the response to acetylcholine does not alter costs or risks. Alternative

Table 2 Endotype-specific medical therapy provided by 13 interventional cardiologists based on a structured consensus process

Endotype	Phenotypic associations	First line therapy	Second line and adjunctive therapies	Likert score (median [IQR])
High resting CBF	Increased flow at rest, increased rate pressure product, female sex, hypertension	B-blocker, ivabradine	Verapamil/diltiazem Adjunctive: SGLT-2 inhibitor, metformin, ranolazine, anxiolytics	7 [7]
High resistance	Older age, higher prevalence of comorbidities, higher rate of heart failure and prior MI	Nebivolol, ranolazine, second-generation DHP Ca-antagonists, SGLT-2 for the association with HF	PDE5 inhibitors, coronary sinus reducer[a]	7 [7]
Compensated high resistance	Smoking, risk factors, decreased rest rate pressure product/flow	Nebivolol, ranolazine, second-generation DHP Ca-antagonists	Carvedilol, Coronary sinus reducer[a] Adjunctive therapy: SGLT-2 inhibitors	7 [7]
Epicardial spasm	(Sub)clinical coronary artery disease	Verapamil/diltiazem, sublingual nitrates, statins, long-acting nitrates[b]	Nebivolol, nicorandil[b] Adjunctive therapy: cilostazol (PDE3 inhibitor), PDE5 inhibitors, supplements (e.g. folic acid, L-arginine, modern antioxidants), nebivolol	7 [7]
Microvascular spasm	Older age, higher prevalence of smoking and impaired renal function	Second-generation dihydropyridine calcium channel antagonists, verapamil/diltiazem	Long-acting nitrates[b] Adjunctive therapy: cilostazol (PDE3 inhibitor), supplements (e.g. folic acid, L-arginine, modern antioxidants)	7 [7]
Endothelial dysfunction	Male sex, risk factors	Nebivolol	Adjunctive therapy: cilostazol (PDE3 inhibitor), supplements (e.g. folic acid, L-arginine, modern antioxidants)	7 [6–7]
Ischaemia w/o haemodynamic changes	Higher resting heart rate, obesity	Xanthine (particularly if angina with adenosine), second-generation DHP Ca-antagonists	Second line: non-DHP Ca-antagonist (e.g. verapamil, diltiazem) Adjunctive therapy: caffeine	7 [6–7]
Enhanced nociception (angina but no ECG or haemodynamic changes)	None	Psychologic intervention, low-dose tricyclic antidepressants	Adjunctive therapy: xanthine, imipramine	7 [6–7]

CBF, coronary blood flow; ECG, electrocardiogram; DHP, dihydropyridine; IQR, interquartile range; MI, myocardial infarction; PDE, phosphodiesterase; SGLT, sodium-glucose co-transporter.
[a]Implantation of the coronary sinus reducer was supported by 10 participants but considered too experimental by three.
[b]Two participants agreed with the opinion but raised concerns about the long-term effects of long-acting nitrates and nicorandil on endothelial function which may be prevented by use of high-dose folic acid. In the endotype with ischaemia and no measured haemodynamic change, one participant abstained from voting ('neither agree nor disagree').

diagnostic methods (continuous thermodilution, Doppler; non-invasive testing) or combinations of methods may offer further insights. Future studies should include more diverse populations and follow-up data. We excluded patients with angiographically evident stenosis and those with FFR < 0.80. However, this does not exclude atherosclerotic burden, and we actually show that subclinical atherosclerosis (FFR > 0.80 but <0.90) is associated with epicardial spasm. Studying the relationship between the latter and coronary vasomotor abnormalities will require the additional use of intracoronary imaging. Finally, we acknowledge that missing data on participants' characteristics is a limitation.

Conclusion

Stratified medicine involving quantitative assessments of coronary vasomotor function identified eight endotypes of ANOCA amenable to mechanism-guided therapy.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

C.B. is employed by the University of Glasgow which holds consultancy and research agreements for his work with Abbott Vascular, AskBio, AstraZeneca, Boehringer Ingelheim, CorFlow, Edwards Lifesciences, Merck, Servier, Novartis, Roche, Siemens Healthcare, and Zoll Medical. T.G. has received research support from Abbott Vascular and Neovasc/Shockwave, speaker's honoraria from Abbott Vascular, Neovasc/Shockwave, BMS, Novartis, and derherzkatheterkurs.de. G.C. has received research support from SMT, Siemens, GE

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Data Availability

Data collected for the study, anonymized, and a data dictionary will be made available to others upon motivated request, approval of a research proposal, and signing of a data access agreement.

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Ethical Approval

Ethics approval for this research database was obtained by T.G. and by site investigators as appropriate. All participants gave written informed consent.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is NCT06125392.

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