Sex-Specific Aspects in the Pathophysiology and Imaging of Coronary Macro- and Microvascular Disease

Floor Groepenhoff1 · Sophie H. Bots2 · Elise L. Kessler2 · Ariane A. Sickinghe2 · Anouk L. M. Eikendal2 · Tim Leiner3 · Hester M. den Ruijter2

Received: 1 February 2019 / Accepted: 25 July 2019 / Published online: 30 August 2019
© The Author(s) 2019

Abstract
Sex differences in coronary artery disease (CAD) are well established, with women presenting with non-obstructive CAD more often than men do. However, recent evidence has identified coronary microvascular dysfunction as the underlying cause for cardiac complaints, yet sex-specific prevalence numbers are inconclusive. This review summarises known sex-specific aspects in the pathophysiology of both macro- and microvascular dysfunction and identifies currently existing knowledge gaps. In addition, this review describes current diagnostic approaches and whether these should take underlying sex differences into account by, for example, using different techniques or cut-off values for women and men. Future research into both innovation of imaging techniques and perfusion-related sex differences is needed to fill evidence gaps and enable the implementation of the available knowledge in daily clinical practice.

Keywords Coronary artery disease · Microvascular disease · Microvascular dysfunction · Coronary imaging · Sex differences · Fractional flow reserve · Index of microcirculatory resistance · Coronary flow reserve (CFR)

Abbreviations
CAD Coronary artery disease
CAG Coronary angiography
CCTA Cardiac computed tomography angiography
CFR Coronary flow reserve
CMD Coronary microvascular disease
CMR Cardiac magnetic resonance imaging
ECs Endothelial cells
FFR Fractional flow reserve
HFpEF Heart failure with preserved ejection fraction
IMR Index of microcirculatory resistance
MBF(R) Myocardial blood flow (reserve)
MPRI Myocardial perfusion reserve index
PCI Percutaneous coronary intervention
PET Positron emission tomography
SMCs Smooth muscle cells

Introduction
Women suffering from coronary artery disease (CAD), one of the leading causes of death globally, have a worse short- and long-term prognosis than men [1, 2]. They also more often present with clean epicardial arteries (non-obstructive CAD) than men [1], suggesting sex differences are present in the underlying aetiology. The Women’s Ischemia Syndrome Evaluation study found that women with persistent angina complaints and non-obstructive CAD had twice the risk of cardiovascular events compared with women without complaints [3]. Additionally, myocardial perfusion was impaired in approximately half of the women, suggesting that coronary microvascular dysfunction (CMD) plays an important role in the pathophysiology of this condition [4]. Since endothelium-dependent dysfunction can result in decreased perfusion of the
myocardium, research suggests that this may be involved in
the development of CMD [5].

However, CMD remains difficult to diagnose because the
cardiac microvasculature is too small to visualise with con-
ventional imaging techniques. In addition, generalised rec-
ommendations regarding treatment for non-obstructive CAD are
still lacking [6]. The most recent guidelines from the European
Society of Cardiology acknowledge that women with non-
obstructive CAD are a special group in need of additional
research [7]. This review summarises both the known sex
differences in the pathophysiology of (non-)obstructive
CAD and the currently available imaging tools for diagnosis,
while also identifying evidence gaps and providing some fu-
ture perspectives.

**Structural and Functional Alterations in Macrovascular Disease**

Coronary macrovascular disease or obstructive CAD occurs
due to formation and/or rupture of atherosclerotic plaques.
Sex differences in atherosclerosis can be observed at different
levels. At the risk factor level, diabetes and smoking have a
disproportionally large effect on atherosclerosis risk in women
compared with men [8]. Other classical risk factors such as
hypertension and dyslipidaemia affect the risk equally in both
sexes [1].

At the structural level, animal data show that female ro-
dents develop less extensive atherosclerosis under high-fat
conditions than male rodents, possibly due to the effect of
oestrogens [8]. Activation of oestrogen receptors in female
rats suppressed the proliferation of smooth muscle cells
(SMCs), an effect that was not seen in males despite the pres-
ence of oestrogen receptors on SMCs of both sexes [9, 10].
This suggests that oestrogens may limit the degree of structural
alterations in the vasculature in a sex-specific manner. In
addition, women more often present with plaque erosion
while men more often have plaques prone to rupture
[11–13]. An extensive review of the (sex-specific) pathophys-
iology of atherosclerotic plaque formation is beyond the scope
of this review and can be found elsewhere [8, 14].

At the functional level, atherosclerosis-related changes in
the vascular wall may reduce arterial compliance, which can
lead to hypertension [15]. Hypertension is the most prevalent
risk factor for cardiovascular diseases [16] and is more com-
mon in elderly women than men [17]. Women with hyperten-
sion maintain better systolic function than men but exhibit
more stiffening of both the myocardium and the vasculature,
suggesting sex differences underlying mechanisms of pressure
overload [17].

Clinical observations show that women are more likely to
have a normal coronary angiogram (CAG) than men, both
when presenting with chest pain complaints [18] or when
having a confirmed diagnosis of myocardial infarction (MI)
[19]. Data from a sudden coronary death registry showed that
40% of the women who died from CAD did not have any
thrombi while this occurred in only 28% of men [11]. This
apparent paradox between unobstructed epicardial arteries and
poor prognosis most often seen in women may be explained
by the presence of microvascular disease.

**Structural and Functional Alterations in Microvascular Disease**

The coronary microvasculature modulates the vascular tone
through vasoconstriction and vasodilation, which is regulated
by systemic and local factors acting on endothelial cells (ECs)
and SMCs [20]. The dysregulation of this adaptive system due
to structural and functional alterations in the microvasculature
is referred to as CMD [21, 22]. Classical macrovascular dis-
ease risk factors such as smoking, age, and hypertension may
also be associated with impaired microvascular function [23].
Hypertension may disproportionally increase the CMD risk in
women because they have lower microvascular arterial com-
pliance than men [24]. Sex differences in structural and func-
tional alterations in CMD have been reported but require
validation.

At the structural level, inflammation can affect the micro-
vasculature by inducing SMC proliferation and differentiation
of fibroblasts into myofibroblasts [25, 26]. In general, nitric
oxide (NO) is needed to maintain the normal functioning and
structure of the arteries. NO is produced by endothelial NO
synthase (eNOS) in reaction to shear stress of the artery walls,
and a drop in NO levels leads to increased perivascular fibro-
sis and subsequent microvascular stiffening. Such a drop may
occur in situations of pressure overload, when cardiomyocyte
mitochondria produce free reactive oxygen species (ROS) in
response to stress [27, 28]. These free ROS induce endothelial
inflammation, which can cause perivascular fibrosis [29].
Oestrogens promote the production of NO and may therefore
protect women against structural changes in the microvascu-
lature. However, this possible protective effect of oestrogens
is lost with the lack of oestrogens after menopause, possibly
leading to increased perivascular fibrosis and subsequent mi-
crovascular stiffening. Oestrogens also inhibit collagen I and
III deposition through activation of oestrogen receptor (ER) α
[30], while androgens such as testosterone promote the depo-
sition of collagen via increasing TGF-β production [31]. This
may also contribute to increased perivascular fibrosis in wom-
en after menopause.

Capillary dysfunction leads to impaired angiogenesis [32],
a process regulated by several myocardium-derived growth
factors stimulating endothelial cell growth [33–36]. ERs can
act as transcription factors for one of these molecules, vascular
endothelial growth factor (VEGF). Animal data show that
female mice have a better angiogenic capacity following ischaemia than male mice, suggesting that oestrogens help in limiting myocardial damage after reduced blood flow in female animals [37, 38], possibly via the stimulation of NO production.

Microvascular instability and dysfunction will eventually lead to pruning of vessels, called rarefaction. This decreases the myocardial capillary density, leading to reduced perfusion of the heart and possibly myocardial hypoxia. Reduced myocardial perfusion has been shown to be a major contributing factor in heart failure with preserved ejection fraction (HFpEF) in both women and men [24]. The prevalence and pathophysiology of capillary rarefaction in the heart have not yet been firmly established as autopsy studies in HFpEF patients are rare. The contribution of microvascular rarefaction to CMD and possibly HFpEF in both sexes needs further investigation and might provide an interesting target for therapy in this HF subtype [39].

At the functional level, imbalance between vasodilating and vasoconstricting factors can lead to an impaired vessel response upon changes in oxygen demand and subsequent perfusion defects. The oestrogen receptors ER-α and ER-β can induce vasodilation by activating eNOS, which may have a protective effect on cardiac function. Low oestrogen levels initiate sustained renin-angiotensin-aldosterone system (RAAS) activation, which promotes ROS production and further decreases NO availability [40]. The lack of oestrogen after menopause may thereby lead to an increase in microvascular dysregulation possibly deteriorating into CMD. This together with the presence of cardiovascular risk factors could render women more vulnerable to macro- and microvascular dysfunction after menopause.

**Functional Assessment of the Coronary Microcirculation**

While direct visualisation of microvascular abnormalities is still impossible, measurements of the coronary flow enable indirect assessment of microvascular function. Under normal physiological conditions, the coronary microcirculation can induce reactive hyperaemia in response to short or prolonged myocardial ischaemia. In the presence of endothelium-(in)dependent abnormalities, both the reactive hyperaemia response and the subsequent (re)perfusion of the myocardium are suboptimal. Inducing stress can mimic this maximal hyperaemic response for functional assessment of the microcirculation in the clinical setting. The difference in perfusion between healthy and diseased states can be assessed with several invasive and non-invasive imaging techniques and can inform healthcare professionals about the degree of microvascular disease.

**Quantification of Perfusion**

Coronary blood flow can be quantified using several different methods. All quantification methods require the use of either an endothelium-dependent [41, 42] or endothelium-independent [43, 44] vasoactive stimulus to achieve maximal hyperaemia. There is no evidence for sex differences in the effect of these stimuli. However, depending on how coronary perfusion is measured, inherent biological sex differences in coronary blood flow may require sex-specific cut-off values for impaired perfusion. We will discuss three commonly used myocardial perfusion metrics below. A more extensive overview can be found in Table 1.

Fractional flow reserve (FFR) is a surrogate estimate of coronary flow based on coronary pressure used to assess the extent of coronary artery stenosis. It is calculated by dividing the distal coronary artery pressure by the mean aortic pressure after maximal vasodilation. The FFR has no sex-specific cut-off point, with a value of 0.8 or higher indicating normal blood flow in both women and men. The FFR cannot differentiate

| Parameter name (abbreviation) | Method used to calculate perfusion | Imaging modalities using this parameter to quantify perfusion | Sex differences |
|------------------------------|-----------------------------------|-----------------------------------------------------------|----------------|
| Fractional flow reserve (FFR) | $P_d/P_a$ at maximal hyperaemia | CAG | None reported [45–52] |
| Index of microcirculatory resistance (IMR) | $P_d$ absolute coronary flow at maximal hyperaemia | CAG | None reported [45, 48] |
| Coronary flow reserve (CFR) | Hyperaemic coronary flow/basal coronary flow | CAG, PET, echocardiography, CMR | Ratio possibly lower in women [48] |
| Myocardial blood flow (MBF) | Absolute myocardial perfusion in mL/min/g | PET, CMR | Rest and stress MBF higher in women. MBF ratio lower in women [53] |
| Myocardial perfusion reserve index (MPRI) | Myocardial perfusion in stress/myocardial perfusion in rest | CMR | Not yet reported |

CAG coronary angiography, CMR cardiac magnetic resonance imaging, $P_d$ mean proximal coronary artery pressure (mean aortic pressure), PET positron emission tomography, $P_a$ mean distal coronary artery pressure.
between CAD and CMD, so additional testing is required to confirm CMD in case of an abnormal FFR [45, 54].

The index of microcirculatory resistance (IMR) is a measure of microcirculatory resistance at maximal hyperaemia calculated by dividing the distal coronary pressure by the absolute coronary flow. The IMR is unaffected by resting haemodynamic parameters or epicardial stenosis and provides a more direct measurement of the coronary microcirculatory function compared with the other metrics discussed here [46, 47]. An IMR ≥ 23–25 U is indicative of increased microcirculatory resistance in both women and men [46].

Coronary flow reserve (CFR) is an estimate of coronary perfusion. It measures the maximal blood flow achieved in both epicardial and microvascular vessels in response to hyperaemic stimulation and is calculated by dividing the coronary flow at maximal vasodilation by the coronary flow at rest. Women have a higher resting flow but similar hyperaemic flow compared to men, leading to a lower CFR value with the same degree of microvascular dysfunction [48]. As of yet, there is no consensus on the cut-off for CFR to denote impaired myocardial perfusion, but the underlying sex difference in haemodynamics supports research into the use of a different value for men and women.

**Invasive Imaging Methods**

Invasive imaging measures the coronary blood flow velocity at rest and stress during coronary catheterisation using either intra-coronary Doppler flow or thermodilution [49, 55]. Impaired microvascular function measured by Doppler flow was associated with an increased risk of long-term cardiac mortality in patients with ST-elevation myocardial infarction [49] and Doppler-derived CFR correlated better with the non-invasive gold standard positron emission tomography (PET) than thermodilution-derived CFR [56]. However, with thermodilution the CFR and the IMR can be obtained simultaneously [55]. There are no reported differences in effectiveness of these techniques between women and men, but underlying haemodynamic differences must be taken into account when interpreting the results [48].

**Non-invasive Imaging Methods**

There are several non-invasive imaging methods available that differ in their approach and use of radiation. PET is considered the gold standard of non-invasive imaging [57], but exposes patients to ionising radiation. Alternatives are trans-thoracic Doppler echocardiograph (TTDE), cardiac magnetic resonance (CMR) [58], and possibly cardiac computed tomography angiography (CCTA) [59, 60]. These methods are summarised in Table 1.

Data show that measurements obtained by TTDE correlate well with those obtained by invasive Doppler echocardiography [61–63]. CCTA is currently only used for evaluation of calcification and stenosis in the epicardial vessels, but research groups are working on expanding its application to measuring myocardial perfusion and developing computational techniques that can extract flow and pressure data from CCTA images [59, 60]. CMR can detect both perfusion defects and obstructive CAD more accurately than invasive Doppler echocardiography and single-photon emission computed tomography (SPECT), respectively [58, 64]. It thus offers the potential to diagnose both obstructive CAD and CMD in a single examination [65]. There are no reported sex differences for these imaging methods.

**Discussion**

In this review, we summarised currently available evidence on sex differences in the pathophysiology and diagnosis of coronary macro- and microvascular disease. In contrast to obstructive CAD, knowledge about non-obstructive CAD and CMD is still lacking on many levels. At the pathophysiological level, sex differences in structural and functional alterations in CMD have been reported but remain understudied. Meanwhile at the clinical level, consensus on the preferred imaging method and perfusion quantification metric is lacking and the prevalence of CMD remains unclear. In addition, perfusion defects are determined using the same cut-off values for men and women, even though research has shown that sex-specific cut-off values may be more appropriate. This unnecessary extra heterogeneity complicates the identification of true differences between women and men. Clear guideline recommendations on the choice of vasoactive stimulus, imaging medium, and perfusion cut-off values will help to streamline and focus research efforts in this field.

**Future Perspectives for CMD Diagnostics**

To gain more insight into the pathophysiology and treatment of patients with non-obstructive CAD, easily accessible and low risk diagnostics are needed to identify patients with CMD. Both non-invasive imaging techniques and blood-based biomarkers may provide future diagnostics for CMD [66].

High reliability and lack of radiation make CMR a promising non-invasive imaging technique for diagnosis of CMD. It is currently not considered a standard diagnostic tool for CMD due to the limited availability of imaging equipment and the lack of agreement regarding acquisition and post-processing. Research efforts aimed at facilitating the use of CMR in standard care are working on creating perfusion measurements without the use of contrast injection [67], creating a fully automated absolute perfusion measurement [68], and building new MRI coils that will reduce MRI scanning times from an hour to 15 min [69]. These improvements will make
CMR a more feasible and attractive diagnostic option for CMD in the future. Machine learning algorithms that support the imaging specialist in interpreting imaging results can be implemented to improve the accuracy of the diagnosis while reducing the reading time [70]. Machine learning can also be applied to clinical care data. Algorithms built using data from electronic health records are emerging as a tool to help clinicians translate the substantial amount of available data to a diagnosis and appropriate treatment [71]. It is important to stress the use of a sex-specific approach in validating these algorithms, since they are only as unbiased as the data they are based upon. If women are underrepresented in the datasets used to power these models, the algorithm could perform poorly for women. For example, a facial recognition software based on an unbalanced dataset used classifiers that performed better on male faces than female faces [72]. Therefore, proportionate representation of both women and men, but also of ethnic groups, should be ensured before using a dataset to develop healthcare algorithms [73].

Biomarkers can be used to both improve risk stratification for and diagnosis of patients with CAD, possibly reducing the need for imaging in these patients. Several different markers of vascular inflammation, oxidative stress, and some others have been proposed as possible biomarkers for CMD, but have not been established or validated yet [66].

### Treatment Perspectives and Related Diseases

Treatment for obstructive CAD is well established and includes revascularisation via stenting or coronary bypass grafting. Data show that women are less likely to undergo these interventions than men, even when they have been diagnosed with acute coronary syndrome (ACS) [19] and have an equal or even higher risk profile [74]. This sex difference is also apparent in prescribed medication, as women with ACS were less likely to receive β-blockers and statins than men with similar disease severity [75]. Women taking cardiovascular medications are more likely to experience (serious) adverse drug reactions than men [76], which may explain why physicians may choose not to prescribe these drugs for women. However, sex-specific evidence per separate drug class is still too limited [77] to support not prescribing these drugs for women and thereby denying them the advantages of treatment.

Treatment for CMD has been largely empirical due to the lack of knowledge about the pathophysiology and the difficulty of reliably diagnosing the condition. Currently available options include medications already used to treat obstructive CAD and cardiovascular risk factors, such as low-dose aspirin, statins, and β-blockers [78]. Persistent angina symptoms can be reduced by using a device to narrow the coronary sinus [79]. Optimal treatment of CMD is important, as several studies have shown that impaired perfusion of the heart is related to a poor prognosis independent of the imaging modality used [80–82]. Given that the currently prescribed medications have already been in use for other indications, it is likely that the sex differences described for obstructive CAD treatment also hold true for CMD treatment. However, data on this are still lacking due to the novelty of the research field.

CMD can be the precursor of chronic cardiac conditions such as HFpEF [58], a subtype of HF that is more common in women [83]. The prognosis of HFpEF is poor with approximately half of patients dying within 5 years after diagnosis but effective treatments are still lacking [83]. Better understanding and earlier recognition of subclinical conditions such as CMD are therefore crucial to tackle this syndrome early on. Next to improvement of diagnosis of CMD, more research is needed into possible treatments of CMD, the underlying pathophysiology, and possible disease phenotypes that can identify subgroups at higher or lower risk of developing HFpEF [84].

### Conclusion

Sex differences in CAD have been identified at all levels of the disease, but such detailed information is still missing for CMD. While research has suggested the presents of such differences, for example through the effect of sex hormones, many evidence gaps still exist. Currently available imaging techniques enable clinicians to evaluate CMD, but international consensus on the optimal procedure is missing and underlying sex differences in baseline perfusion are not always taken into account. Innovative strategies to improve current diagnostic techniques such as the incorporation of machine learning approaches will hopefully enable clinicians to screen for CMD in standard care. However, these approaches must consider sex differences in their development to avoid the introduction of biases in the end product.

### Sources of Funding

This study was funded by the Dutch Heart Foundation (2013T084, Queen of Hearts Program) and by ZonMw grant (849100003, Reviews en Kennissynthesen Gender en Gezondheid).

### Compliance with Ethical Standards

#### Conflict of Interest

The authors have no conflicts of interests to declare.

#### Ethical Approval

No human studies or animal studies were carried out by the authors for this article.

#### Open Access

This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.
References

1. Parvand, M., Rayner-Hartley, E., & Sedlak, T. (2018). Recent developments in sex-related differences in presentation, prognosis, and management of coronary artery disease. Canadian Journal of Cardiology, 34(4), 390–399. https://doi.org/10.1016/j.cjca.2018.01.007.

2. Izadnegahdar, M., Mackay, M., Lee, M. K., Sedlak, T. L., Gao, M., Bairey Merz, C. N., et al. (2016). Sex and ethnic differences in outcomes of acute coronary syndrome and stable angina patients with obstructive coronary disease. Circulation: Cardiovascular Quality and Outcomes, 9(2 suppl 1), S26–S35.

3. Gulati, M., Cooper-DeHoff, R. M., McClure, C., Johnson, B. D., Reichek, N., et al. (2001). Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. American Heart Journal, 141(5), 735–741.

4. Bairey Merz, C. N., Pepine, C. J., Walsh, M. N., Fleg, J. L., Camici, P. G., Chilian, W. M., et al. (2017). Ischemia and no obstructive coronary artery disease (INOCA) developing evidence-based therapies and research agenda for the next decade. Circulation, 135(11), 1075–1092.

5. Paul, T. K., Sivanesan, K., & Schulman-Marcus, J. (2017). Sex differences in nonobstructive coronary artery disease: recent insights and substantial knowledge gaps. Trends in Cardiovascular Medicine, 27(3), 173–179. https://doi.org/10.1016/j.tcm.2016.08.002.

6. Montalescot, G., Sechtem, U., Achenbach, S., Arden, C., Budaj, A., et al. (2013). 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. European Heart Journal, 34(38), 2949–3003. https://doi.org/10.1093/eurheartj/eht296.

7. Mathur, P., Ostadal, B., Romeo, F., & Mehta, J. L. (2015). Gender-related differences in atherosclerosis. Cardiovascular Drugs and Therapy, 29(4), 319–327. https://doi.org/10.1007/s10557-015-6596-3.

8. Szego, C. M., & Davis, J. S. (1967). Adenosine 3’,5’-monophosphate in rat uterus: acute elevation by estrogen. Proceedings of the National Academy of Sciences, 58(4), 1711–1718.

9. Hogg, M. E., Vavra, A. K., Banerjee, M. N., Martinez, J., Jiang, Q., Keesler, L. K., et al. (2012). The role of estrogen receptor α and β in regulating vascular smooth muscle cell proliferation is based on Sex. Journal of Surgical Research, 173(1), e1–e10.

10. Yahagi, K., Davis, H. R., Arbustini, E., & Virmani, R. (2015). Sex differences in coronary artery disease: pathological observations. Atherosclerosis, 239(1), 260–267. https://doi.org/10.1016/j.atherosclerosis.2015.01.017.

11. Kataoka, Y., Puri, R., Hammadah, M., Duggal, B., Uno, K., Kapadia, S. R., et al. (2016). Sex differences in nonculprit coronary plaque microstructures on frequency-domain optical coherence tomography in acute coronary syndromes and stable coronary artery disease. Circulation: Cardiovascular Imaging, 9(8), e004506. https://doi.org/10.1161/CIRCMAGING.116.004506.

12. Hellings, W. E., Pasterkamp, G., Verhoeven, B. A. N., De Kleijn, D. P. V., De Vries, J.-P. P. M., Seldenrijk, K. A., et al. (2007). Gender-associated differences in plaque phenotype of patients undergoing carotid endarterectomy. Journal of Vascular Surgery, 45(2), 289–296. https://doi.org/10.1016/j.jvs.2006.09.051.

13. Libby, P., Ridker, P. M., & Hansson, G. K. (2011). Progress and challenges in translating the biology of atherosclerosis. Nature, 473, 317. https://doi.org/10.1038/nature10146.

14. Hansen, L., & Taylor, W. R. (2016). Is increased arterial stiffness a cause or consequence of atherosclerosis? Atherosclerosis, 249, 226–227.

15. Fisher, N. D. L., & Curfman, G. (2018). Hypertension—a public health challenge of global proportions—hyper tension—a public health challenge of global proportions editorial. Jama, 320(17), 1757–1759. https://doi.org/10.1001/jama.2018.16760.

16. Regitz-Zagrosek, V., & Kararigas, G. (2017). Mechanistic pathways of sex differences in cardiovascular disease. Physiological Reviews, 97(1), 1–37. https://doi.org/10.1152/physrev.00021.2015.

17. Sullivan, A. K., Holdnight, D. R., Wright, C. A., Sparrow, J. L., Cunningham, D., & Fox, K. M. (1994). Chest pain in women: clinical, investigative, and prognostic features. BMJ, 308(6933), 883–886.

18. Hvelp Lund, A., Galatius, S., Madsen, M., Rasmussen, J. N., Rasmussen, S., Madsen, J. K., et al. (2010). Women with acute coronary syndrome are less invasively examined and subsequently less treated than men. European Heart Journal, 31(6), 684–690. https://doi.org/10.1093/eurheartj/ehp493.

19. Shaw, J., & Anderson, T. (2016). Coronary endothelial dysfunction in non-obstructive coronary artery disease: risk, pathogenesis, diagnosis and therapy. Vascular Medicine, 21(2), 146–155.

20. Camici, P. G., D’Amati, G., & Rimoldi, O. (2015). Coronary microvascular dysfunction: mechanisms and functional assessment. [Review]. Nature Reviews Cardiology, 12(1), 48–62. https://doi.org/10.1038/nrcardio.2014.160.

21. Murthy, V. L., Naya, M., Taqueti, V. R., Foster, C. R., Gaber, M., Hainer, J., et al. (2014). Effects of sex on coronary microvascular dysfunction and cardiac outcomes. Circulation, 129(24), 2518–2527. https://doi.org/10.1161/CIRCULATIONAHA.113.008507.

22. Mygind, N. D., Michelsen, M. M., Pena, A., Frestad, D., Dose, N., Aziz, A., et al. (2016). Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study. Journal of the American Heart Association, 5(3), e003064.

23. Coutinho, T., Mielniczuk, L. M., Sriravatharajah, K., Wells, G. A., & Beanlands, R. S. (2018). Coronary artery microvascular dysfunction: role of sex and arterial load. International Journal of Cardiology, 270, 42–47.

24. Baum, J., & Duffy, H. S. (2011). Fibroblasts and myofibroblasts: what are we talking about? Journal of Cardiovascular Pharmacology, 57(4), 376.

25. Suwanabol, P. A., Seedial, S. M., Shi, X., Zhang, F., Yamnouchi, D., Roenneburg, D., et al. (2012). Transforming growth factor-β increases vascular smooth muscle cell proliferation through the Smad3 and extracellular signal-regulated kinase mitogen-activated protein kinases pathways. Journal of Vascular Surgery, 56(2), 446–454.e441.

26. Sansone, R., Stanske, B., Keymel, S., Schuler, D., Horn, P., Saeed, A., et al. (2015). Macroversal and microversal function after implantation of left ventricular assist devices in end-stage heart failure: role of microparticles. The Journal of Heart and Lung Transplantation, 34(7), 921–932.

27. Schwarzer, M., Osterholt, M., Lunkenbein, A., Schrepper, A., Amorim, P., & Doenst, T. (2014). Mitochondrial reactive oxygen species production and respiratory complex activity in rats with pressure overload-induced heart failure. The Journal of Physiology, 592(17), 3767–3782.

28. Dai, Z., Aoki, T., Fukushima, Y., & Shimokawa, H. (2012). Coronary perivascular fibrosis is associated with impairment of
coronary blood flow in patients with non-ischemic heart failure. Journal of Cardiology, 60(5), 416–421.

30. Dworatzek, E., Mahmoodzadeh, S., Schrieve, C., Kusumoto, K., Kramer, L., Santos, G., et al. (2018). Sex-specific regulation of collagen I and III expression by 17β-estradiol in cardiac fibroblasts: role of estrogen receptors. Cardiovascular Research, 115(2), 315–327.

31. Kong, P., Christia, P., & Frangogiannis, N. G. (2014). The pathogenesis of cardiac fibrosis. Cellular and Molecular Life Sciences, 71(4), 549–574.

32. Andrae, J., Gallini, R., & Betsholtz, C. (2008). Role of platelet-derived growth factors in physiology and medicine. Genes & Development, 22(10), 1276–1312.

33. Chen, J.-X., Zeng, H., Reese, J., Aschner, J. L., & Meyrick, B. (2012). Overexpression of angiopoietin-2 impairs myocardial angiogenesis and exacerbates cardiac fibrosis in the diabetic db/db mouse model. American Journal of Physiology-Heart and Circulatory Physiology, 302(4), H1003.

34. Dobaczewski, M., Chen, W., & Frangogiannis, N. G. (2011). Transforming growth factor (TGF)-β signaling in cardiac remodeling. Journal of Molecular and Cellular Cardiology, 51(4), 600–606.

35. Jeansson, M., Gawlik, A., Anderson, G., Li, C., Kerjaschki, D., Henkelman, M., et al. (2011). Angiopoietin-1 is essential in mouse vasculature during development and in response to injury. The Journal of Clinical Investigation, 121(6), 2278–2289.

36. Mahmoodzadeh, S., Leber, J., Zhang, X., Jaisser, F., Messaoudi, S., Morano, I., et al. (2014). Cardiomyocyte-specific estrogen receptor alpha increases angiogenesis, lymphangiogenesis and reduces fibrosis in the female mouse heart post-myocardial infarction. Journal of Cell Science & Therapy, 5(1), 153.

37. Buteau-Lozano, H., Ancelin, M., Lirdeux, B., Milanini, J., & Perrot-Applanat, M. (2002). Transcriptional regulation of vascular endothelial growth factor by estradiol and tamoxifen in breast cancer cells: a complex interplay between estrogen receptors α and β. Cancer Research, 62(17), 4977–4984.

38. Mohammed, S. F., Hussain, S., Mirzoyev, S. A., Edwards, W. D., Malezewski, J. J., & Redfield, M. M. (2015). Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation, 131(6), 550–559.

39. Beale, A. L., Meyer, P., Marwick, T. H., Lam, C. S., & Kaye, D. M. (2018). Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. Circulation, 138(2), 198–205.

40. Huang, H. J., Chung, W. B., Park, J. H., Oh, S. S., Chung, J. W., Choi, Y. S., et al. (2010). Estimation of coronary flow velocity reserve using transthoracic Doppler echocardiography and cold pressor test might be useful for detecting of patients with variant angina. Echocardiography, 27(4), 435–441.

41. Quyyumi, A. A., Dakak, N., Mulcahy, D., Andrews, N. P., Husain, S., Panza, J. A., et al. (1997). Nitric oxide activity in the atherosclerotic human coronary circulation. Journal of the American College of Cardiology, 29(2), 308–317.

42. Aji Jarioudi, W., & Iskandrian, A. E. (2009). Regadenoson: a new myocardial stress agent. Journal of the American College of Cardiology, 54(13), 1123–1130.

43. Youn, H.-J., & Foster, E. (2004). Demonstration of coronary artery flow using transthoracic Doppler echocardiography. Journal of the American Society of Echocardiography, 17(2), 178–185.

44. Kerm, M. J., Lerman, A., Bech, J.-W., Brayne, B. D., Eckhout, E., Fearon, W. F., et al. (2006). Physiological assessment of coronary artery disease in the cardiac catheterization laboratory. Circulation, 114(12), 1321–1341. https://doi.org/10.1161/CIRCULATIONAHA.106.177276.
