

# Renal artery fibromuscular dysplasia and its effect on the kidney

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# Renal artery fibromuscular dysplasia and its effect on the kidney

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## Abstract

Fibromuscular dysplasia is a heterogeneous group of systemic, noninflammatory, and nonatherosclerotic diseases of the vascular wall. It is the second-most common abnormality of the renal artery. Although hypertension is the most common presenting symptom, other symptoms, such as pulsatile tinnitus, stroke, chest pain, or abdominal discomfort, may result from other affected vascular beds. Revascularization of the renal artery appears to be effective at lowering blood pressure in many patients with renal artery fibromuscular dysplasia. For a long time, the intrarenal pathophysiological changes and mechanisms leading to hypertension had hardly been studied in patients with renal artery fibromuscular dysplasia. Recent data, however, has provided more insight into the effects of renal artery fibromuscular dysplasia on the intrarenal microvasculature and the intra-renal renin-angiotensin system in these patients. Moreover, these data have changed our view of the pathophysiological mechanisms leading to hypertension in patients with renal artery fibromuscular dysplasia. In this review, we will discuss recent clinical and scientific developments regarding renal artery fibromuscular dysplasia with an emphasis on its effects on the kidney.

## Introduction

Fibromuscular dysplasia (FMD) is a heterogeneous group of non-inflammatory, non-atherosclerotic diseases of the vascular wall that lead to dissection, aneurysm, or stenosis of medium-sized arteries [1, 2]. After atherosclerotic renal artery stenosis, FMD is the second-most common abnormality of the renal artery [1, 2]. Although FMD is often considered to be a rare disease, several screening studies among potential kidney donors found a prevalence of 2.3–6.6% in the general population [3–8], suggesting that FMD is frequently overlooked in clinical practice. However, over the last few years, FMD has drawn increasing attention by clinicians and researchers, leading to a growing number of diagnoses [9] and the start of several research initiatives [10, 11]. In this review, we will discuss some

recent clinical and scientific developments regarding renal artery FMD with an emphasis on its effects on the kidney.

## Epidemiology

Renal artery FMD is presumably not as rare as often assumed: the estimated prevalence of renal artery FMD among potential kidney donors is 2.3–6.6% [3–8]. Furthermore, the assumption that renal artery FMD is a disease of young women requires revision: most patients are diagnosed in their fifth or sixth decade of life [4, 9, 11, 12], and FMD diagnoses have been made in octogenarians as well [11, 13]. Moreover, even though the US FMD Registry reported that 91% of FMD patients are female [11], the number of male patients in other large studies varies ranges from 19 to 23% [9, 12, 14, 15].

Over the past years, it has become more and more clear that FMD is not a local vascular abnormality of the renal arteries, but, in fact, a systemic vascular disease that can result in a variety of vascular problems. First, FMD has been described in almost every medium-sized human artery, including cervical, visceral, iliac, and upper limb arteries [16–26]. Several patient registries have already suggested that FMD is present in multiple vascular beds in at least 30% of patients but that number was considered to be an underestimate as diagnostic imaging was performed in case of symptoms only [10, 11]. Indeed, the recently

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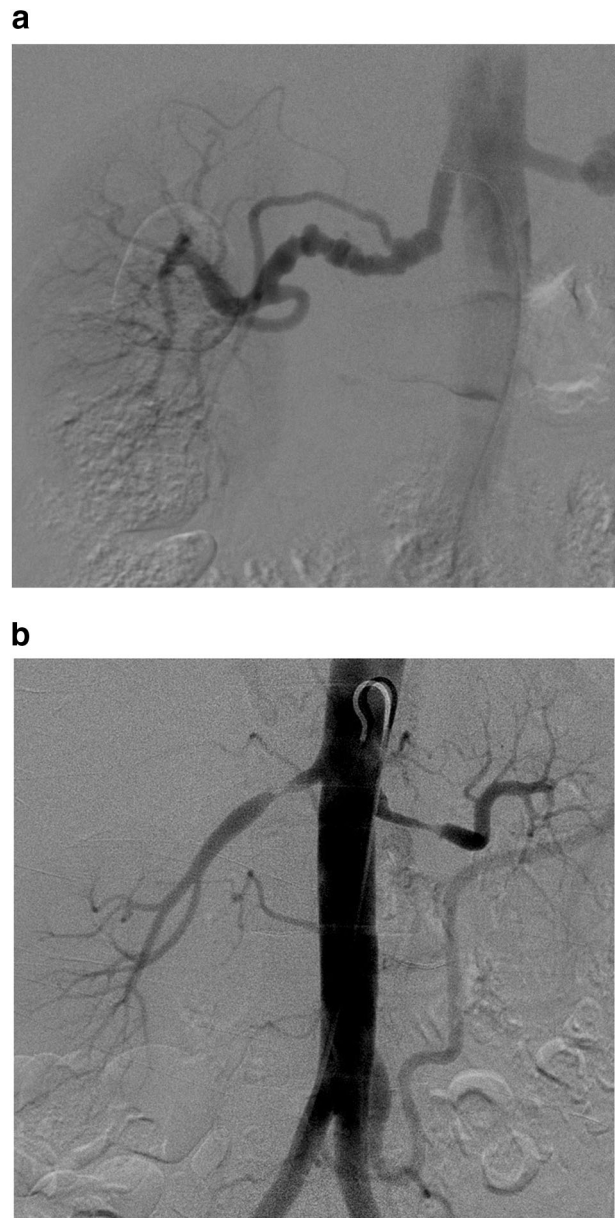
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published ARCADIA study [27] with systematic computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of other vascular beds in all patients with symptomatic renal or cervical artery FMD demonstrated that multisite involvement is higher than expected: 48.0% of patients have dysplastic stenosis in at least one other vascular bed. Moreover, if aneurysms and dissections are also counted, multisite involvement was present in 66.1% of cases. The latter finding is supported by previous patient registries, demonstrating the high prevalence of arterial dissections (25.7%) and aneurysms (overall 21.7%, intracranial aneurysms 4.6–12.9%) [28–31] in other vascular beds. It has also become clear that the coronary arteries can be involved in FMD, and they most often present as a spontaneous coronary artery dissection or coronary tortuosity [32, 33]. Systematic MRA or CTA analyses of other vascular beds revealed that 50–86% of patients with spontaneous coronary artery dissection have FMD in at least one extracoronary artery [34–38]. Furthermore, thickness and distensibility of the radial and carotid artery are increased in patients with FMD [39]. These data strongly suggest that FMD is a systemic vasculopathy that can result in a variety of vascular problems. While recent studies have demonstrated several associations with genetic, hormonal, and environmental factors [40–45], the cause of these vascular abnormalities is still unknown.

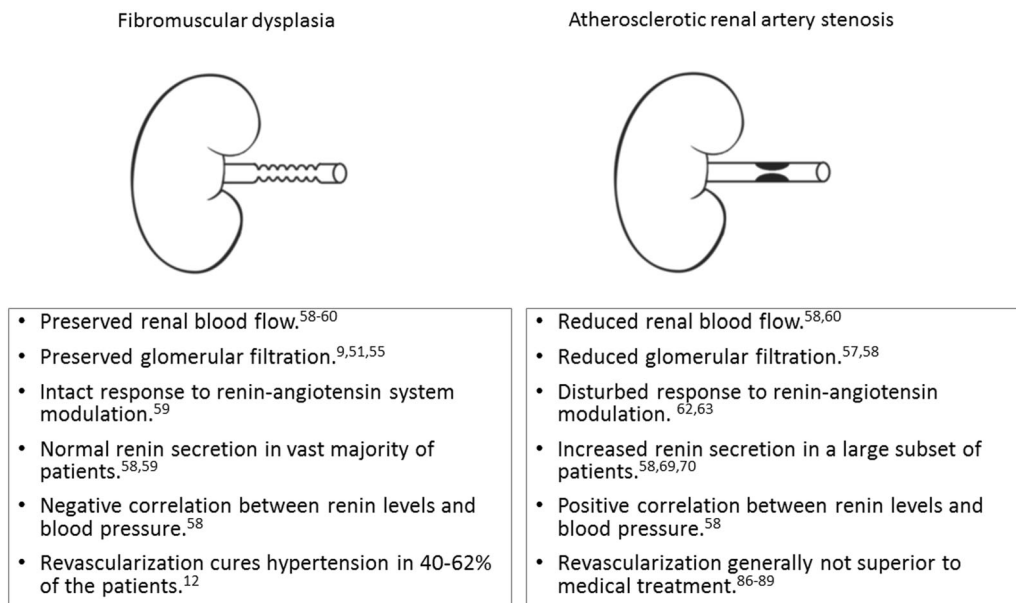
### Classification and histopathology

In the past, various histological classification systems have been proposed, but for clinical use, an angiographic classification system has been adopted to differentiate between the different subtypes of FMD [2, 15]. Multifocal FMD is the most common type in adults and is defined as the presence of at least two stenoses in a vessel segment, typically presenting with a string-of-beads appearance (Fig. 1a). Histologically, the medial layer of the vessel wall is affected in these patients [46]. Deposition of disorganized collagen in the zones of degenerating elastic fibrils leads to the formation of fibromuscular ridges and webs. Alternating areas of thick and thin medial fibroplasia result in the typical string-of-beads appearance [47]. Furthermore, weakening of the vascular wall occurs, making it more vulnerable to dissection, tortuosity, kinking, and aneurysm formation [45, 48]. Unifocal (also known as focal) FMD can present as either a solitary (<1 cm in length) or tubular stenosis (>1 cm in length) [15] (Fig. 1b) and is caused by intimal or adventitial fibroplasia, respectively [46, 49]. Several differences in clinical characteristics between focal and multifocal renal artery FMD have been demonstrated: hypertensive patients with unifocal FMD are more often male (31% in unifocal vs. 17% in multifocal FMD) and are



**Fig. 1** **a** Digital subtraction angiography of a 58-year-old female showing multifocal FMD in the right renal artery (with a typical string-of-beads pattern). She has had hypertension since she was 28 years old and underwent analysis because of a recent myocardial infarction due to spontaneous coronary artery dissection. **b** Digital subtraction angiography of a 43-year-old female showing unifocal FMD in both renal arteries. She was admitted for hypertensive emergency with a blood pressure of up to 230/110 mmHg with grade III hypertensive retinopathy and renal failure (eGFR 29 ml/min/1.73 m<sup>2</sup>)

generally younger at the onset of hypertension (26 vs. 40 years) and time of diagnosis (30 vs. 49 years) [15]. Given these clinical, angiographic, and histopathological differences, it appears plausible that multifocal and unifocal FMD are in fact two different diseases [15, 50] with different effects on the kidney.



**Fig. 2** Summary of the different effects on the kidney and blood pressure by fibromuscular dysplasia and atherosclerotic renal artery stenosis. Some caution is required about the efficacy of revascularization in fibromuscular dysplasia as it has only been studied in (non-

randomized) observational studies, whereas the statement on the efficacy of revascularization in atherosclerotic renal artery stenosis is based on randomized controlled trials. References refer to the references in the main text

## Clinical presentation

The most common presenting symptom of renal artery FMD is hypertension, which was present in 66.6% of the patients in the US FMD Registry [51]. Interestingly, among ‘coincidentally’ diagnosed renal artery FMD in normotensive potential kidney donors, 26–29% developed hypertension within 4–7.5 years after diagnosis [6, 8]. Abdominal pain (17.2%), bruits (10.8%) [51], and (occasionally) renal infarction [52–55] are other presenting symptoms. However, as FMD is a systemic vascular disease, the first symptoms are often not directly related to the renal artery but rather are caused by FMD localizations in other vascular beds, such as pulsatile tinnitus (33.4%), neck pain (27.2%), or stroke/transient ischemic attack (17.5%) in the case of cervical FMD [51], chest pain due to FMD-related coronary artery abnormalities [32, 33], or abdominal complaints in the case of visceral involvement.

## Renal artery FMD and its effects on the kidney

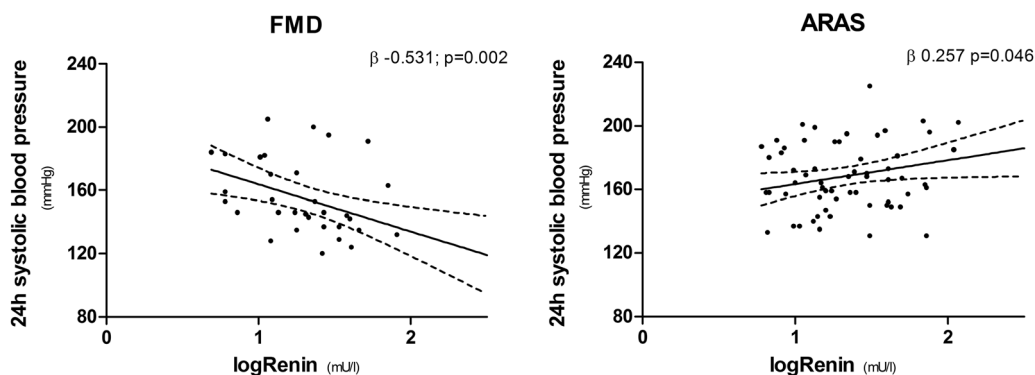
Pathophysiological changes in the kidneys of patients with FMD have hardly been studied. Animal models are not available yet. Therefore, our view of the effects of FMD on the kidney is predominantly based on experiments in patients with atherosclerotic renal artery stenosis [56] and animal models with renal artery clipping [57]. However, recent data from patients with renal artery FMD have provided more

insights into the effects of renal artery FMD on the intrarenal microvasculature, intrarenal renin–angiotensin system, and pathophysiological mechanisms leading to hypertension in these patients.

### Intrarenal microvasculature

The intrarenal microvasculature appears to be relatively preserved in kidneys with multifocal FMD. In patients with multifocal FMD of the renal artery, renal blood flow is significantly higher than in patients with atherosclerotic renal artery stenosis and comparable to that in matched patients with essential hypertension (without renovascular abnormalities) [58–60]. Moreover, in patients with unilateral FMD, renal blood flow is comparable between the affected and unaffected kidney [58, 59]. This suggests that the presence of a string-of-beads does not seriously affect local renal perfusion.

Overall, renal function is also relatively normal in kidneys with multifocal FMD. In a French cohort of 334 patients with renal artery FMD, the mean estimated glomerular filtration rate (eGFR using the Cockcroft–Gault formula) was 88 ml/min/1.73 m<sup>2</sup>, and only 30 patients (8.9%) had an eGFR below 60 ml/min/1.73 m<sup>2</sup> [9]. In the US FMD Registry, only 2.8% out of 615 patients had renal insufficiency upon diagnosis [51]. Moreover, we demonstrated (by side-selective determination of creatinine clearance) that there are no differences in the glomerular filtration rate between the affected and unaffected kidney in patients with unilateral FMD [59], indicating that the



**Fig. 3** Correlation between systolic blood pressure (24-h ambulatory blood pressure measurement) and renin level for patients with renal artery fibromuscular dysplasia (FMD, left panel) and patients with

atherosclerotic renal artery stenosis (right panel) prior to revascularization and off antihypertensive drugs. Figure adapted from Van Twist et al. [54]

presence of a string-of-beads does not substantially alter glomerular filtration.

Furthermore, the intrarenal renin-angiotensin system and the ability to respond to vasoactive stimuli appears to be preserved in kidneys with FMD. Intrarenal blockade of the vasoconstrictory Ang II/AT<sub>1</sub>R-axis (angiotensin II/angiotensin II type-1 receptor axis) by intrarenal infusion of AT<sub>1</sub>R-blocker eprosartan results in vasodilation, whereas intrarenal blockade of the vasodilatory (angiotensin-(1–7) / Mas receptor) axis by L-NMMA (blocking the final common pathway of this axis) [61] results in vasoconstriction [59]. This finding indicates that both axes play a role in the regulation of intrarenal hemodynamics in kidneys with FMD. Moreover, the stimulation of these axes with either angiotensin II or angiotensin-(1–7) resulted in a vasoconstrictory or vasodilatory effect, respectively, with a magnitude similar to that in patients without renal artery abnormalities [59]. This result indicates that neither of these axes acts on its full strength as the infusion of more angiotensin II or angiotensin-(1–7) still results in a hemodynamic effect. It also suggests that microvascular and endothelial function are relatively intact in kidneys with FMD as these functions are a prerequisite to exerting a hemodynamic response to vasoactive stimuli. These findings are in strong contrast to those in kidneys with atherosclerotic renal artery stenosis, where the intrarenal renin-angiotensin system and the ability of the microvasculature to respond to vasoactive stimuli are clearly disturbed given the almost absent effects of angiotensin-(1–7) and L-NMMA infusion [62, 63].

In summary, preserved renal blood flow, glomerular filtration, and the ability to respond to modulation of the renin-angiotensin system all indicate that intrarenal microvascular function is more or less intact in kidneys with multifocal FMD. This finding is in sharp contrast to that of kidneys with atherosclerotic renal artery stenosis (Fig. 2). Possibly, the lack of longstanding atherosclerotic burden (as

in atherosclerotic renal artery stenosis [64, 65]) prevents tubulointerstitial atrophy and glomerulosclerosis [66–68]. However, we cannot rule out that the string-of-beads itself causes other hemodynamic changes (such as changes in local arterial pressure, wall stress, or pulse wave transmission) that have a protective effect on the intrarenal microvasculature.

### Mechanisms leading to hypertension

Until recently, it was assumed that renovascular FMD causes hypertension due to a decrease in renal blood flow, resulting in increased renin secretion, which in turn increases blood pressure (similar to experiments in animal models of renovascular hypertension and a subset of patients with renal artery stenosis caused by atherosclerosis) [2, 56]. However, several data argue against this prevailing concept of renovascular hypertension in patients with FMD.

First and as discussed above, it was demonstrated that renal blood flow is not reduced in kidneys with multifocal FMD [58–60]. Second, renin secretion and renin-angiotensin system activity are relatively normal in kidneys with multifocal FMD. In a systematic analyses of 64 patients with multifocal FMD of the renal artery (off antihypertensive drugs and prior to balloon angioplasty), we found that systemic renin levels were within the normal range in all 64 patients and that renin secretion was comparable to that in patients with essential hypertension [58, 59]. Moreover, in patients with unilateral FMD, renin secretion in the affected kidney is comparable to that in the non-affected contralateral kidney. This finding is in contrast to that of patients with atherosclerotic renal artery stenosis in whom renin secretion is significantly higher and in whom lateralization in renin secretion is observed in a large patient subset [58, 69, 70]. These data suggest that the presence of a string-of-beads itself (generally) does not lead to an increase in renin secretion. In renovascular hypertension due to

unifocal FMD, this observation is still being investigated, but preliminary data suggest that renal blood flow is reduced, resulting in more pronounced renin secretion than that found in multifocal FMD [71]. Third, several studies have demonstrated that revascularization can reduce blood pressure in patients with FMD without increased renin secretion, with no differences in renin secretion between patients who had a decrease in blood pressure and those who did not [59, 70, 72]. Fourth, whereas there is a direct relation (in cross-sectional data) between renin levels and blood pressure in patients with atherosclerotic renal artery stenosis, the association between these parameters appears to be inverse in patients with FMD: the higher the blood pressure, the lower the renin levels (Fig. 3) [58], or vice versa: the lower the blood pressure, the higher the renin levels, which is similar to the physiological response in healthy individuals [73].

However, some caution is required as the above-mentioned findings have not been replicated yet, and all these findings are at odds with the generally accepted view that multifocal FMD induces hypertension via decreased renal blood flow and increased renin secretion. In contrast to kidneys with atherosclerotic renal artery stenosis in whom renovascular resistance is so high that ischemic nephrons secrete excessive amounts of renin, it appears that central blood pressure can still be transmitted to the juxtaglomerular apparatus in kidneys with multifocal FMD, thus preventing an increase in renin secretion. Although increased renin secretion has been reported in some patients with multifocal FMD [74], this finding appears to be the exception rather than the rule.

The question remains why renin secretion was not increased in the abovementioned studies on multifocal FMD. An explanation could be that renin-secretion is only increased in the early phase of the disease: long-lasting renovascular hypertension would result in intrarenal parenchymal damage, leading to renal hypertension (secondary to parenchymal damage) with the normalization of renin secretion again in the long term. However, as intrarenal microvascular function is relatively preserved in kidneys with FMD and parenchymal damage would not be reversible by revascularization (which one would expect given the fairly good results of balloon angioplasty), this appears to be unlikely. Moreover, one would have expected at least some increase or lateralization in renin secretion in some patients (at least in patients in the early stage) but that is not the case either [58, 59]. Furthermore, as renovascular multifocal FMD is also observed in patients without hypertension [4], one could argue that FMD patients without increased renin secretion have in fact essential hypertension. In these patients, the string-of-beads would only be a bystander that is not contributing to hypertension. Unfortunately, it is not yet possible to

differentiate between ‘true’ renovascular hypertension and essential hypertension with FMD as ‘an innocent bystander’. Measurement of the trans-stenotic pressure gradient has been suggested as a possible tool [2, 10], but data on its value in FMD are still restricted to some case reports [75, 76]. Therefore, it is regrettable that trans-stenotic pressure gradients were not routinely measured in the abovementioned mechanistic studies either [58, 59]. However, as the majority of patients with multifocal FMD in these studies had a blood pressure response to balloon angioplasty (48–51% one year after balloon angioplasty, according to pre-specified criteria) [58, 59], it is likely that the string-of-beads contributed to hypertension in many of these patients. Nevertheless, renin secretion was within normal range in all patients in that cohort. Naturally, such observational data on treatment efficacy could be biased by a variety of other factors (e.g., decreasing white-coat effect, regression to the mean, and improved adherence to drug treatment after revascularization), but it is unlikely that all these patients only had essential hypertension with the renovascular string-of-beads being nothing more than an innocent bystander.

Therefore, it appears that mechanisms other than increased renin secretion have to be involved in renovascular hypertension due to multifocal FMD. Without further research, we can only hypothesize about such alternative mechanisms. Other hemodynamic changes aside from reduced blood flow (such as local arterial pressure, turbulence of blood flow, wall stress, and pulse wave transmission) could be involved, but apparently, these changes do not result in increased renin secretion. However, such hemodynamic changes could lead to the activation of other pathways, such as the release of other paracrine stimuli, reactive oxygen species, or activation of the sympathetic nervous system. Future (prospective) studies should focus on changes before and after balloon angioplasty, particularly on other alterations in intrarenal hemodynamics (aside from perfusion alone), and on changes in other signaling pathways involved in hypertension, such as the sympathetic nervous system, reactive oxygen species, and various auto- and paracrine signaling systems, besides the renin–angiotensin system.

## Clinical perspective

### Diagnostic studies

Currently, the diagnosis of renal artery FMD is made based on imaging studies showing a non-atherosclerotic stenosis in the absence of syndromal or inflammatory disease [1, 2]. The radiographic presentation of multifocal FMD is quite typical with its string-of-beads appearance

but is sometimes confused with vasospasms, resulting in typical standing waves that are transient and more regular and symmetrical than FMD [77]. Diagnosing unifocal FMD is often more challenging, as other diseases have similar radiographic presentations, especially atherosclerosis. Hence, the diagnosis can often only be made in younger patients (<40 years) [1] in the absence of multiple risk factors for atherosclerosis and vascular wall calcifications.

The gold standard for diagnosing renovascular FMD is still catheter-based digital subtraction angiography (DSA) [1, 2], optionally accompanied by intravascular ultrasound or optical coherence tomography to obtain a more detailed view in case of doubt regarding the severity of the stenosis or to evaluate the results of balloon angioplasty [78, 79] as the degree of stenosis in multifocal FMD cannot be obtained from the angiographical image alone. Selective catheterization of both renal arteries is required, as FMD lesions are often only found in the distal two-thirds of the renal artery and could easily be missed on aortic angiography.

Duplex ultrasound has been proposed as a non-invasive alternative for DSA, but this technique is highly operator-dependent and its negative predictive value is probably low, especially for more distal lesions [1, 10]. CTA and MRA could be better alternatives [1], but their diagnostic values are reduced as the spatial resolution of these imaging modalities is less than that of DSA. This difference was clearly demonstrated by two prospective studies (i.e., all patients underwent DSA, irrespective of the results of CTA or MRA): in an older study, sensitivity was only 28% for CTA and 22% for MRA [80], whereas a more recent study showed that MRA missed all cases of FMD that were detected with DSA [81]. Two retrospective studies suggested that the sensitivity of CTA and MRA is 100% compared to DSA [82, 83], but this finding could be biased as patients with negative CTA or MRA were not referred for DSA. Perhaps sensitivity has been improved with new CTA or MRA scanners with higher spatial resolution or increased use of reformatted images (affecting the assessment in up to 56% of the patients) [84] but that finding has to be evaluated in future trials. As we have several examples of patients who were diagnosed by DSA despite previous (false) negative CTA or MRA (especially multifocal FMD located distally in the renal artery), we recommend caution with ruling out FMD by CTA or MRA in cases of high clinical suspicion.

Systemic renin levels should not be used to screen for renovascular FMD as these levels are normal in the vast majority of patients with multifocal FMD [59]. Although elevated renin levels occasionally lead toward the diagnosis of FMD [74], this situation is the exception rather than the rule.

## Management of renal artery FMD

In contrast to atherosclerotic renal artery stenosis [85–87], revascularization appears to be effective at lowering blood pressure in many patients with renal artery FMD. Some caution is required as randomized controlled trials on revascularization in FMD are lacking and one cannot exclude that observational studies are biased by other factors, such as decreasing white-coat effect, regression to the mean, or improved adherence to drug treatment after revascularization. Until a double blind, sham-controlled trial is available, we are restricted to observational studies. A large meta-analysis of such observational studies showed that hypertension was cured by balloon angioplasty in 40–52% of the cases and by surgery in 53–62% of the cases [12]. Moreover, in patients in whom cure cannot be achieved, improvements in blood pressure [88–90], renal function (6–8 ml/min/1.73 m<sup>2</sup> on average) [91, 92], and the required number of antihypertensive drugs [93, 94] have been reported. The difference in response to revascularization between FMD and atherosclerotic renal artery stenosis could be explained by the fact that microvascular function is relatively preserved in kidneys with FMD: the qualitatively good kidney tissue distal to the string-of-beads would be able to function relatively well after revascularization.

Currently, revascularization is often considered the treatment of choice, especially in younger patients and patients with more severe or recent onset hypertension. Given its less invasive character and lower risk of major complications (6% vs. 15%) [12], balloon angioplasty is preferred over surgical revascularization. However, in case of complex lesions, *ex vivo* bench repair could be considered [95]. Stenting is generally not recommended (with the exception of treating renal artery dissection) as several cases of stent fractures or in-stent restenosis have been described [96, 97]. As restenosis occurs frequently (10–38%, depending upon duration of follow-up) [12, 13, 94, 98, 99], a second balloon angioplasty should be considered in patients in whom blood pressure rises after an initial response to balloon angioplasty.

Conservative management with antihypertensive drugs is often quite effective in patients with FMD [9, 100], which is probably also due to preserved microvascular function [59]. This finding might explain why many patients with FMD remain undetected: as hypertension responds to antihypertensive drug treatment fairly well, no diagnostic studies to detect secondary causes of hypertension (such as FMD) will be initiated. Since the efficacy of balloon angioplasty decreases with age, the presence of kidney damage and long-standing hypertension (presumably due to irreversible damage and remodeling of the vascular system) [12, 98], conservative management could be considered in

elderly patients without severe hypertension that respond well to antihypertensive drugs [9]. To reduce thrombus formation on the intravascular webs, antiplatelet agents are recommended by several experts [2, 101]. However, studies on the effect of this intervention in patients with FMD are lacking. Screening for extrarenal FMD lesions, such as intracranial aneurysms (present in 4.6–12.9% of the patients) [28–31], should be considered if this screening would have therapeutic implications [10].

## Conclusions and future directions

The effect of renal artery FMD on the kidney and its mechanisms leading to hypertension are complex and incompletely understood. Recent data demonstrate that renal blood flow, glomerular filtration, and the response to vasoactive stimuli are more or less intact in kidneys with multifocal FMD (summarized in Fig. 2), suggesting that intrarenal microvascular function is relatively preserved in these kidneys. Moreover, the assumption that hypertension in patients with renal artery FMD is caused by increased renin secretion due to reduced renal perfusion needs revision: renal blood flow, renin secretion, and the association between renin levels and blood pressure are relatively normal in patients with FMD. Further research is needed to answer questions about which alternative pathophysiological mechanisms are responsible for the development of hypertension in these patients. Furthermore, as renal artery FMD is underdiagnosed, improvement of screening strategies are needed to detect more patients with this potentially curable cause of hypertension.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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