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Different pathologies without coronary artery disease may induce typical chest pain

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Abstract

We studied patients with stable and typical angina pectoris (AP) without coronary artery disease. Patients had either a microvascular dysfunction (MVD) or a hypersensitive heart syndrome (HHS). The study was aimed to detect differences in the two conditions.

MVD and HHS patients show many important clinical differences. Female sex, fibromyalgia, gastroesophageal reflux symptoms are more frequent in HHS patients. The quality of life is significantly worse in HHS patients. Resting heart rate is higher in HHS than in MVD patients.

Cardiovascular risks factors are more frequent in MVD patients. Left ventricular diastolic dysfunction is frequent in MVD patients and rare in HHS. Left ventricular dyskinesia is only present in MVD patients.

In spite of a normal cardiac function without ischemia, HHS patients have more AP and dyspnea, and use more sublingual nitrates than MVD patients with MVD. Also, the time to occurrence of AP is shorter In HHS patients, but the ST-downsloping is absent or smaller. Thus, HSS have more symptoms than those with MVD. The higher heart rate in HHS patients might be due to an activated sympathetic system or reduced vagal activity.

The differences between MVD and HHS patients should allow a differential diagnosis between AP related to cardiac MVD and to the non-cardiac HHS.

Effects of antiischemic and antianginal effects of drugs depend on patients' selection. The data confirm the hypothesis that AP in HHS patients is part of a generalized pain syndrome and not a real cardiac pathology. Indeed, HHS patients have a multisystem pain with some preference for the chest pain. MVD patients have a real cardiac ischemia and can be properly treated with antianginal drugs. On the contrary, antianginal drugs are ineffective in HHS patients.

Introduction

Angina pectoris (AP), *i.e.,* chest pain, is defined as typical when meets 3 or 4 of all of the following criteria: substernal chest discomfort of characteristic quality and duration; provoked by exertional or emotional stress; relieved by rest and/or by sublingual or spray nitrates within minutes. In the past it was assumed that AP is a usually a symptom of coronary artery disease (CAD) [1], but it is now established that AP is always a symptom of CAD. Indeed, almost 50% of patients who undergo selective coronarography because of stable AP attributable to myocardial ischemia are found not to have a CAD [2].

In the large majority of patients with AP without CAD, myocardial ischemia and AP are induced by microvascular dysfunction (MVD) [3-7]. MVD derives from endothelium dependent, endothelium independent mechanisms, and the combination of the two [3-8]. Up to now 5 types of MVD have been recognized [3,4]. In a minority of patients AP without CAD myocardial ischemia and AP are due to an increased coronary constriction [3-8]. CAD, MVD and coronary spam are pathologies which explain ischemia and confirm the cardiac origin of chest pain.

However, we also know a syndrome called hypersensitive heart syndrome (HHS) [9,10]. These patients have typical AP without any organic cardiac or non-cardiac pathology which might explain the symptom. It is hypothesized that these patients have and enhanced pain perception. Indeed it could be demonstrated that these patients report AP after intracardiac injection of saline, contrast medium injection, catheter manipulation, and electrical cardiac stimulation, which usually do not cause pain in other subjects [9].

It may be easy to diagnose CAD. Diagnosing MVD may be more difficult, but is it possible [3-7]. When AP is considered cardiac therapies are aimed to reduce ischemia. However, it is unlikely that antianginal therapies are effective in patients with HHS. It would be important to distinguish patients with cardiac ischemia from those with HHS.

We studied 36 consecutive patients with MVD or HHS. We collected data on symptoms, concomitant diseases and cardiac function. The hypothesis was that the two groups can be distinguished and thus receive appropriated therapy.

Material and methods

This was a registry, *i.e.,* a pragmatic trial [11] which is registered in ClinicalTrial.Org. Patients and their referring physicians gave their authorization to collect and analyze data. Data were available for treating physicians. Data collection did not interfere with diagnostic

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and therapeutic decisions.

Patients: Between January 1999 and January 2016 we checked 36 consecutive Caucasian patients with stable and typical AP. Patients with severe renal, hepatic or hematologic disorders were not selected. Occlusive CAD had been excluded in all by coronarography.

Twenty-four out of 36 (67%) patients had MVD. In 19 cases MVD was demonstrated by acetylcholine stress testing and in 3 cases by increased levels of endothelin-1. Twelve out of 36 patients (33%) had no cardiac or extracardiac explanation for AP and were considered to have HHS.

Concomitant diseases and medications were recorded and are shown in Table 2 and 3. All medications were left unchanged as prescribed from the referring physicians.

General data are shown in table 3. Patients who were not born in Switzerland were recorded as immigrants. Patients who never smoked or quitted smoking since 5 years were nonsmokers.

Quality of life was collected at baseline with the RAND 36-Item Health Survey questionnaire [12]. The questionnaire collects data on physical functioning, role functioning/physical, energy/fatigue, emotional well-being, social functioning, pain, general heath, and health changes. Data are shown in Table 4.

Cardiac data: at baseline and after 6 months we noted grade (CCS classification) and number of weekly AP episodes, number of weekly used sublingual nitrates, blood pressure, and heart rate. We also collected echocardiographic data: left atrial dimensions (LAd), left ventricular ejection fraction (LVEF), systolic time intervals (STIs; *i.e.,* PEP/LVET ratio), dyskinesia (abnormal wall motion of at least 1 left ventricular segment), and left ventricular dysfunction (PW Doppler E/A ratio and tissue Doppler E/e' ratio). Collected ergometric data were the time to the occurrence of AP and maximal ST-downsloping. All data are shown in Table 5.

Table 1. Concomitant diseases.

Diseases	MVD	HHS	p value
Arterial hypertension	16 yes, 8 no	0 yes; 12 no	< 0.0001
Diabetes mellitus	12 yes; 12 no	4 yes; 8 no	< 0.001
Dyslipidemia	8 yes, 8 no	1 yes; 11 no	< 0.0001
Gastroesophageal reflux disease	6 yes; 18 no	10 yes; 2 no	< 0.0001
Hypothyroidism	3 yes, 21 no	1 yes; 11 no	< 0.0001
Mood disorders	6 yes; 18 no	10 yes; 2 no	< 0.0001
Fibromyalgia	16 yes; 8 no	10 yes; 2 no	< 0.0001

Table 2: Medications.

Concomitant therapy	MVD no. of patients	HHS no. of patients
ACE-inhibitors	10	0
Amlodipine	5	0
Angiotensin-2-blockers	6	0
Aspirin 100 mg	24	12
Citalopram or venlafaxine	6	10
Exenatide, or liraglutide, or sitagliptin	9	3
Ibuprofen, or paracetamol	16	10
Levothyroxine	3	1
Metformin	10	4
Pantoprazol	6	10
Statins	8	1
Antianginal therapy		
Sublingual nitroglycerine on need	24	12
Bisoprolol, or metoprolol, or nebivolol	24	12
Ranolazine	24	12

Table 3: General data.

	MVD	HHS	p value
Sex	17 f, 7 m	8 f , 4 m	< 0.0001
Age, years (mean ± SD)	67 ± 3.5	67 ± 2.4	ns
Weight, kg (mean ± SD)	71.0 ± 7.5	65.9 ± 7.2	ns
Immigrants	3 m, 2 f	1 m, 7 f	< 0.0001
Smoker	9 yes; 15 no	8 yes; 4 no	< 0.0001

Legend

f	Female
m	Male
SD	1 standard deviation
p	Non-significant
ns	P difference between MVD and HHS

Table 4: Quality of life.

	MVD Base	MVD FU	HHS Base	HHS FU			
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	p1	p2	p3
Phys. Funct.	61.0 ± 8.6	61.4 ± 6.5	41.1± 3,3	40.7 ± 3.8	p< 0.0001	ns	ns
Role Funct.	47.3 ± 3.4	50.7 ± 4.2	38.3 ± 4.6	38.2 ± 4.7	p< 0.0001	ns	ns
Pain	39.2 ± 4.9	39.6 ± 4.3	58.1 ± 7.4	58.7 ± 6.7	p< 0.0001	ns	ns

Legend

Phys. Funct.	Physical functioning
Role Funct.	Role functioning/emotional
p1	p value MVD versus HHS, at baseline
p2	p value MVD, baseline versus follow-up
p3	p value HHS, baseline versus follow-up
ns	Non-significant

Statistical analysis was performed with Statgraphics software using an intention-to-treat method. Data are expressed as mean ± 1 standard deviation (SD). The within-group difference between MVD and HHS patients was compared. Absolute values and percentual changes in relation to baseline measurements were analyzed. The 2 hypotheses tested were: null hypothesis: mu1-mu2=0.0, and alternative hypothesis: mu1-mu2>>0.0. Within-groups comparisons were made using paired t tests or the non-parametric Wilcoxon signed-rank test, where appropriate. Between-group comparisons were performed by unpaired t tests or the non-parametric Mann-Whitney U test, respectively. Chi-square test or Kruskal-Wallis test were used to compare continuous normally or not normally distributed and qualitative variables, where appropriate. Multivariate analysis of variance was performed. A p value of <0.05 was considered statistically significant.

Results

At follow-up data were available for all patients.

Clinical data: the two groups were similar for age and weight. Female sex, immigrant status and smoking status were significantly less frequent in MVD patients. Data and p values are shown in table 1.

Concomitant diseases were significantly different in the two groups. Arterial hypertension, diabetes mellitus, dyslipidemia and hypothyroidism were significantly more frequent in MVD patients. On the other hand, gastroesophageal reflux disease, mood disorders and fibromyalgia were significantly more frequent in HHS patients. Data and p values are shown in Table 1.

Concomitant medications: The number of treated patients was different in the two groups, but the types of drugs were similar. Cardiac medications were similar in both groups. Used drugs are shown in Table 2.

Table 5: Cardiac parameters.

	MVD Base	MVD FU	HHS Base	HHS FU			
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	p1	p2	p3
AP (CCS grade)	1.75 ± 0.4	1.7 ± 0.5	1.9 ± 0.7	2.1 ± 0.8	ns	ns	ns
AP EPI	1.4 ± 0.5	0-9 ± 0.7	2.0 ± 0.5	2.1 ± 0.5	< 0.5	< 0.5	< 0.5
NITRO	1.4 ± 0.5	0.9 ± 2.3	2.0 ± 0.6	2.3 ± 0.5	< 0.004	< 0.5	< 0.5
Dyspnea	1.8 ± 0.4	2.0 ± 0.0	1.5 ± 0.5	2.0 ± 0.0	< 0.0001	< 0.0001	ns
SBP	141.7 ± 3.3	140.2 ± 3.0	121.2 ± 5.4	141.7 ± 3.3	< 0.04	< 0.003	ns
DBP	80.4 ± 4.7	78.2 ± 4.2	67.8 ± 2.2	68.4 ± 3.0	< 0.0001	ns	< 0.5
HR	64.7 ± 4.7	65.0 ± 3.5	80.0 ± 3.0	64.7 ± 4.7	< 0.0001	ns	< 0.5
LAd	11.5 ± 1.1	9.5 ± 0.5	9.6 ± 0.7	9.5 ± 0.5	< 0.0001	< 0.0001	< 0.5
STIs	0.33± 0.2	0.24 ± 0.1	0.24± 0.1	0.23 ± 0.1	< 0.0001	< 0.5	ns
LVEF	70.3 ± 4.9	70.1± 4.0	72.3 ± 3.8	71.3 ± 3.0	ns	ns	< 0.5
LV-DD E/A	1.6 ± 0.5	1.9 ± 0.3	2.0 ± 0.0	2.0 ± 0.0	< 0.0001	< 0.0001	ns
LV-DD E/e1	14.6 ± 2.0	11.7 ± 1.2	11.7 ± 1.25	13.6 ± 1.2	< 0.0001	< 0.5	< 0.5
LV-DYSK	1.8 ± 0.4	1.9 ± 0.3	2.0 ± 0.0	2.0 ± 0.0	< 0.0001	< 0.0001	ns
Ex Time to AP	7.0 ± 0.5	6.3 ± 0.7	6.3 ± 0.7	6.3 ± 0.6	< 0.005	< 0.002	ns
Max ST-DOWN	1.0± 0.3	1.0 ± 0.2	0.2 ± 0.1	0.3 ± 0.1	< 0.0001	ns	< 0.002

Legend

Base	Baseline
FU	Follow-up
AP EPI	Weekly number of AP episodes
NITRO	Weekly number of used sublingual nitroglycerine
Dyspnea	NYHA grade of dyspnea
DBP	Diastolic blood pressure, mm Hg.
SBP	Systolic blood pressure, mm Hg.
HR	Heart rate, beats/minute.
LAd	Left atrial dimension, cm2.
STIs	Systolic time intervals, ratio.
LVEF	Left ventricular ejection fraction, %.
LV-DD E/A Pulsed	Doppler mitral valve, E/A wave ratio.
LV-DD E/ e1	Tissue Doppler interventricular septum, E/ e1 wave ratio.
LV-DYSK	Left ventricular dyskinesia, number of segments.
Ex-Time	Exercise time to begin of AP, minutes.
Max ST-DOWN	Maximal ST-downsloping at exercise, mm.
p1	p value MVS versus HHS, at baseline
p2	p value MVD, baseline versus follow-up
p3	p value HHS, baseline versus follow-up
ns	Non-significant

Table 6: Differences between MVD and HHS patients.

MVD patients	HHS patients
Female sex is less frequent	Female sex is more frequent.
Immigrant status is less frequent	Immigrant status is more frequent
Smoking is less frequent	Smoking is more frequent
Cardiovascular risks are more frequent	Cardiovascular risks are less frequent
Quality of life is less reduced.	Quality of life is more reduced.
Hypertension is more frequent	Hypertension is less frequent
Heart rate is lower	Heart rate is higher
AP and nitroglycerin consumption are lower	AP and nitroglycerin consumption are higher
Cardiac dysfuntion is frequent.	Cardiac dysfunction is rarer.
Ergometric time to AP is longer	Ergometric time to AP is shorter
Ergometric ST-downsloping is greater	Ergometric ST-downsloping is smaller

Quality of life: quality of life was significantly worse in HHS patients. Data and p values are shown in Table 4.

Cardiac data

• At baseline the grade of AP was similar in both groups. At follow-up the grade of AP decreased significantly in MVD but did not change in HHS. Altogether the grade of AP was statistically lower in patients with MVD. Data and p values are shown in Table 5.

• At baseline the number of weekly episodes of AP was significantly greater in MVD. At follow-up the number of AP episodes decreased significantly in MVD and increased significantly in HHS. Altogether the number of AP episodes was statistically smaller in patients with MVD. Data and p values are shown in Table 5.

• At baseline the number of weekly used sublingual nitrates was significantly greater in HHS. At follow-up nitrates consumption decreased significantly in MVD while it increased in HHS. Altogether nitrates consumption was statistically smaller in patients with MVD. Data and p values are shown in Table 5.

• At baseline the grade of dyspnea was statistical smaller in patients with MVD. At follow-up dyspnea decreased significantly in MVD and increased in HHS. Altogether dyspnea was statistically less severe in patients with MVD. Data and p values are shown in Table 5.

• At baseline blood pressure was significant lower in HHS. At follow-up blood pressure was almost unchanged almost in the two groups. Altogether, blood pressure was significantly lower in HHS. Data and p values are shown in Table 5.

• At baseline heart rate was significantly lower in MVD. At follow-up heart rate decreased significantly in both groups, but the changes were clinically irrelevant. Altogether, heart rate was significantly lower in patients with MVD. Data and p values are shown in Table 5.

Echocardiographic data

• At baseline STIs were normal in both groups but significantly lower in MVD. At follow-up the STIs decreased significantly in both groups, and the difference between groups was statistically significant. However, since the STIs were and remained normal, the statistically significant changes have little clinical relevance. Data and p values are shown in Table 5.

• At baseline LVEF was normal and similar in the two groups. At follow-up LVEF increased significantly in both groups and the difference between the two groups was statistically significant. However, since LVEF remained normal, the statistically significant changes lack clinical relevance. Data and p values are shown in Table 5.

• At baseline LAd were significantly lower in MVD. At follow-up LAd decreased significantly in both groups and the difference between the two groups was statistically significant. However, LAd were always normal and thus the statistically significant changes lack clinical relevance. Data and p values are shown in Table 5.

• At baseline left ventricular dyskinesia was detected in 21% (5/24) of patients with MVD and in none of the HHS patients. The difference between the two groups was statistically significant. At follow-up dyskinesia decreased and was detectable in only 8% (2/24) of MVD patients, the change being statistically significant. At follow-up as at baseline, none of the HHS patients had dyskinesia. Altogether left ventricular dyskinesia was only present in some MVD patients and absent in HHS patients. Data and p values are shown in Table 5.

• At baseline left ventricular diastolic dysfunction at baseline was significantly more frequent in MVD patients. At follow-up dyskinesia remained unchanged in MVD patients and increased in HHS patients, the difference between the two groups being significant. Data and p values are shown in Table 5.

Ergometry

• At baseline exercise time to the occurrence of AP episodes was significantly greater in MVD patients. At follow-up the exercise time

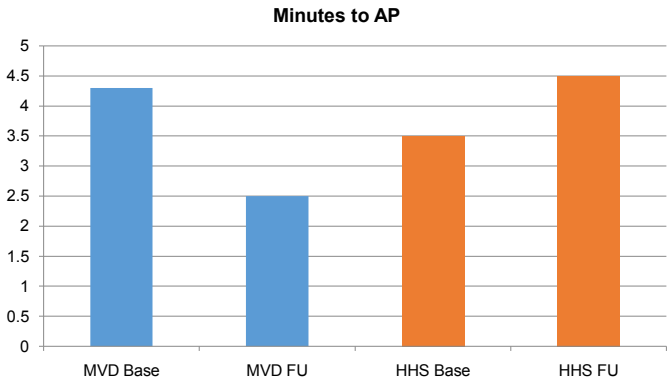
increased significantly in both groups, but the difference between the two groups was statistically significant. Data and p values are shown in Table 3. Exercise time is also shown in Figure 1.

- At baseline maximal stress-induced ST-downsloping was significantly greater in the MVD patients, the difference being statistically significant. In 42% (5/12) of HHS patients AP occurred without a significant ST-downsloping. At follow-up ST-downsloping decreased significantly in the MVD patients and remained unchanged in the HHS patients. The difference between the two groups was statistically significant. Data and p values are shown in Table 3. ST-downsloping is also shown in Figure 2.

Discussion

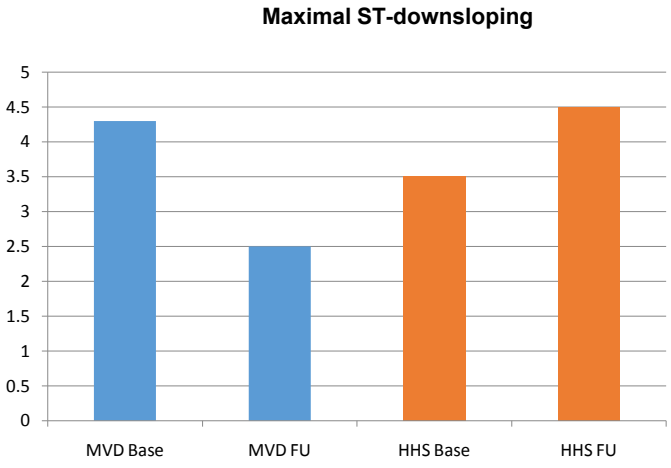
There are no absolutes and AP is indistinguishable in MVD and HHS patients.

However, MVD and HHS patients show many important clinical differences. Female sex, fibromyalgia, gastroesophageal reflux symptoms are more frequent in HHS patients. The quality of life is significantly worse in HHS patients. Resting heart rate is higher (80 beats/min) in HHS than in MVD patients (65 beats/min).



MVD Base MVD. Minutes to AP at baseline.
MVD FU MVD. Minutes to AP at follow-up.
HHS Base HHS. Minutes to AP at baseline.
HHS FU HHS. Minutes to AP at follow-up.

Figure 1. Cycloergometry: minutes to the occurrence of AP.



MVD Base MVD. ST-downsloping at baseline.
MVD FU MVD. ST-downsloping at follow-up.
HHS Base HHS. ST-downsloping at baseline.
HHS FU HHS. ST-downsloping at follow-up.

Figure 2. Cycloergometry: maximal ST-downsloping (mV).

According to the characteristics of MVD cardiovascular risks factors (diabetes mellitus, dyslipidemia, hypertension, smoking status, and hypothyroidism) are more frequent in MVD patients. Left ventricular diastolic dysfunction is frequent in MVD patients and rare in HHS. Left ventricular dyskinesia is only present in MVD patients.

In spite of a normal cardiac function without ischemia, HHS patients have more AP and dyspnea, and use more sublingual nitrates than MVD patients with MVD. Also, the time to occurrence of AP is shorter In HHS patients, but the ST-downsloping is absent or smaller. Thus, HSS have more symptoms than those with MVD. The higher heart rate in HHS patients might be due to an activated sympathetic system or reduced vagal activity.

Our data are summarized in table 6. The differences between MVD and HHS patients should allow a differential diagnosis between AP related to cardiac MVD and to the non-cardiac HHS.

Effects of antiischemic and antianginal effects of drugs depend on patients' selection. E.g., ranolazine has been proven to exert a good antiischemic efficacy when given to patients with real myocardial ischemia [13-15]. On the other hand, the effect of ranolazine was less clear in patients with a different etiology of AP [16]. Consequently, in an editorial, Crea and Lanza [17] have strengthened the need for precision medicine, especially in patients with AP without CAD. Indeed, contrary to epicardial CAD, the etiology of MVD is complex and the coronary microcirculation as yet is elusive to conventional imaging techniques.

Altogether, the data confirm the hypothesis that AP in HHS patients is part of a generalized pain syndrome and not a real cardiac pathology. Indeed, HHS patients have a multisystem pain with some preference for the chest pain. Typically, these patients complain of more pain than patients with organic diseases and also consume more analgesic drugs. By mixing HHS with MVD patients, the effects of an antianginal and antiischemic therapy are flawed. One might wrongly conclude that the given therapy is poorly effective in patients with ischemia due to MVD.

Our study has some weaknesses. Most important, this is a single center study with a small number of patients. Also, we analyzed many data, with a risk for a statistical type I error. However, our data are in line with the rational expectations: patients with HHS have a normal cardiac function, but have more symptoms than those with MVD. It would be strange if the p values would have been be generated by chance.

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