What could be the role of renal denervation in chronic kidney disease?
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Disclosure of Interest
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Consultation:
Boehringer Ingelheim
Vifor
Amgen
Fresenius
Astellas
Apotex
Roche

The details of each Disclosure of Interest are available at the Invited Speakers’ desk (located in the Registration Area).

Ok, good afternoon, thank you very much Chairman for this introduction and thank you to the organisers for inviting me to this session. This is the disclosure, which is not related directly to the topic of my presentation.

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I was asked to say something about the direct effect of the denervation of CKD in patients with kidney disease but also I will give you some information about experimental results of experimental studies, which probably will answer some of your questions to the previous speaker.

Of course, I would like to start with this scheme, which is more or less similar to this which was presented by our Chairman --- and which underlines again, that there is a loop between the kidneys, the brain, the heart, the vessels and again the kidney. So, there is a circle and ischemia is the most important factor, which activates this sympathetic nervous system and the activation of the sympathetic nervous system influences the heart, the vessels and again the kidneys. There is a strong influence of the sodium retention, which may cause hypovolemia, activation of the renin angiotensin system, may produce proteinuria and finally glomerulosclerosis, which again is a factor, which causes the hypoxia and again, stimulates the sympathetic nervous system. What is important from this slide is to underline that there are a lot of contributing factors and we should be aware that when we denervate the kidneys, we still may have some other factors, which can participate in the persistence of hypertension like obesity, like smoking, like hypcholesterolemia, inflammation and so on. So, we should also be aware that when we do renal denervation, we do not eliminate other factors, which can maintain the blood pressure in
So, we have discussed till now about the blood pressure reduction as an effect of denervation but we have also many other potential benefits from the denervation. One of these is for example, the influence on the insulin resistance, which you can see here because after denervation we can improve the insulin resistance, we can also improve the sleep apnoea syndrome score. So, in patients with sleep apnoea quite often there is a severe activation of the sympathetic nervous system and also hypertension. So, in these patients when we perform denervation, we can obtain also not only the reduction of blood pressure but also there is an improvement of this apnoea score. Besides blood pressure reduction, we can also influence the kidney function. In some cases, we can improve the kidney function; I will give you some evidence for this. We can also improve the heart function and we can obtain the regression of the left ventricular mass and in some cases also albuminuria. There is also data in the literature that denervation may be responsible for the improvement of the quality of life, it may improve arterial stiffness and in some cases reduce risk of the arterial fibrillation. So, as you can see, there is a long list of potential benefits besides blood pressure reduction. So, maybe there is not only the one aim for the treatment in the future so just the simple reduction in the blood pressure but also to look for the specific patients, the specific group of patients where we can perform this renal denervation and look for the potential benefits as I already mentioned besides blood pressure reduction.
Potential patient groups likely to benefit of renal denervation

- Chronic kidney disease, not on dialysis
- Chronic kidney disease, on dialysis
- Native kidneys of patients with kidney transplant
- Kidney pain syndromes, including PKD and loin pain hematuria
- Heart failure
- Obesity/metabolic syndrome/Type II diabetes

So, what I would like to focus on today are the potential benefits in patients with chronic kidney disease. What kind of patient groups will likely benefit from this treatment? Patients with CKD who are not dialysed yet, so chronic kidney disease non-dialysed. Patients with CKD who are already dialysed. It's very interesting also that patients after kidney transplantation with very resistant hypertension and the native kidneys as a cause of this resistant hypertension, these patients can also benefit. There are some cases in the literature showing that they can benefit from this. Some patients with kidney pain syndromes, one publication in the literature and also as I have already mentioned, patients with CKD and heart failure and obesity, especially in patients with type II diabetes.

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This is a really very busy slide and I don't want to go into the details of it but it shows the results from experimental studies in rats mostly. You can see here the type of denervation. You see here the length of the observation and the effects on the blood pressure and also the kidney function and albuminuria. As you can see from this long list, in the majority of these experimental studies, the authors were able to either improve the GFR or at least, stabilise it as already mentioned by Professor Mahfoud that in some cases from the Symplicity 1 or 2, it was documented that it was a stabilisation of the GFR obtained. In these experimental studies, it was either improvement of
GFR or stabilisation and also decrease of albumin excretion in the majority of these experiments.

What is very interesting is that when we performed the denervation, we wanted to know who would benefit more, whether or not we have some predictive variables, which will be very helpful for the clinicians to select these patients who will benefit more. I think that this is a very important slide, also very busy but I think that it should be underlined that when you look at the kidneys and some kidney functions, you can maybe predict the effect of the denervation better than just looking at the blood pressure or the resistance to the antihypertensive drugs. It was documented that patients with lower GFR will benefit more than patients with higher GFR and there is an explanation for this especially with low GFR say. Low GFR is mostly associated with high sympathetic nervous activity. Again, patients with high renin or aldosterone concentration because again, this is associated with higher activity of the sympathetic nervous system. Those who benefit more with captopril with the captopril test is positive and of course, those with activation of the sympathetic nervous system with high plasma or urinary catecholamines. So, there are some functional tests, which will may be useful in the future for better selection but just related to kidneys or you can also perform some imaging tests like magnetic resonance, like BOLD MRI, which also reflects the ischemia of the kidneys or some markers, new markers of the kidney function like NGAL or markers of oxidative stress or endothelial dysfunction. So, maybe in the future we have to focus more on some measurements and parameters, which will be predictable for our patients.
So one of the questions from the discussion today was what is the effect of transplantation on the kidney function? Because of course, it is well known that transplantation is also the same as denervation. The transplanted kidney is denervated in fact. You can see this is a very old paper from 1969 where already at that time the authors were able to document that the transplanted kidney can maintain the function.
It was just a conclusion from this very old paper that the denervated transplanted human kidney can maintain clearance comparable to the donor because it was done very carefully that in the transplanted kidney from the living donor the function of this transplanted kidney was compared to the single kidney, which remained in the donor. So it was compared to the donor and the recipient and the clearance was the same and also which is very important the function, which was calculated on the sodium regulation and the renin secretion was also maintained in these transplanted kidneys.

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Sodium balance in kidney transplant recipients and donors on high sodium diet

![Sodium balance chart]

Figure 1. Sodium Balance in Kidney Transplant Recipients on a Diet Containing 200 mEq of Sodium.


This the original figure from this old paper from the New England 1969 and you can see here that the patients were able to maintain the donor and the recipients were absolutely the same.

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Excretion of sodium both on the high sodium and both on the sodium reduction of the diet and also the excretion of the sodium was significantly declined in both donor and recipient. So it is really evidence that without innervation, without nerves, the kidney maintain the function in terms of clearance and also in terms of sodium excretion.

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Preserved kidney function after transplantation

- Plasma renin activity and aldosterone secretion was similar in kidney transplant recipients and donors on a diet containing
  - high (200 mmol/d) or
  - low (10 mmol/d) of sodium

Also, the authors looked at the plasma renin activity and aldosterone secretion and it was similar in the kidney transplant recipients and donors and of course, it was the reaction of the sodium in the diet and high sodium and low sodium with changes in the renin angiotensin system accordingly.
So it seems that without innervation the kidney can maintain also the activity of the renin angiotensin system.

It was confirmed quite recently in this quite recent paper as you can see here there are individual values of some neurohormones, of course, after the denervation; the activity of the sympathetic nerves is reduced. Noradrenaline and other concentrations are significantly reduced but at the same time, plasma renin and aldosterone are at the same level.
Of course, there is a big variability between patients but the mean values are identical in these patients in spite of the significant decrease of blood pressure.

The group of Professor Schmeder published quite recently a paper which documented that also the blood flow renal perfusion is maintained after the denervation again which confirms the same statement that denervation is not influence significantly the kidney function.
This is a documentation of this statement which was made by professor Mahfoud that in Symplicity 1 and Symplicity 2 there was no influence at all on the GFR even the blood pressure was significantly decreased, GFR was in patients who underwent denervation the same as patients before and after denervation.

*Expanded results presented at the American Society of Hypertension annual meeting 2013*
There is data from the Symplicity 2 you see here the GFR value before the baseline and 12 months after denervation and they are absolutely identical.

**Slide 19**

**No influence of bilateral renal denervation on eGFR in patients with CKD**

![Graph showing individual changes in creatinine-based estimated GFR before renal denervation (pre-RDN); at 1 week (W); and at 1-, 3-, 6-, and 12-month (M) follow-up (FU).](image)

**Slide 20**

**RDN in patients with CKD 3-4**

- Baseline BP $174 \pm 22/91 \pm 16$ mmHg
- $5.6 \pm 1.3$ antihypertensivedrugs
- GFR $31 \pm 9$ ml/min $1.73 \text{ m}^2$

![Graph showing changes in blood pressure over time.](image)


Dagmara Hering is from Poland but she did this study in Australia. She followed something like 15 patients with CKD3 and before and after denervation mostly the patients were with diabetic nephropathy. As you can see, there are individual values of GFR and as you can easily recognise, there was no influence of the denervation.
on this value despite the significant reduction of the blood pressure as you can see here at the same time.

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Urineal albumin excretion rate after renal denervation

**Normal**: <20 mg/l, **microalbuminuria**: 20-200 mg/l, **macroalbuminuria**: >200 mg/l

Well this is the influence of the albuminuria. There is some data in the literature that denervation can improve albuminuria. There are patients with normal elimination of albumin in the urine as you can see after 6 months the number of patients without albuminuria was increased and the improvement was statistically significant.

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Pathophysiology of sympathetic activation in patients with chronic kidney disease (CKD)

What is the situation in patients with advanced kidney disease, who are dialysed? This situation is much more complex because there is of course, the same interaction between the kidneys and the brain but at the same time, there are some important factors like accumulation of asymmetric dimethyl arginine, calcification of the vascular wall, autonomic neuropathies, many more factors which can influence the blood pressure on the one side but also the activity of the sympathetic nervous system in these patients.
It is therefore true that in the patients who are dialysed the activation of their sympathetic nervous system, this green line here is significantly higher. It was measured as muscle sympathetic nervous activity here by neurography and it was documented as these patients were characterised with a significantly elevated sympathetic nervous system in comparison to patients whose CKD non-dialysed and of course, in controls which is this blue line.

As you see here very nicely the micro angiography, which presented the activity of the sympathetic nervous system here hemodialysed patients, the activity is very high in comparison to the normal subjects and of course, after bilateral nephrectomy the activity of the sympathetic nervous system is significantly reduced. So it is very elegantly documented that patients who are hemodialysed are characterised with significantly elevated activation of the sympathetic nervous system.
Therefore, there is a question, what is the potential influence of the renal denervation in patients who are dialysed with ESRD? Additionally with small arteries, because when they have the shrunken kidneys at the same time the arteries are relatively smaller and they can create some technical problems to go into the small arteries and to perform the denervation. Therefore, it is indicated in this particular topic that patients not only with CKD but also with small arteries.

But you see here the nice results. There is a 24-hour blood pressure measurement before and one month after in one single haemodialysis patient and there is before the red and in blue after systolic and diastolic blood pressure, you see very nicely that there is a big difference in this situation.
There is some data from the Chinese literature quite recently. The sympathetic denervation was also effective in patients with chronic kidney failure with resistant hypertension. So even called a first man experience but it was in fact not the first description in the literature.
Other evidence from the literature from Marcus Schlaich from Melbourne from Australia again they documented that it is feasible to obtain good blood pressure reduction but not in all patients.

![Graph](image)

**Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with ESRD**

You see here there is a nicely documented effect of the denervation of the noradrenalin spillover. So there is reduction of the nerve activity of the nervous system in these patients with ESRD.
Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with ESRD

and there is a reduction of the blood pressure, significant reduction of the systolic blood pressure but not important and a non-significant reduction of the diastolic blood pressure,

Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with ESRD

at least in these patients with ESRD.
Successful Renal Artery Denervation in a Renal Transplant Recipient With Refractory Hypertension

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Keywords: blood pressure; hypertension; renal denervation; transplant recipient.

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Arterial hypertension in renal transplant recipients is the main risk factor of cardiovascular disease, which remain the primary cause of death in patients with a functioning renal graft.1,2 The risk of cardiovascular death is four times higher in patients with kidney transplants compared with the general population.3 In renal transplant recipients, a 10-mm Hg rise in systolic blood pressure increases the risks of death by 18% and increases the risk of graft failure by 37%.4 The existing literature indicates that 70%–90% to smooth muscle contraction and a subsequent rise in sodium tubular absorption.

Excessive adrenergic activity in renal transplant recipients is a primary pathogenic mechanism in the development of arterial hypertension and organ complications. Therefore, we performed percutaneous denervation of native kidney arteries to treat resistant arterial hypertension in a renal transplant patient. To the best of our knowledge, this treatment has not been previously performed in this type of patient.

There is also a nice and interesting a very recent publication with one single patient after transplantation. This patient underwent denervation of his native kidneys and after this denervation of the native kidneys

Renal denervation in transplant patient with resistant hypertension

In summary, we described the case of a renal transplant recipient who underwent safe denervation of the native renal arteries. The procedure successfully lowered arterial blood pressure. However, the procedure's efficacy in such a specific and diverse group of patients requires further study. The assessment of native renal artery morphology and illness duration and etiology are of great importance prior to renal denervation in transplant patients.

in these transplanted patients
• RD does not affect the response for orthostatic stress (Lenski M. et al., Int. J. Cardiol., in press)

• BP reduction achieved after RD in patients with accessory renal arteries is less pronounced than in patients with bilateral single arteries (id D. et al., JACC, 2013, 6, 1085 – 1091)

• Low serum vitamin D concentration is associated with decreased SBP response and higher rate of non-response (Poes J. et., Clin. Res. Cardiol., published on line 2013, Oct. 31st.)

the blood pressure was significantly reduced.

So I would like to switch now for the next 5-10 minutes and give you some evidence on what the effect of denervation is in experimental models. There is a lot of interesting data.
For example, here in this experiment the renal denervation of rabbits with chronic heart failure and as a cardiorenal syndrome also renal failure not only with heart failure but also with renal failure as you can see here the renal blood flow was significantly elevated at the beginning and of course, this decreased cardiorenal syndrome was decreased but after the renal denervation was significantly improved, the renal vascular resistance was significantly increased in this cardiorenal syndrome in rabbits and significantly decreased after denervation.

For example, here in this experiment the renal denervation of rabbits with chronic heart failure and as a cardiorenal syndrome also renal failure not only with heart failure but also with renal failure as you can see here the renal blood flow was significantly elevated at the beginning and of course, this decreased cardiorenal syndrome was decreased but after the renal denervation was significantly improved, the renal vascular resistance was significantly increased in this cardiorenal syndrome in rabbits and significantly decreased after denervation.

This is an interesting observation that the number of the receptors for angiotensin II, AT1 receptor for angiotensin II was significantly increased in these animals, which express also the activation of the system, the renin-angiotensin system and was significantly decreased after denervation. So the denervation acts like a blocker, like sartans in this particular case.
This is another nice experiment that the glomerular injury can be reduced in this model, --- rats.

As you can see here, there is a sham procedure and after denervation the glomerular score, the glomerular index is significantly reduced and you see here an example of this that rats after denervation present much lower index of sclerosis of the glomerulus than rats which were operated but without real denervation.
Also the number of damaged podocytes is significantly reduced after the denervation as you can see here in comparison to the sham operated rats.

So there is some evidence that renal denervation can really be very protective against glomerulosclerosis, against progression of chronic kidney disease and also in terms of the reduction of the reactive oxygen species as you can see here, also the denervation can reduce this, which is one of the factors that participates in progression.
Renal Nerves Drive Interstitial Fibrogenesis in Obstructive Nephropathy

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This is a model of the CKD with fibrogenesis in CKD it's obstructive nephropathy.

Renal denervation markedly reduces collagen deposition in rats with unilateral ureteral obstruction (UUO)

E

Sirius red stain

Intact DNx

Sham

UUO 10 d

F

Sirius red-positive area (%)

G

Hydroxyproline (μg/mg kidney)

You see here an example of how this unilateral renal obstruction can produce of course, glomerulosclerosis or tubulointerstitial fibrosis and after denervation as you see here, the fibrosis of the interstitium is significantly reduced and the collagen deposition in the interstitium is significantly reduced after the denervation in these rats.

So there is a lot of evidence also that denervation can reduce the neutrophil and macrophage infiltration as in this model, which is also a part of the protection against the fibrosis in the kidneys, and you see here significantly reduction of this infiltration.
Also, production of some pro-inflammatory cytokines or factors like for example ICAM or TNF-α that were significantly reduced after denervation. So we have a lot of animal research, which can document the very beneficial effect of denervation.

Renal Sympathetic Denervation Suppresses De Novo Podocyte Injury and Albuminuria in Rats With Aortic Regurgitation

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Background—The presence of chronic kidney disease is a significant independent risk factor for poor prognosis in patients with chronic heart failure. However, the mechanisms and mediators underlying this interaction are poorly understood. In this study, we tested our hypothesis that chronic cardiac volume overload leads to de novo renal dysfunction by coactivating the sympathetic nervous system and renin-angiotensin system in the kidney. We also examined the therapeutic potential of renal denervation and renin-angiotensin system inhibition to suppress renal injury in chronic heart failure.

Methods and Results—Sprague-Dawley rats underwent aortic regurgitation and were treated for 6 months with vehicle, olmesartan (an angiotensin II receptor blocker), or hydralazine. At 6 months, albuminuria and glomerular podocyte injury were significantly increased in aortic regurgitation rats. These changes were associated with increased urinary angiotensinogen excretion, kidney angiotensin II and norepinephrine (NE) levels, and enhanced angiotensinogen and angiotensin type 1a receptor gene expression and oxidative stress in renal cortical tissues. Aortic regurgitation rats with renal denervation had decreased albuminuria and glomerular podocyte injury, which were associated with reduced kidney NE, angiotensinogen, angiotensin II, and oxidative stress. Renal denervation combined with olmesartan prevented podocyte injury and albuminuria induced by aortic regurgitation.

Conclusions—In this chronic cardiac volume-overload animal model, activation of the sympathetic nervous system augments kidney renin-angiotensin system and oxidative stress, which act as crucial cardiorenal mediators. Renal denervation and olmesartan prevent the onset and progression of renal injury, providing new insight into the treatment of cardiorenal syndrome. (Circulation. 2012;125:1402-1413.)

of the progression of CKD.
So as already was mentioned, we have two abstracts during this congress from Professor Schmider's group and he will present a study that renal denervation was very helpful and reduces the progression of CKD before the denervation this decrease of GFR was something like 4 ml/min and then after denervation was improved and it was positive plus 1.5 ml/min of GFR.

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Also, another paper will document that there is an improvement of albuminurina in these rats.

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So, I would like to conclude giving you some messages for your memory. Sympathetic denervation is safe and effective. Of course, the recent results from the Symplicity 3 brought us some doubts about the effectiveness but Professor Mahfoud explained to you why we should be very careful with the interpretation of these results. Sympathetic denervation may improve cardiac function, glucose metabolism and improve symptoms of sleep apnea syndrome, exercise capacity in heart failure, atrial fibrillation.

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In terms of kidney function, sympathetic denervation does not influence the progression of the kidney disease at least in humans but we have very promising results, experimental models in animals, which are documented to you. Most probably longer observation and larger cohorts of patients especially with CKD are needed and I'm sure that the effect of renal denervation on morbidity and mortality in patients with CKD will be documented in the near future.

- Sympathetic denervation does not influence renal function in patients with CKD, however the results in experimental models of CKD are very promising.
- Longer observation and larger cohorts of patients are still needed - especially for assessment of the effect of RDN on morbidity (e.g. kidney function) and mortality.
Thank you for your attention.