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Autonomic Nervous System Imbalance Reflected by Reduced Heart Rate Variability in Patients with Coronary Slow Flow

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SOUHRN

Kontext: Syndrom zpomaleného koronárního průtoku (coronary slow flow, CSF) je angiografická entita charakterizovaná zpožděným pomalým průtokem kontrastní látky koronárními tepnami bez významné obstrukce epikardu. Jako potenciální faktor přispívající k patofyziologii tohoto jevu byla popsána autonomní dysregulace. Validovaným neinvazivně měřeným parametrem pro hodnocení autonomní funkce je variabilita srdeční frekvence (heart rate variability, HRV).
Cíl: Zjistit změny v parametrech HRV u pacientů s CSF a popsat potenciální úlohu nerovnováhy (imbalance) autonomního nervového systému v patogenezi tohoto jevu.
Metody: Do této průřezové studie bylo zařazeno 50 pacientů s CSF a 50 kontrol odpovídajícího věku a ve stejném poměru muži-ženy s normálním průtokem krve koronárními tepnami. Průtok krve koronárními tepnami se měřil metodou korigovaného TIMI frame count (corrected TIMI frame count, cTFC). Parametry HRV se zjišťovaly z výsledků 24hodinového holterovského monitorování EKG s následnou analýzou v doménách času i frekvence.
Výsledky: Vstupní klinické i laboratorní charakteristiky se mezi skupinami statisticky významně nelišily (p > 0,05). Hodnoty HRV v časové doméně – SDNN, SDANN a pNN50 – byly ve skupině CSF statisticky významně nižší než u kontrol (p = 0,019, resp. 0,037 a 0,008). V parametrech frekvenční domény nebyly mezi skupinami nalezeny žádné statisticky významné rozdíly. Tyto výsledky ukazují na predominanci aktivity sympatiku a sníženou vagovou stimulaci u pacientů s CSF.
Závěr: Snížená HRV u pacientů s CSF ukazuje na významnou imbalanci autonomního nervového systému se zvýšeným sympatickým tonem a sníženou modulací parasympatiku. Tyto změny mohou přispívat k dysfunkci mikrovaskulatury jako základnímu faktoru vzniku CSF a představují potenciální cíl léčby.

Keywords:
Autonomic nervous system
Coronary slow flow
Heart rate variability
Microvascular angina
Sympathetic dominance

ABSTRACT

Background: Coronary slow flow (CSF) is an angiographic entity characterized by delayed contrast progression in coronary arteries without significant epicardial obstruction. Autonomic dysregulation has been suggested as a potential contributor to its pathophysiology. Heart rate variability (HRV) is a validated, non-invasive tool for assessing autonomic function.
Objective: To evaluate alterations in HRV parameters among patients with CSF and to explore the potential role of autonomic nervous system imbalance in its pathogenesis.
Methods: This cross-sectional study included 50 patients with CSF and 50 age- and sex-matched controls with normal coronary flow. Coronary flow was assessed using corrected TIMI frame count (cTFC). HRV parameters were derived from 24-hour Holter ECG monitoring and analyzed in both time and frequency domains.
Results: Baseline clinical and laboratory characteristics did not differ significantly between groups (p >0.05). Time-domain HRV indices—SDNN, SDANN, and pNN50—were significantly reduced in the CSF group compared to controls (p = 0.019, 0.037, and 0.008, respectively). Frequency-domain parameters showed no significant between-group differences. These findings suggest a predominance of sympathetic activity and diminished vagal modulation in CSF patients.
Conclusion: Reduced HRV in CSF patients indicates a significant autonomic imbalance, with increased sympathetic tone and reduced parasympathetic modulation. These alterations may contribute to the microvascular dysfunction underlying CSF and represent a potential therapeutic target.

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Introduction

Coronary slow flow (CSF) refers to a delayed opacification of coronary arteries in the absence of obstructive epicardial coronary disease. Though often overlooked, CSF can present with angina-like symptoms and is associated with increased cardiovascular risk. Pathophysiological mechanisms proposed for CSF include microvascular and endothelial dysfunction, subclinical atherosclerosis, and, notably, autonomic nervous system imbalance.[1–3]

The autonomic nervous system (ANS), comprising sympathetic and parasympathetic branches, modulates heart rate and coronary vasomotor tone. Heart rate variability (HRV) quantifies variations in successive RR intervals and serves as a reliable marker of autonomic activity.[4,5] Decreased HRV is associated with adverse cardiovascular events, including arrhythmias, ischemia, and sudden cardiac death.[6]

Despite growing evidence linking autonomic dysfunction to cardiovascular pathology, its role in CSF remains underexplored. This study evaluates HRV indices in CSF patients to elucidate potential autonomic abnormalities contributing to the condition.

Materials and methods

Study design and population

This cross-sectional study was conducted at Adiyaman Education and Research Hospital between March 2017 and January 2018. A total of 120 patients presenting with palpitations were screened. After applying exclusion criteria—such as hypertension, diabetes mellitus, coronary artery disease, structural heart abnormalities, and medication use affecting HRV—100 patients were enrolled: 50 with angiographically confirmed CSF (Group 2) and 50 with normal coronary flow (Group 1, controls).

Coronary flow assessment

All participants underwent coronary angiography using the Judkins technique. The corrected TIMI frame count (cTFC) was calculated by two independent cardiologists blinded to patient status. The cTFC for the left anterior descending artery (LAD) was normalized by dividing by 1.7 due to its greater length.[7]

Electrocardiographic monitoring and HRV analysis

Twenty-four-hour ambulatory ECG monitoring was performed using a two-channel Holter system (DR-512 VX3, Biomedical Systems, USA). Time-domain HRV indices (SDNN, SDANN, rMSSD, pNN50) and frequency-domain measures (ULF, VLF, LF, HF, LF/HF ratio) were analyzed according to established guidelines.

Statistical analysis

Statistical analyses were conducted using SPSS v21.0. Data distribution was evaluated with the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± SD or median (IQR) and compared using t-tests or Mann–Whitney U tests. Categorical variables were compared using chi-square tests. A *p*-value <0.05 was considered statistically significant.

Table 1 – Baseline clinical and laboratory characteristics of the study population

	CSF (n = 50)	Control (n = 50)	*p*-value
Age, year	47.2 ± 1.1	45.3 ± 1.0	0.152
Gender, male, n, (%)	27 (55)	26 (52)	0.564
Smoking	22 (45)	17 (35)	0.212
BMI (kg/m^2)	26.3 ± 3.6	27.6 ± 5.1	0.156
HR (beats/min)	73.9 ± 1.0	72.5 ± 1.0	0.465
Glucose (mg/dL)	99.5 ± 11.7	105.1 ± 29.4	0.102
BUN (mg/dL)	12.2 ± 2.8	13.4 ± 3.0	0.633
Creatine (mg/dL)	0.83 ± 0.13	0.83 ± 0.15	0.859
T. chol (mg/dl)	192.7 ± 34.0	191.5 ± 34.7	0.240
TG (mg/dl)	143.0 ± 11.5	160.0 ± 10.8	0.855
HDL (mg/dl)	49.5 ± 10.4	47.1 ± 10.7	0.254
LDL (mg/dl)	112.7 ± 31.9	110.8 ± 30.4	0.761
LVEF (%)	61.2 ± 2.9	62.0 ± 2.7	0.140
IVS (mm)	1.1 ± 0.2	1.1 ± 0.4	0.936
PABP (mmHg)	24.9 ± 2.3	24.6 ± 2.9	0.232

BMI – body mass index; BUN – blood urea nitrogen; HDL – high density lipoprotein; HR – heart rate; LDL – low density lipoprotein; LVEF – left ventricular ejection fraction; PABP – pulmonary artery pressure; TG – triglycerides; T. chol – total cholesterol.

Table 2 – Heart rate variability of the study group

	CSF (n = 50)	Control (n = 50)	*p*-value
24-hour HRV time analysis			
SDNN	105.1 ± 34.2	123.9 ± 33.2	**0.019**
SDANN	76.6 ± 35.2	103.0 ± 27.2	**0.037**
PNN50	6.9 ± 7.7	10.9 ± 9.8	**0.008**
rMSSD	52.3 ± 62.5	62.7 ± 86.1	0.490
24-hour HRV frequency analysis			
Total power (ms^2)	9475.6 ± 6144.1	11684.3 ± 7472.3	0.110
ULF power (ms^2)	4705.8 ± 3174.2	5765.5 ± 3487.7	0.115
VLF power (ms^2)	2504.5 ± 1753.3	3015.9 ± 1928.6	0.169
LF power (ms^2)	1741.8 ± 1239.4	1522.2 ± 867.2	0.307
HF power (ms^2)	871.9 ± 697.3	840.6 ± 523.7	0.800
LF NUs	54.6 ± 12.2	55.4 ± 12.9	0.756
HF NUs	41.3 ± 9.3	39.4 ± 12.3	0.385
LF/HF ratio	1.6 ± 0.6	1.4 ± 0.4	0.256

HF – high frequency; LF – low frequency; NUs – normalized units; ULF – ultra low frequency; VLF – very low frequency.

Results

Baseline characteristics

No significant differences were observed between the CSF and control groups in terms of age, sex, smoking status, heart rate, ejection fraction, or laboratory para-

meters (p >0.05). This ensured the comparability of the groups (**Table 1**).

Heart rate variability findings

Time-domain HRV parameters were significantly lower in the CSF group:

- SDNN: Reflecting overall HRV was significantly reduced (p = 0.019).
- SDANN: Indicative of long-term variability, was also decreased (p = 0.037).
- pNN50: A marker of parasympathetic tone showed a marked reduction (p = 0.008).

In contrast, rMSSD and all frequency-domain indices did not differ significantly (p >0.05) (**Table 2**).

Discussion

This study demonstrates that CSF is associated with significantly reduced HRV, particularly in time-domain measures. These findings suggest an underlying autonomic imbalance characterized by increased sympathetic drive and reduced vagal activity.

CSF pathophysiology is multifactorial. Prior intravascular ultrasound (IVUS) and flow-reserve studies have identified diffuse intimal thickening and subclinical atherosclerosis in CSF patients. Moreover, studies report impaired flow-mediated dilation and elevated markers of endothelial dysfunction.[8–10]

Autonomic nervous system dysregulation may exacerbate coronary microvascular resistance. Elevated sympathetic tone and diminished parasympathetic influence impair vasodilation, reducing coronary reserve. Reduced HRV, particularly SDNN and SDANN, has been associated with poor cardiovascular outcomes, including arrhythmias, myocardial ischemia, and sudden death.[11–15]

In our study, decreased pNN50 further supports parasympathetic withdrawal. This dysregulation may explain anginal symptoms in CSF patients despite normal angiograms. HRV analysis could thus serve as a diagnostic and prognostic tool in CSF, identifying patients at risk for adverse events and guiding treatment decisions, including autonomic modulation through pharmacotherapy or lifestyle intervention.[16–21]

Limitations

This study is limited by its single-center, cross-sectional design and modest sample size. Longer-term follow-up and multicenter studies are needed to validate these findings and assess the prognostic value of HRV in CSF.

Conclusion

Coronary slow flow is associated with significant reductions in HRV time-domain parameters, indicating autonomic imbalance. The predominance of sympathetic tone and reduced parasympathetic activity may contribute to microvascular dysfunction and symptomatology in CSF patients. HRV monitoring provides a non-invasive method for identifying high-risk individuals and may aid in tailoring therapeutic strategies aimed at restoring autonomic balance and improving clinical outcomes.

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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Ethical statement

This study was performed in line with the principles of the Declaration of Helsinki.

Informed consent

All patients provided written informed consent to participate in the study.

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