

## Kate and Leopold: the odd couple

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**Summary.** Cardiovascular disease (CVD) was traditionally considered a purely male disease, and for many years it was underestimated and under-recognized in women. Nevertheless, the burden of CVD in women is increasing, so much so that CVD presently represents the leading cause of female mortality and disability in developing countries. The increased interest in this field highlighted the presence of gender-specific differences in terms of clinical presentation, prevention, treatment, and prognosis. Biological and hormonal differences between sexes should not be underestimated, as they can affect clinical presentation and drug responses.

This report is an example of the current gender-related practice in the evaluation and treatment of high-risk cardiovascular patients. A 70-year-old lady with a history of coronary disease, diabetes, hypertension, Parkinson's, rheumatoid arthritis, and hypothyroidism attended our outpatient clinic for continuous chest pain, exertional dyspnea, malleolar edema. A diagnosis of heart failure with preserved ejection fraction was reached after discussing several confounding factors.

**Key words.** Cardiovascular disease, gender differences, hypertension, diabetes, heart failure.

### *Caterina e Leopoldo: la strana coppia*

**Riassunto.** La malattia cardiovascolare (MCV) è stata tradizionalmente considerata una malattia puramente maschile e per questo motivo è stata per molti anni sottovalutata nelle donne. Tuttavia, la MCV rappresenta attualmente la principale causa di mortalità e disabilità femminile nei paesi in via di sviluppo. Il crescente interesse in questo campo ha permesso di individuare la presenza di differenze di genere sia in termini di presentazione clinica, prevenzione, trattamento e prognosi delle MCV. Ciò ha fatto capire come sia fondamentale non trascurare le innegabili differenze biologiche e ormonali tra i sessi, in quanto responsabili di possibili condizionamenti non solo nella presentazione clinica ma anche nelle diverse risposte ai trattamenti della MCV. Questo case report è un esempio di pratica clinica di genere nella valutazione e nel trattamento di pazienti ad elevato rischio cardiovascolare. Una signora di 70 anni con storia di cardiopatia ischemica cronica già rivascolarizzata per via chirurgica, diabete mellito, ipertensione arteriosa, Parkinson, artrite reumatoide ed ipotiroidismo è giunta alla nostra attenzione per la comparsa di dolore toracico continuo, dispnea da sforzo, ed emi perimalleolari. Dopo la valutazione dei

multipli fattori confondenti, veniva infine posta diagnosi di insufficienza cardiaca a funzione contrattile conservata.

**Parole chiave.** Malattia cardiovascolare, differenze di genere, ipertensione, diabete, insufficienza cardiaca.

### History and presentation

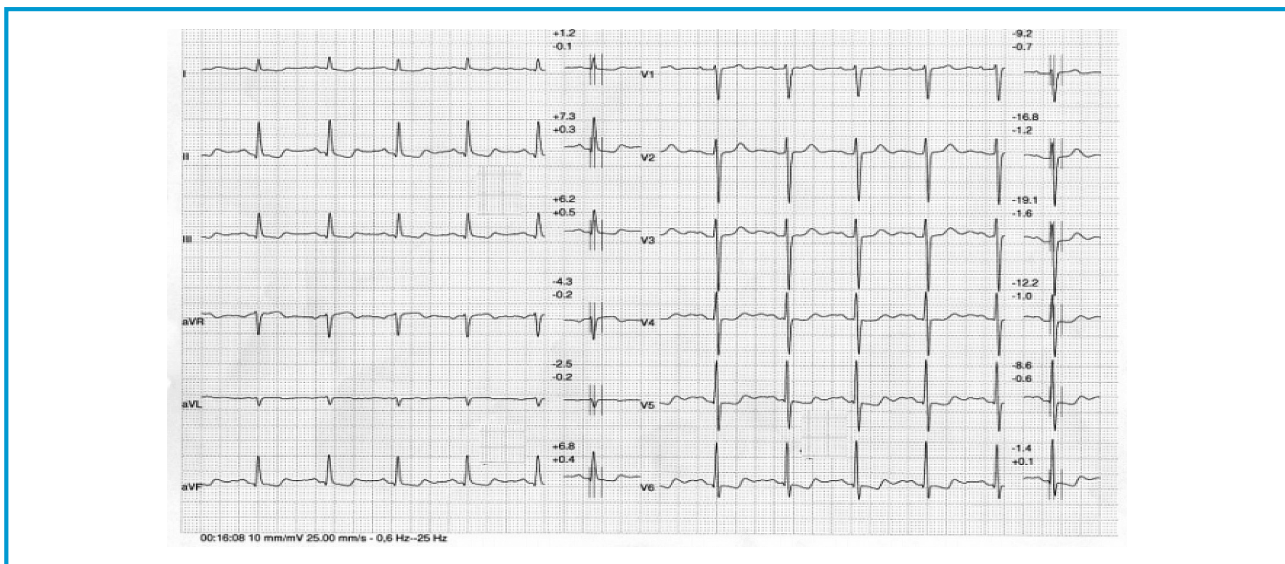
Caterina, a 70-year-old lady, was referred to our outpatient clinic complaining of continuous chest tightness unrelated to physical exertion, worsening dyspnea, and bilateral leg swelling over the prior three-four weeks. Her shortness of breath was exacerbated by exertion and lying down, and worsened during the night. Over the same time, she developed a dry, raspy, non-productive cough. She was accompanied by her husband Leopoldo, an 80-year-old gentleman, heavy active smoker (20 cigarettes per day), with a high cardiovascular risk profile (including essential hypertension, type II insulin-dependent diabetes mellitus for 30 years, dyslipidemia), stage I/II of Parkinson's disease and prostatic hypertrophy.

### Physical examination

Our physical examination revealed a small woman (160 cm and 50 kg) with dyspnea after mild exertion. Her blood pressure was 170/70 mmHg with orthostatic hypotension, and her heart rate was 78 beats per minute. Her respiratory rate was 22 breaths/min, with an oxygen saturation of 94% by pulse oximetry while breathing room air. Heart auscultation revealed a regular rate and rhythm, without any pathological heart murmurs or rubs. Lung auscultation revealed slight bibasal inspiratory crackling, as well as bronchial wheezes. Upon an examination of the extremities, severe bilateral ankles edema was detected. She appeared alert, oriented, and collaborative. She presented considerable movement instability and poor physical balance.

### Past medical history

Caterina had been affected for a long time by type II diabetes mellitus (requiring oral medication), dyslipidemia, essential hypertension, hypothyroidism, and in



**Figure 1.** Regular sinus rhythm, 80 bpm, diffuse infero-lateral ST-T segment abnormalities.

the last two years by stage III of Parkinson's disease. She had also been suffering from rheumatoid arthritis for eight years, with a poor control of pain, because of a low-dosage steroid therapy. Her doctor, in fact, feared the possible adverse side effects of an appropriate dose of steroids on diabetes, blood pressure, and osteoporosis, being the patient at high risk of falls, due to the considerable motor impairment and disability for Parkinson's. She denied any past and/or present smoking habit.

She had undergone cardiac surgery in 2017 for unstable angina. Coronary angiography showed diffuse calcific coronary three-vessel disease: circumflex sub-occluded at the ostium, followed by critical stenosis of the middle tract; left descending artery with diffuse atheromasia on all parts of the vessel; a 60% occlusion of the proximal right coronary artery; and a 70% occlusion of the crux cordis. Ejection fraction was preserved. It was only possible to perform a bypass graft on the circumflex and a left internal mammary artery anastomosis on the left descending coronary artery, with an acceptable clinical condition for two years.

### Differential diagnosis

Exertion angina was the first diagnosis to be ruled out, because of her history of chronic ischemic heart disease and diabetes; however – due to the presence of movement impairments and limitations related to the Parkinson's disease, and also in consideration to the basal electrocardiogram alteration – we decided not to perform an exercise test. We decided first to perform an echocardiogram with lung ultrasound, in order to rule out heart failure.

### Investigations

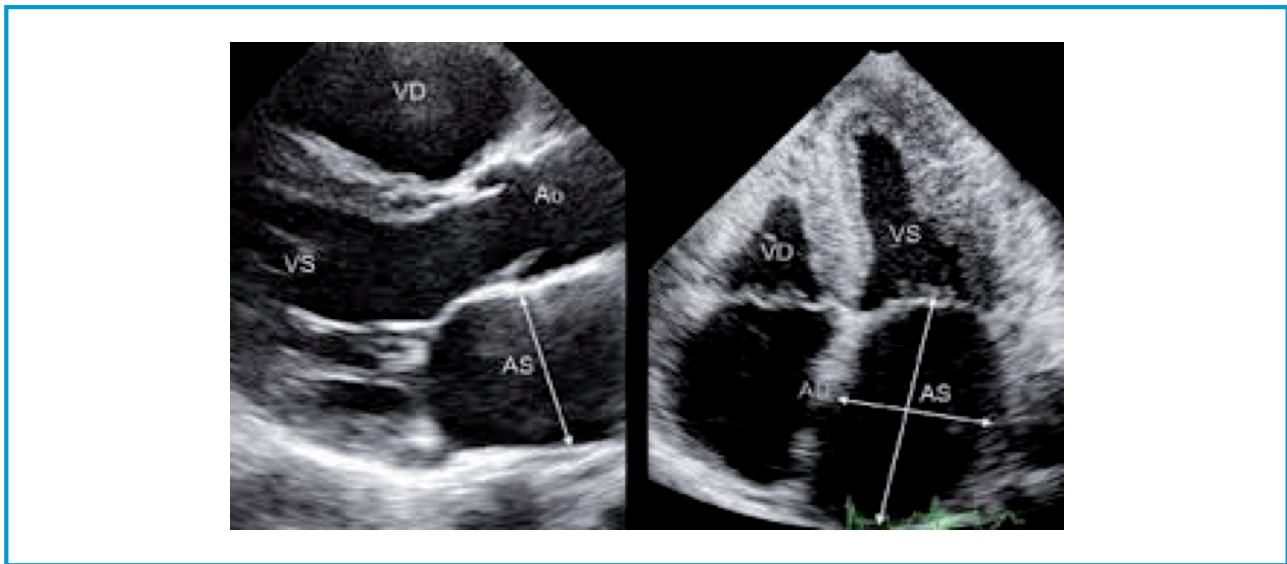
At the electrocardiogram (ECG), we observed a regular sinus rhythm, diffuse ST-segment depression in the infero-lateral leads, already reported in previous post-operative ECGs (Figure 1).

The echocardiogram (Figure 2) showed severe left atrial dilatation (53 ml/mq), fibrous-calcific degeneration of the mitral leaflets, and posterior mitral annulus calcification, with trivial regurgitation. Normal left ventricular end-diastolic volume (62 ml/m<sup>2</sup>), with severe concentric hypertrophy (left ventricular mass index 155 g/m<sup>2</sup>; RWT 0.58), normal segmental and global kinesis, with preserved ejection fraction (EF 52%) and a first-degree diastolic dysfunction were recorded. The longitudinal right ventricular function (TAPSE >20mm) was preserved. Lung ultrasound showed some bilateral B-lines, but no pleural effusion.

### Medication

Caterina was on multiple home medications:

- Sinemet® (levodopa/carbidopa) 200 mg + 50 mg t.i.d.;
- Aspirin 100 mg q.d.;
- Metoprolol 50 mg q.d.;
- Amlodipine 5 mg b.i.d. 8 am and 8 pm;
- Furosemide b.i.d. at 11 am and 5 pm;
- Metformin 500 mg t.i.d.;
- Requip® (ropinirole) 8 mg b.i.d.;
- Atorvastatin 20 mg q.d.;
- Levothyroxine 100 mg/die
- Prednisone 2 mg/die



**Figure 2.** Parasternal long-axis view and apical 4 chamber view showing a severe left atrium dilatation; fibrosclerosis of mitral leaflets with calcification of the posterior annulus. Normal left ventricular volume, with severe concentric hypertrophy.

We decided not to carry out any further investigation, interpreting the clinical picture as an early stage of heart failure with preserved ejection fraction. We just modified her therapy, with the aim of re-evaluating the patient after three weeks.

We stopped amlodipine, as a possible cause either of peri-malleolar edema or too low diastolic pressure, introducing valsartan 160 mg (she reported having suffered from cough with ACE-inhibitors in the past), maintaining furosemide, not to fix amlodipine-induced edema, as previously prescribed by her doctor, but to reduce congestion. We advanced furosemide at 7:00 am for two reasons: to stop the patient from getting up during the night – a quite dangerous feat, due to her instability (Parkinson's disease) – and to improve its effectiveness in treating congestion, being furosemide more effective after lying down in bed. We also replaced furosemide in the afternoon with a combination of furosemide and an anti-aldosteronic agent (spironolactone) at 4 pm, for dyspnea. Finally, we replaced metoprolol with nebivolol 5 mg, once a day, in order to reduce systolic blood pressure and bronchial wheezes. We did not change the remaining therapy.

After all the exams and investigations, we decided not to consider the chest discomfort reported by Caterina as angina. In fact, it was persistent during the entire day, it was not related to physical exertion, and it was described by the patient as not similar to the previous ischemic episode of 2017, that required myocardial revascularization with double coronary artery bypass graft surgery. For this reason, we decided to improve her medical treatment as described above, with the aim of re-evaluating the patient after three weeks, eventually

performing a pharmacological stress echocardiography in case of persistence of symptoms.

Caterina was accompanied by her husband Leopoldo, an 80-year-old gentleman, heavy active smoker, affected by essential hypertension, type II diabetes mellitus for 30 years, stage I/II of Parkinson's disease and prostatic hypertrophy. They shared many drugs, but he was also insulin-dependent and on well-tolerated ACE-inhibitors. Leopoldo had not had any cardiovascular event in his past medical history, neither he had reported any sign and/or symptom of heart disease. Moreover, also from a neurological point of view, he did not report any relevant motor impairment or disability due to the Parkinson's disease. Therefore, he was theoretically exposed to a higher cardiovascular risk, in his position of: male, older, smoker, diabetic, hypertensive; however, his cardiovascular history was, in terms of events, incredibly silent.

## Discussion

We report this case as an example of gender difference in the current practice evaluation and treatment of a high-risk cardiovascular patient. CVD, traditionally considered a male disease, is presently the leading cause of death and disability in women in developing countries<sup>1</sup>.

The importance of the risk factors in relation to gender has not been clarified as well as their treatment. Most of the CVD burden can be explained by traditional risk factors affecting men and women alike, but the prevalence and the relative risk weight of some of these are gender-specific; what is more, there are some risk factors



related to changes in the hormonal environment that are woman-specific. In this regard, various data suggest that hypertension and diabetes are more relevant risk factors in women than in men<sup>2,3</sup>, and the clinical history of our patients reflects this consideration, since Caterina and Leopoldo both presented these conditions; however, only Caterina had a history of severe CVD.

Diabetes is a major risk factor for CVD in both men and women, with a more significant impact in the latter. It has been demonstrated, in fact, that women affected by type II diabetes mellitus are 3-fold more at risk for CVD compared with non-diabetic women, and this spread is higher than between diabetic versus non-diabetic men. In a meta-analysis of over 850,000 subjects, the relative risk for CVD was 44% greater in women with diabetes mellitus than in similarly affected men<sup>4</sup>.

Even arterial hypertension, the most prevalent and potent risk factor for CVD, has shown to be a “super” risk factor for females, since hypertensive women were seen to be at higher cardiovascular risk than their male peers. Hypertension is common in both men and women; however, it tends to follow different patterns during the life of men and women. In their fertile age, women tend to have lower blood pressure compared to men; this trend starts to change with the transition through menopause and afterwards, when blood pressure in women begins to increase at a faster rate than in men, so that after the age of 75 there are more hypertensive women than men. With age, not only the prevalence of hypertension changes, but also some specific types of high blood pressure become more prevalent in women than in men. Through menopause, women experience a much higher increase in systolic blood pressure than diastolic pressure; this pattern is called isolated systolic hypertension, and is related to the increased arterial stiffening that women experience late after menopause<sup>5</sup>. The different lifetime patterns of blood pressure in women are related to reproductive changes and hormonal settings, that can deeply vary through a woman’s life. In addition, pregnancy may induce hypertension, the so called “gestational hypertension”, with the possible complication of pre-eclampsia and eclampsia, both predictive of a future risk of CVD<sup>6</sup>. Finally, the contraceptive pill may induce hypertension, whereas the hormone replacement therapy does not appear to have the same effects on blood pressure. Compared to men, therefore, the pathophysiology of hypertension in women presents peculiar differences in relation to the phases of life, with an undeniable impact on the treatment<sup>7</sup>. All these gender differences must be taken into account in prescribing medications, both in terms of efficacy, for example, because it is known that isolated systolic hypertension pattern responds better to certain classes of medications than others, and also in terms of safety, for example, been aware of the most common side effects of ACE

inhibitors in women or of the possible risks of certain drugs in women likely to become pregnant or who are breastfeeding. Despite these pieces of evidence, the only, very few certainties we have today regarding the women-targeted hypertension therapy may be summarized in: how to treat or, better, what *not* to use in the treatment of hypertension during pregnancy, and how to treat acute severe hypertension in pregnancy<sup>8</sup>. The most recent ESC/ESH 2018 guidelines for the management of arterial hypertension still don’t differentiate between men and women, probably underestimating the biological and hormonal differences between the sexes, which can instead affect various clinical pictures and drug responses.

Our patient is a typical example of high-cardiovascular-risk woman with stable ischemic heart disease, but with signs of heart failure and preserved ejection fraction, more related to hypertension and diabetes than to coronary artery disease. She presented as a small, thin old woman, with systolic hypertension, poorly controlled by calcium antagonist, prescribed after the withdrawal due to the onset of cough – of an ACE-inhibitor, which caused the development of peri-malleolar edema. In other words, she was treated correctly following current guidelines, which are similar for males and females, but she presented the most common side effects of the most recommended drugs. Due to all these issues, her doctor changed her therapy in order to control her symptoms, rather than her systolic hypertension.

This patient is also an example of how often old women with CVD present several comorbidities, which may impact both on the risk of developing CVD and on the treatments.

Caterina was affected by rheumatoid arthritis, an inflammatory and autoimmune disease much more prevalent in women, which demonstrated to lead to an increased cardiovascular risk both in terms of morbidity and mortality. This seems to be related to the chronic inflammation status with the release of pro-inflammatory cytokines (such as TNF $\alpha$ , IL-1, IL-6), causing pro-atherogenic and pro-thrombotic alterations that lead to premature and accelerate atherosclerosis<sup>9</sup>. In addition to being a risk factor for the development of CVD, this condition can interfere with other cardiovascular risk factors (and/or their treatments) that can coexist in the same individual. In our case, Caterina was on a low dose of steroids for rheumatoid arthritis, because of their possible negative impact on the glycemic and blood pressure profiles, resulting in a poor control of pain. To further complicate the clinical setting, the symptoms of rheumatoid arthritis and Parkinson’s disease limited the possibility to perform an exercise test, which would have been useful to obtain more diagnostic and prognostic information. Moreover, her current treatment (levodopa/carbidopa and ropinirole), together with a calcium

antagonist and diuretics, were the cause of her orthostatic hypotension.

To further increase Caterina's cardiovascular risk profile was her hypothyroidism. Hypothyroidism affects between 4% and 10% of the population, with a much higher prevalence in women, and it has been shown to be a risk factor for CVD and cardiac mortality<sup>10</sup>. Thyroid hormones play a variety of effects on the entire body, and an essential role in regulating cardiac, vascular, and metabolic physiology. Hypothyroidism is associated with a lower cardiac output, due to an impaired relaxation of the vascular smooth muscle and a decreased availability of endothelial nitric oxide. Hypothyroidism is associated with alterations in the renin-angiotensin-aldosterone system, since renin substrates are synthesized in the liver under the stimulus of thyroid hormone T3, the hormone that also increases erythropoietin secretion, thus explaining the normochromic, normocytic anemia often found in hypothyroidism. Thyroid hormones even regulate pacemaker-related genes and the lipid metabolism; as a result, in hypothyroidism heart rate decreases, and there is an elevation of total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B. Elevations of both C-reactive protein and homocysteine are often found. Hypothyroidism can also be associated with a decrease in insulin sensitivity, due to the down-regulation of glucose transporters and the direct effects on insulin secretion and clearance. As widely reported, Caterina presented dyslipidemia and diabetes.

Paradoxically, as an example of an outlier subject, her husband presented a more severe global cardiovascular profile, without any cardiovascular event, with a better quality of life, since he was not reporting about any sign and/or symptom<sup>11</sup>. As previously said, Leopoldo was affected by a more severe form of diabetes mellitus, with the need of insulin therapy; furthermore, he had been a heavy active smoker for a long time: despite this, he had never suffered from cardiovascular events. He was very active, also from a functional point of view, and he had no significant motor impairments or limitations.

They were nevertheless happy, because Leopoldo was a perfect caregiver and an affectionate husband.

### Follow-up

Caterina came back after three weeks, reporting a marked improvement in her dyspnoic symptoms and exercise tolerance; her blood pressure was 135/70 mmHg, her heart rate was 70 beats per minute. Non-signs of congestion were detected at clinical examination. The diagnosis and therapy for heart failure with preserved function were confirmed.

### Conclusion

CVD was traditionally considered a purely male disease, and for many years it was under-researched and under-recognized in women, but the reality is that CVD represents the leading cause of mortality and disability in women in developing countries.

Furthermore, specific gender differences concerning CVD have been described increasingly more widely, both in terms of clinical presentation, prevention, treatment, and prognosis. The role and weight of the risk factors in relation to gender have not been clarified as well as their treatment, but they play a fundamental role. We do not have gender-related guidelines, since it is well known that guidelines are derived from trials conducted mainly on a male population, and subsequently transferred to women without evidence. We have to follow the current guidelines as an expression of evidence-based medicine, but for women it is mandatory to adopt a personalized approach, since the biological and hormonal differences between the sexes could affect the clinical presentation and therapeutic response. What is more, for the evaluation and management of high-risk women it is essential to take into account symptoms, past and present history, but also comorbidities, both for the diagnosis and for the treatment. This report aims at highlighting the essential role played by prevention strategies, especially in women, since they have a longer life expectancy than men (and it is well known that, with ageing, multiple chronic conditions emerge), but in whom, paradoxically, prevention is often underestimated and under-practiced. Caterina is an example of an old woman – although not that old – affected by multiple comorbidities affecting each other and her quality of life. Thanks to the diagnostic and therapeutic improvements, it is now possible to live for many years with several conditions, although with huge costs in terms of quality of life and money, hardly quantifiable both for the health systems and the families, who assign important resources to the care and assistance of their beloved ones. In this regard, the main conclusion is that the majority of non-communicable diseases (including CVD, diabetes, lung disease, cancer...) could be avoided by preventive strategies, mainly based on a healthy lifestyle, gained by reducing smoking, practicing physical activity, following a healthy diet and limiting the harmful consumption of alcohol. This calls for the need to act in favor of healthy lifestyles, since this situation is no longer sustainable, both from an ethical point of view – since there are interventions of proven efficacy that could counteract the onset of multiple conditions, including CVD – and from an economic perspective – since these measures could prevent the burden of disease and its related costs for a large number of people.

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*Patient consent:* written informed consent for publication of their clinical details and clinical images was obtained from the patients. A copy of the consent form is available for review by the Editor of this journal.

*Author contribution statement:* all Authors contributed in conceiving the content and in the final review of the article.

*Conflict of interest statement:* the Authors declare non conflicts of interest.

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