In Ischemic Heart Disease Men and Women are Different... But the Same

"... can society inscribe on its banners: from each according to his ability, to each according to his needs."

Karl Marx, Critique of the Gotha Programme

INTRODUCTION

A few decades ago cardiovascular disease was considered a men´s disease; while it was thought that women´s risk of coronary heart disease was very low. However, the medical community now admits that ischemic heart disease is the leading cause of mortality in middle-aged women.

But are both gender presentations the same? Let us see what happens in two forms of the disease, chronic stable angina (CSA) and acute coronary syndrome (ACS).

SIGNS AND SYMPTOMS OF OBSTRUCTIVE CORONARY DISEASE ACCORDING TO GENDER

Chronic Stable Angina and female gender

Compared to men, the most common initial presentation of women with symptoms of chest pain is stable angina.

Interestingly, in the eastern Denmark register, including 11223 subjects between 1998 and 2009, coronary angiography for suspected stable angina as an initial symptom revealed that men had 19% (1226/6512) of normal coronary arteries (0% stenosis in all arteries) and women 48% (2253/4711). In the study period, the ratio of patients without coronary obstruction (none or lesion <50%) increased from 54% to 73% in women and from 19% to 41% in men. (1) With the same degree of symptoms at onset of stable angina, the presence of normal coronary angiographies steadily increased over the past 10 years analyzed. In turn, women presented a lower degree of epicardial coronary obstruction than men.

It was already known that in the Women's Ischemia Syndrome Evaluation (WISE) of 883 women referred for coronary angiography, 62% had normal coronary arteries (<50% stenosis) and the remaining 38% had significant coronary lesions (> 50% stenosis), 50% presenting with a single coronary vessel lesion and 50% with two to three coronary vessel lesions. (2)

In the cohort of patients in British Columbia (Canada), of 32856 patients with suspected ischemic heart disease, 7.1% of men versus 23.3% of women had a completely normal coronary angiography (0% obstruction). (3)

In the Swedish Coronary Angiography and Angioplasty Register (SCAAR) which covered the period 2006-2008 and included 12200 patients with stable chest pain referred for diagnostic coronary angiography for the first time, 30.1% of men versus 64. 5% of women had a normal coronary angiography or no significant lesions (<50% obstruction). (4)

In an even larger register made in the United States, of 375886 patients with suspected stable angina, 51% of women and 33% of men had no significant coronary stenosis (defined as < 70% stenosis) and the results are consistent with the data shown above. (5)

Acute coronary syndrome and female gender

In the large GUSTO IIb study (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb) of 12142 patients with ACS, 30.5% of women with unstable angina (versus 13.9% of men) and 10.2% of women with acute myocardial infarction (AMI) with ST-segment elevation (versus 6.8% of men) had normal coronary angiography. (6)
In another series, 10% of men and 25% of women admitted to hospital with a diagnosis of ACS had "normal" coronary angiography. (7)

Hospital variability of normal coronary angiography frequency

In the CathPCI registry retrospective analysis performed between 2005-2008 in 565504 patients without prior MI or revascularization, who underwent elective coronary angiography in 691 hospitals in the United States, the incidence of non-obstructive coronary artery disease (<50% in any vessel) was assessed. The ratio of non-significant coronary disease was 55% and varied between different hospitals from 0% to 77%, with a median of 55% (interquartile range 48-61%). (8)

It was more probable that hospitals with higher incidence of non-obstructive coronary disease would perform procedures in younger patients with lower Framingham risk score, whether asymptomatic or with atypical symptoms and negative or unperformed functional assessment and in addition with small number of catheterizations in the hemodynamic laboratories.

ARE SYMPTOMS WITHOUT CORONARY LESIONS TRIVIAL OR RECURRENT?

It may be considered that in symptoms suggestive of angina without coronary lesions confirmed by angiography the patient will evolve without further chest pain.

However, already in the WISE study (2) 45% of women without obstructive coronary disease still presented with angina at 5-year follow-up with a similar frequency than those with one to three coronary vessel lesions. At 5 years, 20% of women with normal coronary arteries had been hospitalized for chest pain, compared to 38% of those with three-vessel lesions.

In a recent review of long-term prognosis in patients with cardiac syndrome X (angina on a positive stress test with normal coronary arteriography), which included 16 studies with 1694 patients, chest pain recurrence ranged between 13.2% and 89.9% for the different registries, with an average frequency of 55% (CI 95% 53-58) that might recur weekly for a long time. (9)

The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) clinical trial evaluated the optimal treatment of 2368 patients with diabetes and documented coronary disease. At the time of enrollment women were more likely than men to present with angina, 67% versus 58% ($p < 0.01$) despite lower coronary disease on angiography (number of significant lesion 2.3 ± 1.7 vs. 2.8 ± 1.8, $p < 0.01$). However, women significantly reported more angina than men over the course of the 5-year follow-up (OR 1.51, 99% CI 1.21 to 1.89, $P < 0.0001$). (10)

In the Canadian registry of British Columbia in patients with normal coronary angiography, hospital readmission for ACS or chest pain requiring cardiac catheterization at 180 days was significantly higher in women compared to men (adjusted OR 4.06, 95% CI 1.15 to 14.31). (3)

We may conclude that angina in patients with normal coronary angiography is not indicative of an outcome with few symptoms; on the contrary, it is indicative of long term pain recurrence, even with new admissions. Additionally, in patients with documented coronary lesions, women have more symptoms of angina during follow-up.

LONG-TERM PROGNOSIS BY GENDER

With coronary artery obstructive lesions

The aforementioned BARI 2D clinical trial followed up for 5 years 702 (30%) women and 1666 (70%) men included in the study. The 5-year cumulative incidence of the composite end point of death, AMI or stroke did not differ between genders (26% in women versus 22% in men) [HR 1.11 (0.85 to 1.44), $p = 0.69$], nor did the need for subsequent revascularization, 35% and 32%, respectively [HR 1.04 (0.82 to 1.31), $p = 0.69$]. (10)

With no coronary artery obstructive lesions

Although the WISE study reported that cardiovascular death or nonfatal AMI at 5 years ranges from 4% to 38%, respectively, in women with non-obstructive (<50%) to three-vessel coronary disease (> 50%) ($p < 0.0001$), (2) in a more recent study comparing cardiovascular events (cardiovascular death, AMI, stroke or hospitalization for heart failure) at 5 years between the group of 540 WISE women presenting with angina and non-obstructive coronary disease (stenosis <50%) and a control cohort of 1000 WTH women without coronary disease, event rates were 16.0% in the WISE study women with non-obstructive CAD (stenosis in any coronary artery of 1%-49%), 7.9% in WISE women with normal coronary arteries (stenosis of 0% in all coronary arteries), and 2.4% in asymptomatic WTH women ($p <$ or $= .002$), (11)

In the mentioned review of long-term prognosis in patients with cardiac syndrome X (16 studies with 1694 patients), (9) major cardiac events (cardiovascular death, AMI and revascularization) ranged from 0% to 3.8% (average of 1.5% at 5 years; CI 95% 1-2.2), an estimated annual major cardiac event rate of 0.3%.

Returning to the retrospective cohort of coronary angiography for suspected angina as initial symptom of all patients in eastern Denmark (11223 subjects between 1998 and 2009), (1) this cohort population was compared with a standard population (no history of cardiovascular disease and a negative Rose questionnaire for angina) of 5705 people in Copenhagen.

Stable angina groups were divided in 3479 patients with normal coronary arteries (0% stenosis), 1709 patients with obstructive coronary lesions (< 50% stenosis) and 6040 patients with obstructive coronary lesions (50% stenosis); in turn, each group was divided into men and women.

Women were 2.4-4.3 years older than men when compared within each group with the same degree of coronary heart disease, and both in women as in men the average age increased with the increase in coronary artery disease. Fewer patients with normal coronary arteries had diabetes or were taking antihypertensive or lipid-lowering drugs.

As there was no interaction between men and women in mortality or major adverse cardiovascular events (MACE) (cardiovascular death, AMI, stroke or hospitalization for heart failure), pooled gender data were analyzed for each group.

The 5-year MACE endpoint for the normal coronary group yielded a HR of 1.52 (95% CI 1.27 to 1.83, $P < 0.001$) (8.5% events), compared to the standard reference population (4.0%). The group with non-obstructive coronary lesions had a HR of 1.85 (95% CI 1.51 to 2.28, $P < 0.001$) (11.0% events). The significant difference with the control group occurred both in the first year and in the subsequent period.

Mortality also increased to a HR of 1.29 (95% CI 1.07-1.56, $P = 0.007$) in patients with normal coronary arteries and even more in those with non-obstructive lesions [HR 1.52 (95% CI 1.24-1.88); $p < 0.001$].

This cohort study determines that, compared to

a normal population without heart disease, patients with normal coronary arteries and non-obstructive coronary lesions are associated with 53% and 85% increased risk of MACE and with 29% and 52% increased risk of all-cause mortality, with no difference between men and women. For both women and men there is a gradual increase in the risk of future MACE and mortality with increasing degrees of coronary disease.

The results of this study support our knowledge that stable ischemic heart disease predicts increased risk of adverse cardiovascular outcomes even in the absence of obstructive coronary disease.

IS MICROVASCULAR ANGINA POSSIBLE?

In patients with typical symptoms of angina pain for myocardial ischemia and objective demonstration by ST segment depression or impaired perfusion in exercise testing with completely normal coronaries, the possibility of "microvascular angina" is suspected and it is thought that coronary "microvascular dysfunction" can lead to signs and symptoms of ACS or stable angina.

The evaluation of the coronary microvasculature lies in its functional assessment and not in direct visualization as with coronary epicardial lesions. (12)

Many different tests are being evaluated to detect changes in coronary microcirculation. For example, transthoracic Doppler echocardiography measuring epicardial coronary flow, which has no risk and allows repeated measurements with different stimuli achieving coronary microvasculature dilation such as adenosine or dipyridamole. If coronary flow velocity (CFV) at peak vasodilation is < 2.0 times resting flow velocity, it strongly suggests coronary microvascular dysfunction. (13) A correlation has been recently shown between altered CFV induced by adenosine in the anterior descending coronary artery and myocardial perfusion defects induced by dobutamine in cardiac magnetic resonance in 10 patients with syndrome X, compared with 10 controls. (14)

Other methods under assessment are myocardial contrast echocardiography during adenosine stress, magnetic resonance imaging with pharmacological drugs, gadolinium as flow tracer of local myocardial perfusion defects, and positron emission tomography (PET) that allows measurement of myocardial blood flow per gram of tissue. (13)

In the WISE study 3-year follow-up of women with normal coronary arteries, the group with abnormal magnetic resonance spectroscopy showed that for each 1% reduction in phosphocreatine-ATP, consistent with myocardial ischemia, there was 4% increased risk of hospitalization for unstable angina, which is associated with repeated catheterization and higher healthcare costs. (15) In a more recent WISE study of 152 women with normal coronary arteries and a mean follow-up of 5.4 years, peak CFV (by intracoronary Doppler flow measurement) < 2.32 after intracoronary adenosine, an endothelium-independent microvascular vasodilator, increased MACE, with a HR of 1.20 (95% CI 1.05-1.38, p = 0.008). (16)

Impaired reactivity to intracoronary acetylcholine as a microvascular dysfunction indicator and prognostic marker for cardiovascular events has also been studied. In the WISE study, women with abnormal coronary dilation response to acetylcholine had less time free of cardiovascular events (p = 0.004). (17)

In a recent study, which reached important conclusions, 42 patients presenting unstable angina with normal coronary arteries (lesions <50%) underwent: a) a perfusion study with cardiac magnetic resonance (CMR), first passage of gadolinium before and after an intravenous adenosine infusion looking for ischemia, b) a coronary angiography and c) intracoronary acetylcholine test, after excluding significant obstructive coronary artery disease. (18) In 52% of patients (22/42) CMR revealed ischemia. Acetylcholine showed epicardial vasospasm (defined as luminal narrowing ≥75% from baseline in a coronary segment associated with ST segment alteration and clinical symptoms) in 24% of patients (10/42), whereas 48% (20/42) presented with microvascular dysfunction, defined as ischemic ST segment changes (continuous ECG) with clinical symptoms. This means that microvascular or coronary epicardial vasoreactivity was present in 76% of patients (30/42). In patients with reversible CMR perfusion, 91% (20/22) presented with vasoreactivity during intracoronary acetylcholine test compared to 50% (10/22) evidencing no perfusion abnormality on MRI (p <0.01), whereby the reversible perfusion defect detected on MRI in patients without significant coronary artery disease was mostly due to microvascular or coronary epicardial dysfunction.

Recently, in the ACOVA study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries), 124 patients with exercise-induced symptoms of angina with normal coronary angiography or minimal irregularities (<20% diameter reduction) underwent intracoronary acetylcholine testing. (19) Sixty-two percent (77/124) of patients had coronary artery spasm, 28% (35/124) with epicardial spasm (≥75% diameter reduction with reproduction of the symptoms of the patient) and 34% (42/124) with microvascular spasm (reproduction of symptoms, ischemic electrocardiographic changes and no epicardial spasm ≥75%).

Women constituted 70% (87/124) of patients, representing 77% and 83% of those in whom epicardial and microvascular spasm were induced, respectively, but only 53% (25/47) of those without response to acetylcholine.

The authors remark that epicardial spasm was often diffuse and located in the distal segment of the coronary artery and was often preceded by ischemic ST deviation and/or reproduction of the patient's symptoms, suggesting that epicardial spasm often began with microvascular spasm. This explains why there

was a spectrum of coronary vasomotility in response to acetylcholine, which ranged from subtle changes compatible with microvascular spasm to diffuse and distal severe spasm of the epicardial coronary artery.

Microvascular spasm was established in patients with stress-induced angina symptoms, indicating that abnormal microvascular vasomotility can be triggered on exertion.

SOME CONCLUSIONS

For decades, and still nowadays, we have assumed that in order to label chest pain as ischemic heart disease, even a typical agina pain, the patient had to present an obstructive lesion, which we called *significant*, in the coronary angiography. Perhaps this is due to the fact that we wholly believe in the animal experiments performed by Gould and Lipscomb in 1974, where they established the effect of progressive coronary artery narrowing on maximum and resting coronary blood flow. (20) They showed that ≥ 50% occlusion limited maximum vasodilating capacity while ≥ 85% occlusion limited resting coronary blood flow. These concepts were transferred to the clinic and we started speaking about critical coronary subocclusions (≥ 85% coronary occlusion) in patients with unstable angina, and in turn, we spoke of a significant coronary lesion (≥ 50% coronary occlusion) in chronic stable angina. Based on this mechanism, these lesions were converted into "ischemic stenosis" and this prevented acknowledging – what was evident before our eyes- that a considerable number of patients presenting with typical pain, ST segment depression or perfusion or exercise motility disorders… but had normal or completely normal coronary arteries, were therefore, not sick. This trend was further pursued when a relatively simple percutaneous technique that could reduce coronary occlusion, as coronary angioplasty, was introduced. The simple idea that blood must flow through many more vessels than epicardial extramyocardial coronary arteries to reach the myocardium was forgotten.

The complete coronary system has three compartments with different functions and blood flows due to the difference between aortic sinus pressure (origin of coronary arteries) and coronary sinus pressure (right atrial pressure). In the absence of obstructive lesions, epicardial arteries offer little resistance (≈ 10%) to flow, similar to that of capillaries and venules (another (≈ 10%), though the latter with a main capacitance function containing 90% of total myocardial blood volume. (12) The proximal compartment is represented by the large "epicardial coronary arteries" seen in the coronary angiography, whose diameter spans approximately from 2 - 5 mm up to 0.5 mm (500 μm) and have "capacitance" function offering little resistance to coronary flow. The intermediate compartment is represented by "*prearterioles*", with diameters ranging from 500 to 200 μm. They are characterized by a measurable and progressive drop in pressure during their course, and are responsible for ≈ 25% of total coronary vascular resistance. These vessels are not under the direct vasomotor control of diffusible myocardial metabolites due to their extramural location and their wall thickness. (13) The most distal compartment is represented by intramural "*arterioles*", in this case characterized by a considerable drop in pressure along their course, as they constitute the real component regulating intramyocardial coronary circulation, denoting the greatest proportion (≈ 50%) of total coronary vascular resistance. (21)

Arterioles with diameter < 200 μm are subdivided into three categories according to their size and the mechanisms regulating their tone. Endothelium-dependent vasoreactivity prevails in "*large arterioles*", 200 to 100 μm in diameter, transferring flow-related stimulus to a vasomotor response; for example, vasoconstriction with flow reduction and vice-versa.

"*Medium-sized arterioles*", with diameters ranging from 100 to 40 μm, which mainly react to intraluminal pressure changes sensed by stretch receptors located in the vascular smooth muscle cells. This myogenic control produces cell relaxation when intramural pressure falls and inversely, induces cell contraction when pressure increases.

Finally, "*small arterioles*", which are <40 μm in diameter, are modulated by myocardial metabolic activity.

If metabolic activity increases, direct contact with metabolites leads to small arteriole vasodilation, reducing pressure in medium-sized arterioles, and hence to a vasodilator miogenic reflex. This, in turn, increases flow in the above arteries, resulting in endothelium-dependent vasodilation of prearterioles and larger extramural epicardial vessels. (13)

Therefore, coronary blood flows down a pressure gradient between the aorta and the capillary bed, with different microcirculatory compartments influenced by physiological mechanisms controlling vascular tone, with cardiac metabolism as the final decisive factor. However, microcirculation is also modulated by different "*neural factors*", as adrenaline and noradrenaline, and mainly acetylcholine, regulating prearterioles and large arterioles, and also "mechanical factors", represented by left and right ventricular end-diastolic pressures (LVEDP and RVEDP, respectively), acting at the level of medium-sized intramyocardial arterioles through extravascular compression.

Clinically, there are drugs that unmask alterations in these regulators of the different compartments. In practice, when the endothelium is affected, the intracoronary acetylcholine test inducing vasoconstriction by stimulating unopposed muscarinic receptors due to lack of functional endothelium, exposes endothelium-dependent reduced vasodilation, and probably also by direct potential effect on prearterioles and large arterioles. Other tests using endothelium-independent vasodilating drugs, such as dipriridamol, papaverine and adenosine, show reduced blood flow response, suggesting an important role of primary

relaxation alteration in medium-sized arteriole smooth muscle cells.

EPILOGUE

Although multiple experimental studies have shown that altered coronary microcirculation may elicit myocardial ischemia, in clinical practice, coronary vascular disturbances, beyond epicardial arteries, are badly understood and often questioned for different reasons.

Contrary to the common observation of epicardial vessel obstruction, small coronary arteries cannot be directly visualized in the coronary angiography. There are numerous complex time-consuming methods not sufficiently tested to evaluate coronary microcirculation during invasive and non-invasive assessment of individual patients.

Also in patients where microvascular angina is suspected, the landmarks of myocardial ischemia, as myocardial metabolites released by ischemia or stress-induced left ventricular contractile dysfunction, are not always detected. This happens because when stenosis limits flow in a large coronary artery, altered myocardial perfusion is evenly distributed in all the perfused myocardial layers of the obstructed artery producing lactate in the coronary sinus and segment contractile dysfunction, allowing its detection.

Conversely, in the case of coronary microvascular dysfunction, the abnormality may not involve all the microvessels corresponding to the coronary branch and may be scattered in the myocardium. This distribution of myocardial perfusion abnormalities may provide a plausible explanation for difficulties in obtaining objective evidence of myocardial ischemia, be it in coronary sinus metabolites because patchy myocardial ischemia cannot be detected due to its dilution in the greater flow of normal areas, or to the impossibility of detecting contractile abnormalities due to the normal function of the surrounding tissue. It would also explain the scarcely elevated enzymes in Tako-Tsubo disease.

However, this scattered distribution of myocardial ischemia is enough to produce symptoms, electrocardiographic changes and also myocardial perfusion defects that can be detected with different methods.

In a patient with typical effort angina and evidence of myocardial ischemia in challenge tests, these findings are accepted when significant obstruction of one or more coronary arteries is shown. A similar patient, with comparable evidence of ischemia, but without coronary artery obstruction, is generally considered to present with suspected ischemia or no ischemia. But as sensitivity and specificity of challenge tests are based on the presence or absence of at least one significant coronary lesion and, actually, not in true evidence of myocardial ischemia, these tests are labeled as "*false positives*".

Therefore, all known tests in which the gold standard is coronary angiography will have low "*specificity*" due to the presence of "*false positives*" for significant lesion, even when the patient may present a true myocardial ischemia due to microcirculatory alterations. Hence, when these tests are used, we should say that they have low specificity and a high proportion of false positives "only" for the presence of significant coronary lesions. However, none of these tests can rule out that the patient has symptoms and a positive challenge test due to myocardial ischemia elicited by another mechanism.

In this setting of high suspicion without angiographic lesions to justify it, maybe the study should end after coronary angiography, with stepwise intracoronary acetylcholine provocation testing to detect that two out of three patients have coronary microvascular dysfunction.

Finally, we should not omit that women present more frequently with normal coronary arteries, a fact that has led to the myth of "*high proportion of false positives*" in women. Perhaps this difference in the efficiency of the tests and unconscious gender discrimination, produce the practical consequences of these assumptions: less referral for cardiac evaluations, as challenge tests and coronary angiography, and less aggressive preventive treatment with drugs as aspirin and statins in women compared to men. (22)

Women present with less obstructive coronary disease in stable angina, though with similar outcome, as they are older than men. In turn, in follow-up cohorts of patients with normal coronary arteries, women are not different from men in the occurrence of long-term events.

Therefore, even though the presentation of acute and chronic coronary ischemia is different in women than in men,…their long-term outcomes are similar.

A comparison is necessary in order to speak of people´s equal rights, which with the rise of middle class uses the metaphor of equivalent merchandise exchange or equal values. As Marx says (23): "*equal right is still bourgeois right*…. meaning that the measurement is made with a *standard scale*… This equal right is unequal right for unequal labor…..tacitly recognizes unequal individual endowment and thus productive capacity, as a natural privilege. It is, therefore, *in its content, a right of inequality like every right*. But unequal individuals (and they would not be different individuals if they were not unequal) are measurable only by an equal standard insofar as they are brought under an equal point of view, when they are considered from one *definite* aspect only… To avoid all these difficulties, right, instead of being equal, would have to be unequal… after the productive forces have expanded together with the development of the individual in all its facets, and all the springs of co-operative wealth flow more abundantly -- only then can the narrow horizon of bourgeois right be crossed in its entirety and society inscribe on its banners: *from each according to his ability, to each according to his needs!*

To achieve this prediction in our medical work, and knowing that the clinical presentation of myocardial

ischemia is different in men than in women, in order to provide equal treatment, this should be adapted to unequal gender *needs*.

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