

# Cardiovascular Disease in Women: What the Radiologist Needs to Know

## Kardiovaskuläre Erkrankungen: Was die Radiologin und der Radiologe wissen müssen

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### ABSTRACT

**Background** Sex-specific disparities are well documented for cardiovascular disease (CVD). There are differences in physiology and pathophysiology, pain perception, spectrum of disease, risk, therapeutic aspects, prognosis, and outcome. CVD represents a broad spectrum of disorders. This review focuses on cardiovascular and cardiac pathology.

**Method** This review summarizes the current state of the literature on cardiovascular disease in women from a radiological viewpoint. It aims to provide a deeper understanding of these differences and thereby alerts the reader to the potential of CT and MRI for diagnosing CVD in women. Special attention is paid to disparities in the underlying physiological and pathophysiological processes, clinical presentation, and the quality of care to provide a deep understanding of the

topic. Cardiovascular and cardiac pathologies with a sex-specific pattern of disease are presented and typical CT and MRI findings are arranged and illustrated with imaging findings.

**Results and Conclusion** Sex-specific differences are not only sex hormonal in nature but are rooted in the epigenome and encompass a multitude of physiological systems. In fact, cardiovascular disease shows sex-specific characteristics spanning from incidence to clinical presentation, course of disease, and prognosis. This is of significance regarding pretest probabilities, the power of tests, imaging strategies, and interpretation of imaging results. Key sex-specific issues encompass obstructive and non-obstructive coronary artery disease (CAD), microvascular angina, myocardial infarction with non-obstructive CAD, and coronary artery dissection. Sex-specific patterns are also noted in myocardial disease and heart failure such as pregnancy-related heart disease, Takotsubo syndrome, and anthracycline-induced cardiotoxicity.

### Key points:

- Cardiovascular diseases have sex-specific characteristics.
- Imaging strategies and interpretation of imaging results should be adjusted for women.
- Imaging helps in the improvement of the sex-specific management of cardiovascular disease.

### ZUSAMMENFASSUNG

**Hintergrund** Geschlechtsspezifische Unterschiede sind bei kardiovaskulären Erkrankungen gut dokumentiert. Sie beziehen sich auf Physiologie, Pathophysiologie, Schmerzwahrnehmung, Krankheitsspektrum, Risiko, therapeutische Aspekte, Prognose und Ausgang. Kardiovaskuläre Erkrankungen umfassen zahlreiche Krankheitsbilder. Diese Übersicht fokussiert auf kardiovaskuläre und kardiale Pathologien.

**Methode** Diese Übersicht fasst den aktuellen Stand der Literatur zu kardiovaskulären Erkrankungen bei Frauen aus einem radiologischen Gesichtspunkt zusammen. Ziel ist es, geschlechtsspezifische Unterschiede darzustellen und das Potenzial der CT- und MR-Bildgebung zu präsentieren. Besondere Aufmerksamkeit wird auf zugrunde liegende physiologische und pathophysiologische Prozesse gelegt, die Klinik und die Qualität der Versorgung, damit die Thematik umfassend verstanden werden kann. Kardiovaskuläre und kardiale Pathologien mit einem geschlechtsspezifischen Muster wer-

den präsentiert und mit typischen CT- und MR-Befunden illustriert.

**Ergebnisse und Schlussfolgerung** Geschlechtsspezifische Unterschiede sind nicht nur durch Geschlechtshormone verursacht, sondern wurzeln im Epigenom und beziehen zahlreiche physiologische Systeme ein. Kardiovaskuläre Erkrankungen zeigen ein Spektrum geschlechtsspezifischer Charakteristika, das von der Inzidenz über die Klinik, Krankheitsverlauf zur Prognose reicht. Das ist von Bedeutung für Vortestwahrscheinlichkeiten, Aussagekraft von Tests und für die Strategie und Interpretation der Bildgebung. Schlüsselthemen sind die obstruktive und nicht obstruktive koronare Herzerkrankung (KHK), die mikrovaskuläre Angina, der Herzinfarkt mit nicht obstruktiver KHK und die koronararterielle Dissektion. Geschlechtsspezifische Muster finden sich auch bei den Erkrankungen des Myokards und dem Herzversagen,

wie bei den Schwangerschafts-assoziierten Herzerkrankungen, dem Takotsubo-Syndrom und der Anthracyclin-induzierten Kardiotoxizität.

#### Kernaussagen:

- Kardiovaskuläre Erkrankungen haben geschlechtsspezifische Charakteristika.
- Strategie und Interpretation der Bildgebung sollten für Frauen adaptiert werden.
- Die Bildgebung unterstützt einen geschlechtsspezifischen Ansatz im Management von kardiovaskulären Erkrankungen.

#### Citation Format

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## Introduction

Cardiovascular disease (CVD) represents a broad spectrum of disorders ranging from coronary heart disease, cerebrovascular disease, atherosclerosis, and peripheral artery disease to aortic disease, and even heart failure (HF), cardiomyopathies (CMP), and hypertension. In this review we focus on cardiovascular and cardiac pathology. CVD is the most common cause of death worldwide for both sexes [1]. Until the 1990s, women were underrepresented in research on cardiovascular disease. As a result, data was only valid for the male population [2]. Novel research clearly documents sex-specific disparities in cardiovascular physiology and disease. Data on the sex-specific use and value of CT and MRI in cardiovascular disease is sparse which has an impact on the current guidelines.

## Sex disparities in cardiovascular physiology and pathophysiology

Genetic activity and gene expression have sex-specific variability in all human tissue types, even in non-dimorphic organs such as the heart. Sex-specific epigenomic patterns seem to evolve in early embryogenesis at a timepoint before sex hormones appear and are already manifest in utero [3]. Sex hormones affect cardiomyocytic gene expression and protein regulation via direct and indirect pathways. Estrogen receptor-mediated calcium channel subtype increase may be the physiological basis for the longer QT interval in females [4]. Estrogen plays a role in glucose uptake in skeletal and cardiac muscle cells, cardio-protection in the context of ischemia reperfusion injury, cardiac hypertrophy, and heart failure [5]. During an ischemic injury, the phenomenon of microvascular obstruction (MVO) as seen in MR imaging is less frequent and less pronounced in females. This may well be related to the stronger estrogen action in the female endothelium and myocardium due to the higher number of estrogen receptors via mechanisms such as estrogen-triggered inhibition of Endothelin-1 resulting in vasoconstriction and protection of myocytes against

deleterious intracellular Ca. As a consequence, the female myocardium might exhibit stronger tolerance to ischemia than the male myocardium [6]. The autonomic modulation of the cardiovascular system also shows a sex-specific pattern, the cardioprotective vagal system being more dominant in premenopausal females [7]. Corrected for body size, the left ventricular chamber size and stroke volumes are smaller in females. Cardiac output, however, is comparable to males due to higher resting heart rates in females. Systolic and cardiac stiffness is higher in women. Myocardial hypertrophy is a physiological mechanism during pregnancy and female hearts seem to be better protected against the development of ventricular maladaptation and hypertrophy than male hearts. The number and mass of cardiomyocytes decline more heavily in the aging female heart. Consequently, hypertrophy tends to be less intense, concentric, left ventricular dilation less pronounced, systolic function better, and relative wall thickness greater than in males with pressure overload [8]. Variables to be considered in the context of cardiovascular disease include age at menarche and menopause, peculiarities of the menstrual cycle, pregnancy, concomitant disease, depression, and stress. Complications of pregnancy, such as hypertension, gestational diabetes, and preterm delivery, may be associated with an increased risk for cardiovascular disease later in life.

## Coronary artery disease and ischemic heart disease

Stenosis and occlusion of large epicardial coronary arteries is usually referred to as coronary artery disease (CAD). For disorders of smaller arteries and the capillary bed, the terms ischemic heart disease (IHD), non-obstructive CAD, and microvascular disease are used. We suggest CAD as the umbrella term for the entire spectrum of abnormalities of the arterial component of the cardiac vasculature covering a spectrum of obstructive, non-obstructive, stable and unstable conditions (► **Table 1**). We use the term ischemic heart disease exclusively for conditions in which reduced blood flow to

► **Table 1** Spectrum of pathophysiological mechanisms in coronary artery disease.

Macrovascular disease	Microvascular disease
Epicardial coronary arterial occlusion	Microvascular dysfunction (structural, functional, extravascular)
Flow-limiting stenosis	Microparticle occlusion
Non-flow-limiting stenosis	Microembolic occlusion
Vasospastic angina (Prinzmetal angina)	Inflammation (autoimmune disease)
Inflammation (autoimmune disease, rheumatoid arthritis, vasculitis)	
Spontaneous coronary artery dissection	

myocardial tissue leads to temporary or permanent damage of cardiac function and/or structure.

Acute myocardial infarction (AMI) is the leading cause of death in women worldwide. Mortality from coronary heart disease is higher in women aged 35–55 than from breast cancer [2]. Whereas the overall incidence and mortality of CAD has been in decline for the last decades, there has been a relative increase in younger women (usually defined as under 55 years of age) [9]. The risk of CAD in women under 55 years of age is 4 times lower than that of men and manifestation usually occurs 10 years later [10]. 30-day mortality is higher in young women with AMI than in young men.

### Stratification of cardiovascular risk – the asymptomatic woman

Risk and risk factors in CVD show significant sex-specific differences. Traditional risk factors are more frequent in young women as are co-morbidities such as mood disorders, autoimmune disease, and pulmonary disease [9]. Gestational hypertension and preeclampsia may predispose to premature acute coronary syndrome in young women through prolonged endothelial dysfunction [11]. Premenopausal women frequently present with the non-obstructive type of CAD and women generally depict a heightened inflammatory status [12]. Especially in younger women, traditional risk factors underestimate risk, and sex-specific risk calculators are recommended, such as the Reynolds risk score [13]. In postmenopausal women, similar to males, IHD is usually related to obstructive CAD. Even in this age group, however, there are differences regarding risk factors such as the calcium score. For comparable levels of risk, females have less coronary arterial calcifications, and multi-vessel involvement is more common [14]. Geographic and ethnic differences in calcium percentiles are described.

### Signs of ischemia – the symptomatic woman

In IHD, pre-menopausal women frequently have different symptoms compared to men. One explanation is the interaction of sex hormones with the endogenous opioid system and serotonin and

dopamine facilitated pain pathways [15, 16]. Anginal pain, which does not fit into the male norm, is referred to as atypical and it is usually the typical type of pain in women under 55 years of age. It includes a prodromal phase of several days or weeks with fatigue, sleep disturbances, restlessness, nausea, arm weakness and discomfort, abdominal pain, and jaw pain [2, 17]. The fact that non-obstructive CAD is much more frequent in younger women might be another cause of differences in the clinical presentation. Consequently, the Global Registry of Acute Coronary Events (GRACE) and the Thrombolysis in Myocardial Infarction (TIMI) scores work better for men than for women. To improve risk assessment in stable symptomatic women, the American Heart Association (AHA) proposes an alternate method in a 2014 consensus statement which is based on age and comorbidity. For the low-intermediate and the intermediate risk group, exercise testing is suggested [18]. Since the ECG treadmill test cannot be used in many females due to an inability to achieve over five metabolic equivalents and the lower specificity of ST depression (dependent on the hormonal status), stress MRI and CCTA are recommended as alternative tests. Stress MRI can detect microvascular disease. Of note is an exceptionally strong association of CCTA with the clinical outcome [18]. CTA for the further evaluation of symptomatic women is especially helpful when considering the high proportion of non-obstructive CAD. CAD with positive remodeling may be missed with angiography, as documented in a WISE sub-study [19]. Plaque analysis, dual-energy stress CT perfusion, and calculating fractional flow reserve from a CT data set further increase the diagnostic accuracy of CCTA [20].

### Non-obstructive CAD

Structural and functional changes in arteries with a diameter of under 500 µm can cause ischemic heart disease irrespective of stenosis in large epicardial arteries. This microvascular type of CAD, also called non-obstructive CAD, can cause stable and unstable angina, STEMI, and non-STEMI. Women have a higher probability to present with microvascular disease (MVD) than men [21]. Structural changes of the arterial wall, an abnormal response to stimuli, and effect of various extravascular contributors are mechanisms in microvascular angina (MVA) leading to reduced coronary blood flow (CBF) and coronary flow reserve (CFR) [21] (► **Table 2**). Microvascular changes do not relate to epicardial arterial territories but involve the entire heart leading to diffuse or patchy changes of flow (► **Fig. 1**). Intracoronary acetylcholine testing identifies epicardial and microvascular functional abnormalities in MVD and vasospastic angina as a perfusion deficit and changes in contractility but is not recommended as a standard procedure. MVD can be an isolated occurrence or a component in a variety of myocardial diseases such as cardiomyopathy, myocarditis, obstructive disease, and iatrogenic disease [22].

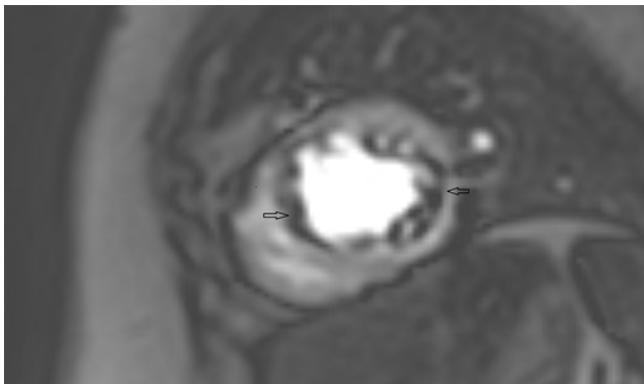
### Microvascular angina

Microvascular angina (MVA) is myocardial ischemia caused by microvascular disease. In 2010, Patel et al. published data showing that 39% of 398,978 patients with angina had normal or non-obstructive (<20% stenosis) epicardial arteries in elective invasive coronary angiography [23]. Females were more likely to present with non-

► **Table 2** Types and underlying mechanisms in microvascular disease.

Type	Clinical presentation	Diagnosis	Mechanisms in MVD	Imaging
1	No obstructive CAD No myocardial and/or valvular disease	Microvascular angina	Endothelial dysfunction Smooth muscle cell dysfunction Vascular remodeling Capillary rarefaction	MR stress test Calculation of CFR Exclusion of stenosis with CCTA Exclusion of myocardial disease with MR
2	No obstructive CAD Myocardial and/or valvular disease	Amyloidosis Storage diseases Myocarditis Hypertrophic CMP Dilated CMP	Smooth muscle cell dysfunction Vascular remodeling Extramural compression and luminal obstruction (perivascular fibrosis, increase of myocardial volume and pressure)	Identification of diffuse and focal myocardial disease
3	Obstructive CAD	Angina pectoris	Endothelial dysfunction Smooth muscle cell dysfunction Luminal obstruction (extramural compression, microembolization)	Identification of flow-limiting stenosis in epicardial arteries with CCTA and MR stress test
4	Iatrogenic	Percutaneous coronary artery intervention Coronary artery grafting Cardiac transplantation	Luminal obstruction (microembolization) Autonomic dysfunction (reperfusion injury)	MR stress test Calculation of CFR CCTA

MVD: microvascular disease; CAD: coronary artery disease; CMP: cardiomyopathy.



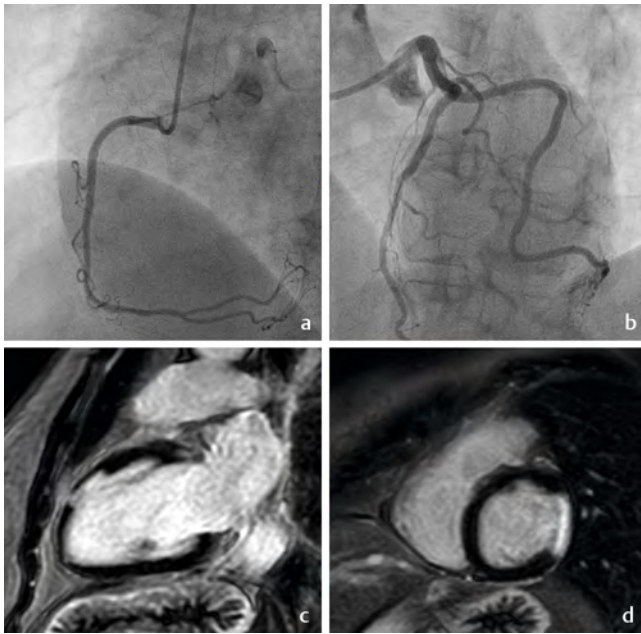
► **Fig. 1** 53-year-old woman with angina pectoris and non-obstructive coronary artery disease in invasive angiograms. Dynamic Turbo Field Echo stress perfusion (adenosine) sequence with parallel imaging in short axis shows concentric subendocardial hypoperfusion (arrows) compatible with microvascular disease. Corresponding T1 15 minutes post-contrast PSIR sequence showed no scarring.

obstructive MVD. Diagnostic clinical and imaging criteria have been published [21]. The absence of significant stenotic disease and the presence of stress perfusion abnormalities can be documented with MRI and CT. MRI stress perfusion for measuring CFR is best performed with endothelium-independent vasodilators (e. g., adenosine, dipyridamole, regadenoson) since achievable flow increase is higher than with dobutamine [24]. Myocardial perfusion reserve can be measured semi-quantitatively or quantitatively by calculating data from perfusion images or coronary sinus flow measurements. Contractile dysfunction is not a reliable diagnostic parameter in MVD since compromised myocardial tissue is surrounded by myocar-

dial tissue with normal function. Diagnosis and treatment of MVA is critical because of a high risk of major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke, heart failure, all-cause mortality) [12, 25]. On identifying abnormalities consistent with MVA, MRI can be used for prognosis prediction in women with suspected myocardial ischemia and absence of obstructive (> 50 %) disease [26].

### Myocardial ischemia with non-obstructive coronary arteries

The prevalence of myocardial infarction without obstructive coronary disease (MINOCA) is between 5 % and 25 % [27]. Female sex, younger age, and renal insufficiency are major predictors, and the number of females is twice as high in non-obstructive disease compared to males [28]. Patients with MINOCA have a lower risk of recurrent myocardial infarction, but a higher all-cause mortality than those with obstructive disease independent of sex. Diagnosis is based on clinical symptoms, deflection of cardiac biomarkers, ECG changes, new wall motion abnormalities, or new loss of viable myocardium and non-obstructive (no coronary stenosis  $\geq$  50 %) coronary arteries on angiogram [29] (► **Fig. 2**). MINOCA is reserved for conditions where there is an ischemic mechanism involved, stressing the importance of ruling out non-ischemic causes of troponin elevation, such as pulmonary embolism, and making sure not to overlook obstructive disease. Imaging has a key role for both diagnosis as well as identifying the pathological substrate for MINOCA (► **Table 3**). Currently, non-obstructive CAD is identified with invasive angiography. Based on data from the ARIAM-SEMICYUC registry, a MINOCA prediction score has been suggested to categorize patients according to their prob-



► **Fig. 2** **a** 59-year-old woman with acute coronary syndrome and positive biomarkers and Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA). Invasive angiography of the right coronary artery without evidence of flow-limiting stenosis. **b** 59-year-old woman with acute coronary syndrome and positive biomarkers and Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA). Invasive angiography of the left coronary artery without evidence of flow-limiting stenosis. **c** 59-year-old woman with acute coronary syndrome and positive biomarkers and Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA). T1 PSIR 15 minutes post-contrast shows an ischemic scar anterior apical. **d** 59-year-old woman with acute coronary syndrome and positive biomarkers and Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA). T1 PSIR 15 minutes post-contrast shows ischemic scar midventricular lateral.

ability for obstructive CAD [30]. CCTA could replace invasive angiography in those with low probability of obstructive CAD. This is supported by the fact that the extent, composition, and stability of plaque load and positive remodeling cannot be fully appreciated on invasive angiograms (► **Fig. 3**). Additionally, the diagnosis of obstructive CAD as defined by luminal stenosis of  $\geq 50\%$  on invasive angiography is hampered by interobserver variability, variability of vasomotor tone, and volume of thrombotic apposition [31]. Invasive and noninvasive (with CT) measurement of Fractional Flow Reserve (FFR) and CCTA might be helpful in defining the risk for subgroups with minimal ( $< 30\%$  stenosis) and moderate ( $\geq 30\%$  and  $< 50\%$ ) coronary stenosis.

### Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is typically found in women aged 44 to 50 years [29, 32]. In 35% of females under 60 years of age presenting with acute coronary syndrome, SCAD is the underlying pathology [32]. Patients present with NSTEMI more frequently than with STEMI or ventricular tachycardia or fibrillation [32]. SCAD may occur spontaneously or secondary to an intramural hematoma caused by rupture of the vasa vasorum. Usually, the separation of the vessel wall occurs between media

and adventitia. SCAD is associated with emotional (40%) or physical stress (25%). Sympathomimetic drugs and increase of intrathoracic pressure such as in coughing, child labor, and isometric exercise act as trigger factors. In a recent study on 327 SCAD-patients, Saw et al. identified co-existing fibromuscular dysplasia in 62.7%, connective tissue disorders (e.g. Marfan syndrome, Ehlers-Danlos syndrome type 4, polycystic kidney disease, neurofibromatosis I) in 4.9%, and systemic inflammatory disease (e.g., systemic lupus erythematosus, polyarteritis nodosa, Crohn's disease) in 11.9% of patients [32]. Diagnosis of SCAD is challenging with angiography and is rarely possible with CTA due to the limited resolution (► **Fig. 4**). Intravascular imaging is the method of choice as intravascular ultrasound has a resolution of  $\sim 150\ \mu\text{m}$  and optical coherence tomography of  $\sim 10\text{--}20\ \mu\text{m}$ . SCAD heals within one month in most patients. CCTA is suitable for noninvasive follow-up [33].

### Vasospastic angina

Vasospastic angina (VSA) affects women less frequently than men. It is a disease with focal or diffuse vasospasms of epicardial arteries causing transient ischemia, and sometimes even infarction. Females usually present with combined macrovascular and microvascular dysfunction. Diagnosis is based on evidence of total or subtotal coronary artery occlusion, a clinical presentation of nitrate-responsive angina, and ischemic ECG changes [34]. Noninvasive stress test (e.g., MRI stress test) and CCTA can be used to exclude the differential diagnosis of obstructive CAD. Pharmacologic provocation of vasospasms with acetylcholine during angiography is a diagnostic test reserved for specialized centers. CCTA before and after application of vasodilator might be an alternative [35].

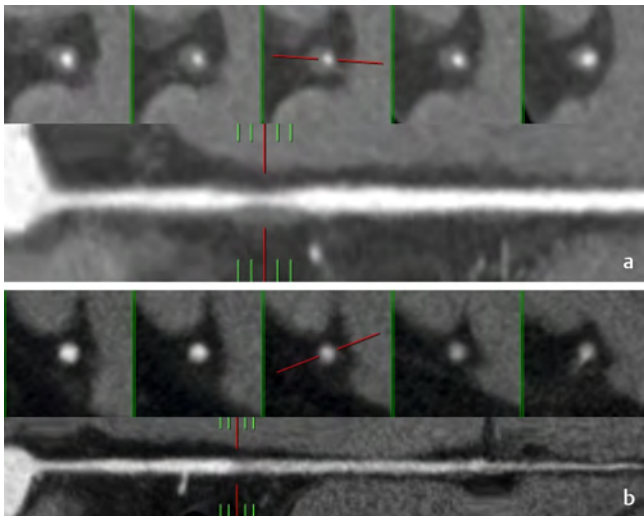
### Heart failure

In the western world the prevalence of chronic heart failure (HF) is 100–300 cases per 100 000 person years. Heart failure is a debilitating disease with a 5-year mortality of about 50% for both sexes and all types of heart failure [36]. Women develop HF later than men, have more symptoms, and a lower quality of life. The most common type of HF is HF with preserved ejection fraction (HFpEF), defined by an EF  $> 50\%$ , affecting women twice as much as men. Concentric myocardial hypertrophy, preservation of EF, microvascular disease, and diastolic dysfunction are typical but nonspecific findings of HF in women. Management of underlying and associated conditions is the therapeutic target in HF. In HFpEF identification of diastolic dysfunction is essential as it influences therapy (► **Fig. 5**). Specific etiologies of HF in women include peripartum and stress-induced cardiomyopathy (Takotsubo Syndrome). Inflammatory and autoimmune disorders are etiologies with a significant predominance in women and a strong association with MVD and diastolic dysfunction. The level of proinflammatory cytokines correlates with the degree of diastolic dysfunction and predicts adverse clinical outcome in HF [8]. Fibroblasts play a role in myocardial inflammation, fibrosis, and cardiac remodeling. MRI and CT imaging help to identify the underlying etiology and to assess cardiac structure and function. It is indicated in

► **Table 3** Role of MR and CT imaging in MINOCA.

Diagnostic steps	Pathophysiological mechanism	Modality	Key findings
Differential diagnosis	Pulmonary embolism	CCTA	Identification of embolus, defect in iodine map (DECT), right heart dilation
	Cardiac trauma	MRI	Myocardial edema, myocardial hemorrhage, functional abnormalities
Working diagnosis	Coronary artery occlusion or flow-limiting stenosis	CCTA, stress test	Direct or indirect Identification of stenosis
	Spontaneous coronary artery dissection	CCTA	Low accuracy, follow-up
	Takotsubo	MRI	RWMA, myocardial edema, function
	CMP and myocarditis	MRI	morphology, myocardial assessment (mapping, edema, LGE), function
	Exclusion of CAD	CCTA	
Specific diagnosis	Myocardial infarction	MRI	Morphology, myocardial assessment (mapping, edema, LGE), function
	Coronary artery occlusion or dissection	CCTA stress test	direct or indirect identification of stenosis
	Vasospasm (epicardial)	CCTA	Adenosine provocation CCTA
	MVD	MRI	Morphology, Myocardial assessment (mapping, edema, LGE), function, stress test, CFR

MINOCA: myocardial infarction with non-obstructive coronary arteries, RWMA: regional wall motion abnormalities, CFR: coronary flow reserve.



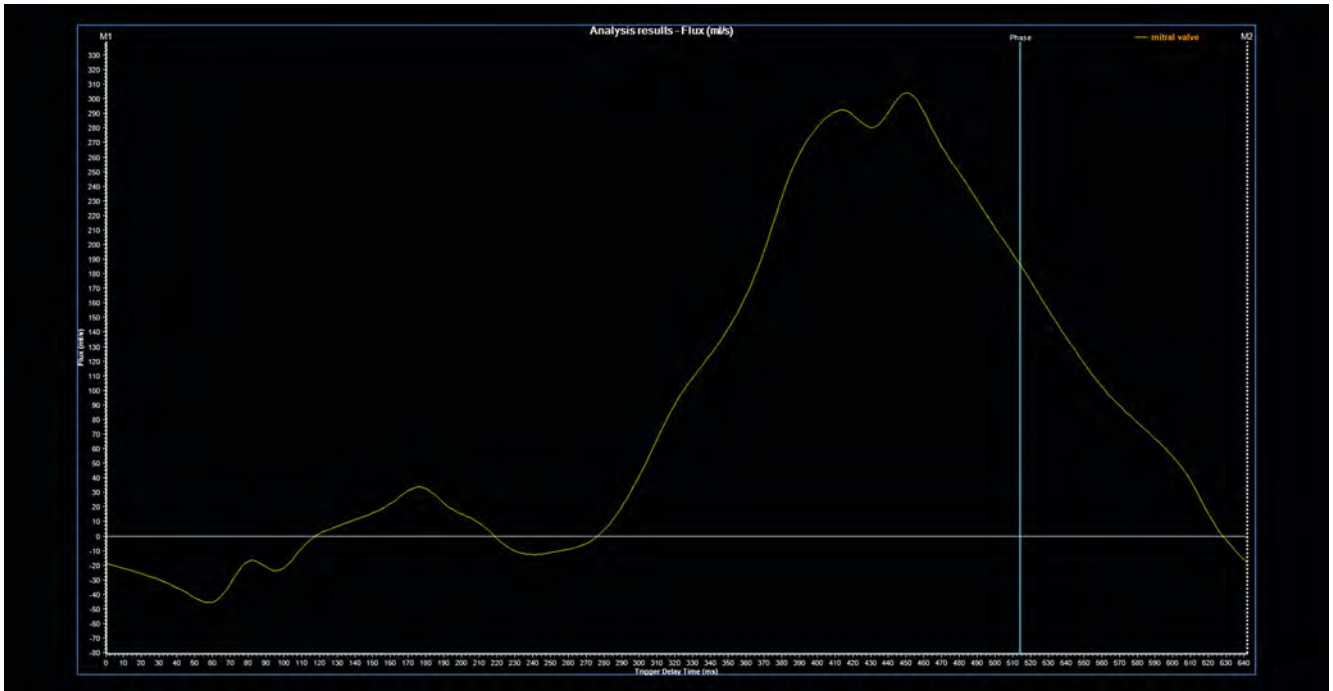
► **Fig. 3** **a** 38-year-old asymptomatic woman with low to intermediate risk according to the Framingham Risk Score and coronary artery disease on CT angiography. Contiguous transverse and corresponding straightened multiplanar reconstructions of the right coronary artery show segmental stenosis with enlargement of both the vessel wall as well as the overall arterial diameter consistent with remodeling. **b** Same patient as Fig. 3a. Reconstructions of a follow-up CTA 3 years later depicting the same segment show resolution of the stenosis after secondary prevention medication only.

newly suspected HF, HF with AMI, HF with unknown etiology, before revascularization and device therapy (e. g. CRT), and in the follow-up [37]. CCTA and perfusion imaging is for obstructive and non-obstructive CAD and MVD. T1, T2 mapping and extra-



► **Fig. 4** **a** 45-year-old woman with sudden chest pain after closing the car door. With a suspicion of Takotsubo syndrome, CTA is performed to rule out obstructive coronary artery disease. Curved multiplanar reconstruction of the left anterior descending artery depicts a short stenosis and a flap-like filling defect compatible with spontaneous coronary artery dissection. **b** Same patient as in ► **Fig. 4a**. Volume rendering shows corresponding expansion of the vessel caliber due to the mural hematoma.

cellular volume (ECV) values are biomarkers for inflammation and fibrosis. Of note are sex-specific differences in T1 relaxation time and ECV. Generally, pre-contrast T1 relaxation times and ECV values are higher in females but show a lower increase over age compared to males. The latter may be related to the observation that structural myocardial integrity is better preserved in females at an older age. [38] Quantification of left atrial structure and function with MRI or CT is a suggested novel biomarker in HFpEF and strongly correlates with N-terminal pro-BNP [39]. LV



► **Fig. 5** 63-year-old woman with clinical signs of heart failure, left ventricular dilation, an ejection fraction of 63 %, and absence of late enhancement on MR imaging. MR measurement of mitral valve flow reveals an abnormal relationship of early to late left ventricular chamber filling, the early component being smaller than the flow caused by atrial contraction, consistent with impaired relaxation – grade 1 diastolic dysfunction. Findings are consistent with a diagnosis of heart failure with preserved ejection fraction.

stiffness in HFpEF can be quantified with CMR elastography (CMRE), a 3D phase contrast technique to measure shear waves.

## Takotsubo syndrome

About 90 % of patients with Takotsubo syndrome (TTS), a form of acute heart failure, are women and the majority of those affected are over 55 years old [40]. TTS has an incidence of 2–7.5 % in patients presenting with ACS. Chest pain, dyspnea, ischemic ECG abnormalities, and elevated serum biomarkers (troponin, BNP, NT-proBNP) mimicking ACS are frequent clinical presentations. The range of symptoms includes syncope, (life-threatening) tachyarrhythmia, mitral valve regurgitation, severe left ventricular outflow obstruction, cardiogenic shock, and embolization of associated ventricular thrombi. A physical stressor (e. g., hemorrhage, stroke, seizure, surgery, exacerbation of chronic disease) precedes TTS in up to 36 % of cases, positive or negative emotional stressors (“happy heart syndrome”, “broken heart syndrome”) can be identified in about 30 % of cases. 7.8 % have both and in about a third of cases no stressor is found [40]. An excessive sudden increase of circulating and local catecholamine is the central pathophysiological mechanism and leads to direct myocardial injury, endothelial dysfunction, and epicardial and microvascular vasospasm. The resulting supply-demand mismatch is further aggravated by the increased cardiac workload. Clinical sequelae are acute systolic dysfunction and heart failure. The regional distribution of  $\alpha$  and  $\beta$  adrenoceptors is considered responsible for characteristic patterns of left ventricular wall motion abnormalities (WMAs) [41].

The right ventricle is affected in about 25 % of cases. TTS diagnosis is based on the presence of reversible typical WMAs, new ECG changes, the identification of trigger events, and absence of myocarditis. The ruling out of flow-limiting stenosis or occlusion with invasive coronary angiography is usually required but does not exclude TTS diagnosis. In stable patients CCTA may be considered as an alternative. MRI is of great diagnostic utility as it not only shows WMA but also structural changes. Areas with WMA typically show edema characterized by T2 hyperintensity and increased T2 relaxation time and an absence of late enhancement. Minor late enhancement is reported in some cases in the acute and subacute phases. Myocardial T1 relaxation time is found to be diffusely increased. MRI is an excellent tool to identify ventricular thrombi, a complication in TTS which usually develops during the first week in up to 8 % of patients. Therefore, MR imaging is recommended to be performed within 7 days after presentation in all suspected TTS cases [42]. MR imaging with ultrasmall superparamagnetic particles of iron oxide (USPIO) shows greater diffuse myocardial T2\* shortening in the acute phase of TTS than in healthy controls. This is explained by an increase in myocardial macrophages and a biomarker of a cellular inflammatory response in TTS. TTS usually resolves spontaneously within 4 months after onset. Persistent long-term changes, however, have been identified in some patients. This includes persistent myocardial edema, functional impairment in strain imaging, increased T1 mapping values, and metabolic changes in <sup>31</sup>P-MR spectroscopy studies despite normal LVEF and normal ECV values. These findings support a hypothesis that TTS is associated with inflammation and subtle fibrosis leading to remodeling even after

resolution of the acute episode. TTS patients show an in-hospital mortality of 4.1%, in the long term there is a major adverse cardiac and cardiovascular event (MACCE) rate of 9.9%, and the rate of recurrence is up to 10% [40].

## Myocarditis

Myocarditis is an inflammatory disease of the heart with a female to male ratio of up to 1:2 that is most frequently caused by viral infections. There are some etiologies with a strong female predominance and a higher rate of complications such as exposure to radiation for breast cancer, psychiatric medication (benzodiazepine and certain antidepressants), hypersensitivity reaction, auto-immune and systemic inflammation [43]. Myocarditis causes a broad spectrum of clinical presentations ranging from sudden cardiac death and heart failure to minor symptoms such as fatigue. Patients with a reduced left ventricular ejection fraction (<50%), low cardiac output syndrome, and ventricular arrhythmias have a 5-year incidence of complications (death, heart transplantation, chronic heart failure, and conduction disorders) of 10.8%, and women are more frequent in this group [44]. The extent and distribution of focal MR imaging abnormalities help with the differential diagnosis and have therapeutic implications. The diagnostic algorithm in suspected myocardial inflammation is based on the Lake Louise criteria. MR imaging with mapping techniques has been shown to be of additional value. Imaging targets are myocardial edema, hyperemia and capillary leakage, necrosis and fibrosis, and the assessment of cardiac function and the pericardium. In autoimmune disorders myocardial involvement usually shortens survival and early identification is important as it allows for timely intervention. MRI is of especially great value in this situation. Acute myocarditis generally leads to an increase in T1 and T2 relaxation times and extracellular volume and causes early (EGE) and late gadolinium enhancement (LGE). For specific autoimmune etiologies, certain MR patterns are described (► Table 4) (► Fig. 6) [45]. Tagging techniques are helpful for the identification of pericardial adhesions.

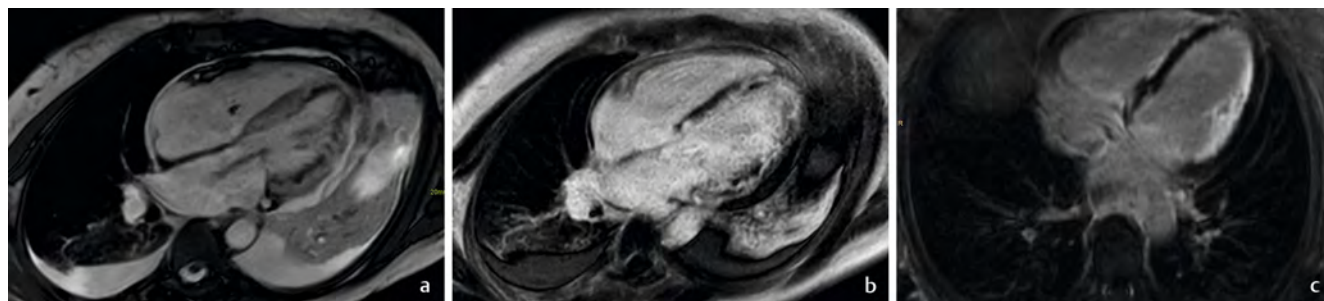
## Anthracycline-induced cardiotoxicity

Anthracycline is a widely used chemotherapeutic agent in breast cancer. Up to 10% of treated women develop irreversible cardiotoxicity. The clinical diagnosis is based on a reduction of left ventricular ejection fraction of more than 10 percentage points, to a value of less than 53% as documented on a baseline and a 2–3-week follow-up scan [46]. MRI is superior to echocardiography in detecting LVEF drops [46]. An acute, early onset chronic and late onset chronic form are defined based on the time of onset – within 2 weeks, 1 year, and years or decades after therapy, respectively. Oxidative stress, mitochondriopathy, and effects on topoisomerase II-beta are potential mechanisms. Clinical presentation ranges from left ventricular systolic heart failure to deflec-

► Table 4 Imaging patterns in autoimmune myocarditis.

Type	Imaging pattern
SLE	LGE rare Pericardial effusion in up to 50% Stress perfusion defects due to MVD in about 30% T2 relaxation time correlates with disease activity; values over 80 ms are described
RA	Myocarditis (high relapse rate within 6 weeks) Myocardial fibrosis CAD Myocardial ischemia (including silent ischemia)
SS	Myocarditis – myocardial T1 relaxation time and ECV cannot be used for myocarditis diagnosis due to the myocardial fibrosis; T2 relaxation times are best for diagnosis; LGE in only 4% Myocardial fibrosis Myocardial ischemia (including silent ischemia) Valvular and pericardial involvement CAD Microvascular dysfunction

SLE: systemic lupus erythematoses, LGE: late gadolinium enhancement, MVD: microvascular dysfunction, RA: rheumatoid arthritis, CAD: coronary artery disease, SS: systemic sclerosis, ECV: extracellular volume.



► Fig. 6 a Myocarditis in autoimmune disease: 43-year-old woman with lupus erythematoses with heart failure and chest pain. SSFP postcontrast in 4-chamber view shows subendocardial hypoperfusion, mitral regurgitation, and pleural effusions. b Same patient as in Fig. 6a. Marked late enhancement in a vascular pattern including microvascular obstruction is identified on the postcontrast T1 PSIR sequence. c Myocarditis in autoimmune disease: Dermatomyositis in a 34-year-old woman presenting with increased troponin and poor general condition. Postcontrast T1 PSIR in 4-chamber view shows marked late enhancement in a non-vascular pattern resembling sarcoidosis.



tion of cardiac enzymes in only mild forms. Pericardial and valvular changes can be observed. In animal models an increase in myocardial T2 relaxation time is one of the earliest signs of anthracycline cardiotoxicity. In humans, a decrease in native T1 values probably due to lipid peroxidation or an increase of intracellular lipids is reported to be an early biomarker [47]. At later stages native T1 values and relative ECV values increase due to myocardial fibrosis and myocardial atrophy [47]. Additional MRI markers in anthracycline cardiotoxicity include left atrial dilation and altered strain indices. LGE is a rare finding and LV mass will be reduced in the long term. MR perfusion imaging may reveal stress and rest ischemia due to early obstructive epicardial disease, MVD, or direct myocardial cardiotoxic damage. Reduced myocardial blood flow and coronary flow reserve can be identified with MRI. Discontinuation of anthracycline treatment at the early edema stage stops progression to chronic heart failure mostly in the form of dilated CMP.

## Pregnancy-related heart disease

Cardiovascular disease during pregnancy includes aggravation of preexisting conditions such as congenital heart disease, hemodynamic maladaptation, and peripartum cardiomyopathy (PPCM) [48]. Preeclampsia, eclampsia, and HELLP syndrome are manifestations of vascular dysfunction during pregnancy and are characterized by hypertension, end-organ injury, edema, and neurological symptoms. Healthy women with clinical signs of heart failure in the last month of pregnancy or up to 5 months after delivery, without preexisting or other identifiable cardiac disease who have LV systolic dysfunction (LVEF < 45%) meet the criteria for peripartum cardiomyopathy (PPCM), a form of idiopathic CMP. In the western world the incidence is estimated to be 1:3000 to 1:4000 live births [49]. Up to 3% of patients die from PPCM and up to 4% will need a cardiac transplant. Normal cardiac function will return in half of patients within 6 months. Those who have permanent cardiac dysfunction have a high risk of mortality and a worsening situation during subsequent pregnancies. There are two pathophysiological mechanisms under debate, an inflammatory pathway with underlying viral myocarditis and abnormal immune response, and a non-inflammatory hypothesis including malnutrition, a genetic familial type, hormonal dysfunction, and changes in the adrenergic system. Imaging findings are varied mostly due the range of underlying etiologies. A fraction of patients show myocardial edema in the acute phase. LGE is rare in the acute phase but may be seen in the follow-up and might be a negative prognostic predictor [50]. Diastolic dysfunction and myocardial fibrosis are frequent findings and focal LGE is a very rare finding in the long-term follow-up of clinically recovered patients.

## Conclusion

Diagnostic and therapeutic algorithms in cardiovascular disease are broadly based on data collected from a predominantly male population. Current physiological and pathophysiological concepts suggest the importance of a sex-specific approach, a conclusion

strongly supported by clinical data. Sex-specific differences are not only sex hormonal in nature but are rooted in the epigenome and encompass a multitude of physiological systems. In fact, cardiovascular disease shows sex-specific characteristics spanning from incidence to clinical presentation, course of disease, and prognosis. Diagnostic algorithms need to be adjusted to sex-specific pretest probabilities and the power of tests and imaging strategies and the interpretation of imaging results should be adjusted for women and men. Novel imaging techniques provide additional tools and are expected to help in the improvement of the sex-specific management of cardiovascular disease.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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