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CURRENT OPINION

Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design

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Introduction

Approximately 8–18% of all patients with high blood pressure (BP) are apparently resistant to drug treatment.[1,2] In this situation, new strategies to help reduce BP are urgently needed but the complex pathophysiology of resistant hypertension makes this search difficult. Not surprisingly in this context, the latest non-drug treatment which triggered controversy is catheter-based renal denervation (RDN).[3,4] The method uses radiofrequency energy, or alternatively ultrasound or chemical denervation, to disrupt renal nerves within the renal artery wall, thereby reducing sympathetic efferent and sensory afferent signalling to and from the kidneys.[5,6] Various experimental models of hypertension strongly support this concept[7,8] and available evidence also suggests that sympathetic nervous system activation contributes to the development and progression of hypertension and subsequently to target organ damage.[7–11] Historical observations have shown that surgical sympathectomy can reduce BP as well as morbidity and mortality in patients with uncontrolled hypertension.[12,13] However, the clinical evidence in support of RDN as an effective interventional technique in patients with resistant hypertension is conflicting. A number of observational studies and three randomized, controlled trials (Symplicity HTN-2, Prague-15, and DENERHTN) support both safety and efficacy of this new therapy[14–22] but some smaller studies and the large, single-blind, randomized, sham-controlled symplicity HTN-3 trial failed to show superiority of RDN when compared with medical therapy alone.[23–25]

Whatever the shortcomings of individual trials may be, the possibility remains that the observed BP responses were due to placebo

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response, the Hawthorne effect, regression to the mean, unknown co-interventions or other bias.[26] The design, conduct, and interpretation of the trials in RDN have been discussed extensively elsewhere.[27–30] Accordingly, since the publication of the Symplicity HTN-3 results, some health care providers have been unwilling to endorse RDN in the absence of incontrovertible efficacy data. However, current evidence also seems equally insufficient to declare the technology a proven failure. Whenever doubts arise around the effectiveness of new treatment approaches, an assessment by rigorously designed studies is necessary to furnish conclusive evidence. With this controversy in mind, a multidisciplinary European Expert Group has convened on 9 December 2014 to assess the current gaps in our knowledge about RDN, unmet needs and where clinical trials may best be focused in the future. The current document represents a summary of the main conclusions of this clinical consensus conference. The topics are divided into three sections: procedural aspects, patient populations, and design considerations for future clinical trials.

Procedural aspects

In the years, since the first studies on RDN, our view of the technique has significantly evolved.[31–34] Far from being a simple procedure that could be performed with little training by any interventionist regardless of their subspecialty, it is now recognized as a complex, specialized therapy whose primary and secondary success depends on a large number of influencing factors and uncertainties that may not be filled by our current knowledge. Moreover, there are a number of different systems, methods, and strategies currently employed in RDN (using uni- or bipolar radiofrequency energy, high-energy ultrasound and chemical ablation), which make it difficult to standardize treatment recommendations and compare different treatment modalities in patients.

The European Expert Group agreed that several procedural aspects need to be considered for future clinical trials, as they would help to improve reliability and thereby efficacy of the denervation technique:

(i) Preclinical studies to assess the safety and efficacy of any RDN system are currently performed in healthy, normotensive animals. Our knowledge of peri-arterial renal nerve distribution in chronically hypertensive patients is very limited and it is unclear how far preclinical results can be applied to vessels subject to atherosclerosis. A suitable, hypertensive animal model would greatly help to answer open questions and to compare the different available catheters in terms of both surrogate markers (e.g. histological renal nerve ablation, renal norepinephrine content) and BP effects.

(ii) The optimal degree of contact against the renal artery wall and the depth, location, duration, and intensity of energy delivery to provide the best procedural results are still being investigated. An extensive human autopsy study has shown the large variation in distribution and density of the renal sympathetic nervous system in the adventitia of renal arteries (*Figure 1*)[33]: the highest average number of nerves was observed in the proximal and middle segments of the renal artery and the lowest in the distal segments. Additionally, the mean distance from the lumen to the nerve was much longer in proximal than in distal segments. These human and other preclinical observations suggest that asymmetric and most probably distal renal artery targeting is required to achieve effective ablation of renal sympathetic nerves.[34,35] However, in many of the clinical trials there was no specific advice on how to apply energy and thus interventionists did not specifically treat in this area, potentially thereby reducing the efficacy of the procedure.[28]

(iii) The degree of RDN has been documented by norepinephrine spillover before and 30 days after the procedure in a small subgroup of 17 patients.[36] The response to RDN was 40% on average, but was highly variable, ranging from 0 to 80%. Such a variability of treatment effects has also been documented in preclinical studies in pigs, when four radiofrequency ablations were applied in the main renal artery.[28] The application of radiofrequency energy post-bifurcation has been shown to reduce variability in treatment effects in pigs. It should be kept in mind that, if distal ablation may improve the effectiveness of RDN, it should also not increase the risk of the procedure. However, the occurrence of distal RDN-induced renal artery stenosis (RAS), if any, may be more challenging to revascularize by angioplasty, stenting or surgery. Further, the proximity to the ureter and other soft tissue need be considered.

(iv) Maximum procedural efficacy would also mean the achievement of ablation in all four quadrants, the whole circumference, of both renal arteries. In Symplicity, this was achieved in only a small proportion of patients (<30%). A *post hoc* analysis indicated that per-protocol bilateral 4-quadrant RDN was associated with the greatest reductions in office, home and ambulatory systolic BP.[29] Low-pressure balloon catheters designed for RDN[20,37] may achieve a more complete and reproducible circumferential ablation with less between-interventionists procedural variability, but head-to-head comparisons of available catheters are lacking.

(v) There appears to be a 'dose–response' dependency between the number of ablation attempts and the efficacy of renal nerve ablation in both *post hoc* clinical and prospective preclinical investigations.[29] However, the minimum and maximum 'effective dose' of energy delivery and ablation attempts at the individual level remains to be determined precisely, although there is no simple way to assess it in humans.

(vi) The feasibility, need and consequences of treating small renal arteries (<4 mm), accessory, polar or segment arteries remains to be clarified. Indeed, some of these small arteries cannot be treated by the available catheters. The new emerging systems may need modification of their profile to enable better and safer access to renal arteries of different calibre. Furthermore, induction of a *de novo* RAS or progression of pre-existing RAS after RDN and long-term vascular safety need to be carefully investigated.[38,39]

(vii) The lack of reliable markers of procedural success to immediately establish on time whether denervation has been completely achieved in a specific patient remains the major unmet need. As a result, it is uncertain if the negative trials arise from sub-optimal application of the technology or if the technique, even when optimally applied, does not work. A number of efficacy markers have been explored but there is no consensus on

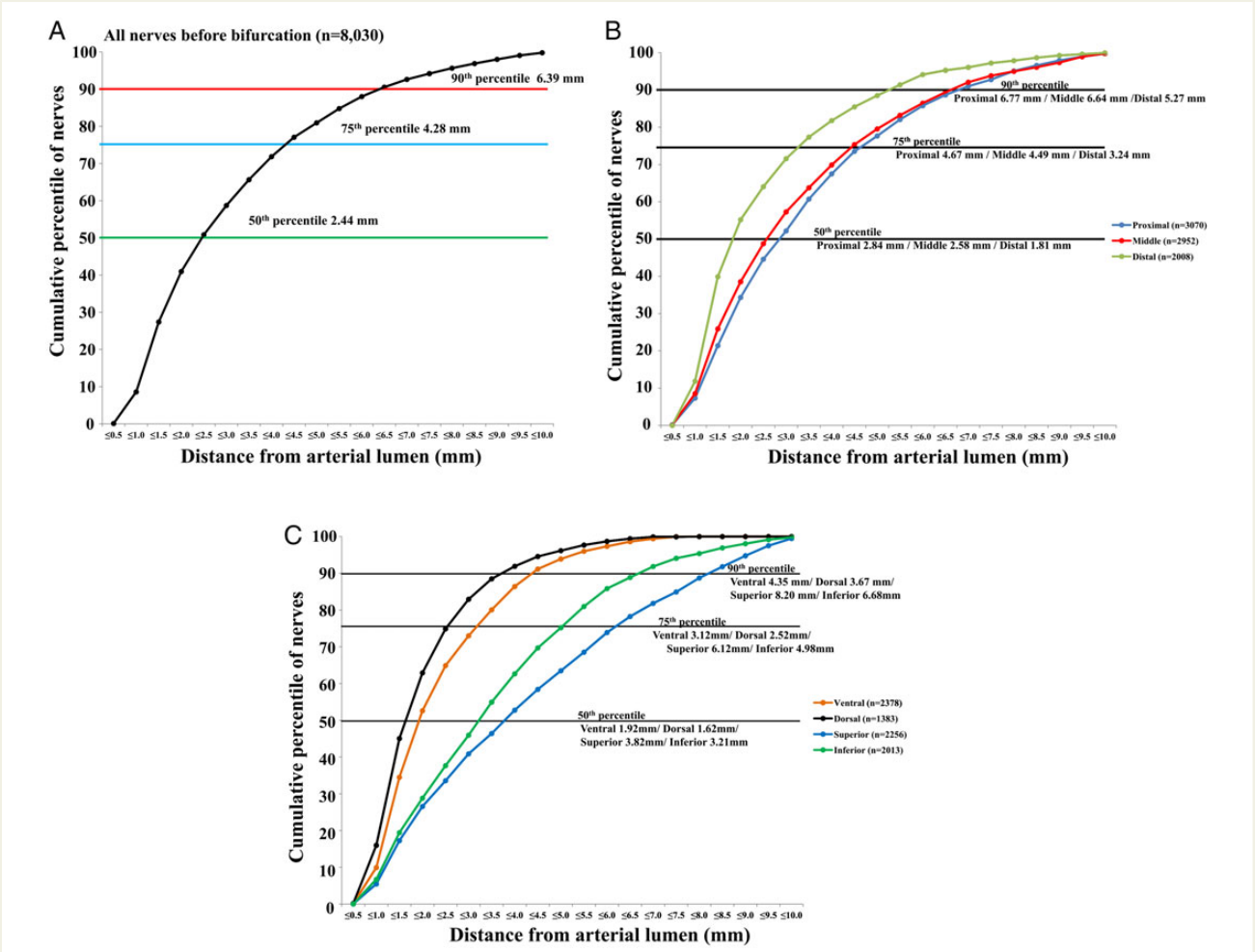

Figure 1 Cumulative distribution of nerves at distance from lumen before the bifurcation (*A*), divided into proximal, middle, and distal segments (*B*), and divided into ventral, dorsal, superior, and inferior regions (*C*). With permission from Sakakura *et al.*[33]

their usefulness, even when indices of sympathetic control, such as baroreflex function, has been taken into account.[40] Some early studies indicated that noradrenaline levels or electrical stimulation of the renal artery may correlate with ablation efficacy,[41,42] but this would need confirmation in larger studies and besides the latter is associated with pain and substantial discomfort to patients.

Patient population

Catheter-based RDN has been investigated and used primarily as a last resort in patients with resistant hypertension (defined as systolic BP $\geq$160 mmHg, $\geq$150 mmHg in diabetes mellitus while on a regimen of $\geq$3 anti-hypertensive drugs of different classes, including a diuretic, at maximal or highest tolerated dose).[1,3] The rationale was the great need to lower BP and thereby cardiovascular events in high-risk patients lacking suitable alternative treatments, as these patients are per definition resistant to standard drug treatment.[1] Renal denervation was not developed to replace the ongoing anti-hypertensive treatment. Standardized evaluation of patients referred to specialized hypertension clinics because of apparent resistant hypertension, has shown that this patient group is characterized by a variable mix of conditions not necessarily likely to exhibit the greatest response to RDN therapy.[18,43] Indeed, the high prevalence of target organ damage, including renal fibrosis and vascular stiffness, which are difficult to reverse, renders BP control difficult to achieve whatever methods are used. Moreover, in these patients, the ongoing oral anti-hypertensive treatment prescribed by the physicians in a variable and non-reproducible manner and taken by the patients in a variable and non-reproducible manner remains a major confounding factor to analyse precisely the true BP effect of any procedure. There was an extensive and controversial discussion within the European Expert Group, which patients will have the highest likelihood to benefit from RDN.

Identification of the appropriate patient population

To improve the efficacy of RDN, the procedure needs to be targeted upon a population with high probability of BP response. This is complicated by (i) the complex pathophysiology of hypertension,

especially resistant hypertension, (ii) the lack of clinically applicable, reliable, easy, and reproducible measures of 'increased sympathetic activity' that could be used to guide treatment decisions, and (iii) the absence of pre-procedural useful predictors of the long-term BP response following RDN. Although the importance of renal nerve signalling in hypertension has been shown by a number of studies in humans,[8,10] there are many factors besides sympathetic nervous system activation that can drive increases in BP. To date, there is no clearly established link between sympathetic nervous system activity and response to RDN[44,45]; however, this does not necessarily mean that the concept is mistaken. Rather an appropriate investigative method to quantify precisely and reliably the central sympathetic activity in humans with such a precision to delineate predictive parameters in each individual patient is missing. Clearly, there is a need for more research on this topic. A caveat with the above discussion is therefore that there is currently insufficient evidence to conclude that reducing sympathetic activity to the kidneys would inevitably reduce BP in patients with increased sympathetic nervous system activity.

Isolated systolic hypertension (ISH), defined as office systolic BP $\geq$140 mmHg and diastolic BP $<$90 mmHg is the pre-dominant hypertensive subtype in elderly patients.[46,47] ISH is characterized by an increased aortic stiffness, increased pressure wave reflections, and low pulse pressure amplification.[48] Data indicate that ISH is associated with limited response to RDN,[49,50] as it could be expected from drug trials. Accordingly, increased central pulse pressure indicate of aortic stiffness is related to worse BP response after RDN.[50] Furthermore, patients who failed to respond to RDN exhibited striking BP lowering in the ROX Coupler Study,[51] suggesting that targeting arterial stiffness rather than sympathomodulation would be a superior approach in such patients.

Methodology and clinical trials

Any new trial in RDN needs to undoubtedly demonstrate that the technology is actually effective, i.e. that catheter-based RDN reduces the generally accepted surrogate marker BP. The European Expert Group did not attempt to design a comprehensive clinical trial protocol in detail. The discussion did focus on a number of salient methodological points that need to be taken into consideration and identified open questions as follows.

What is the most suitable patient population?

Patients with resistant hypertension currently considered eligible for RDN therapy may not be the population most likely to respond with the greatest decrease in BP. Also, it is challenging to find a sufficient number of proven, treatment-resistant severely hypertensive patients for an adequately powered trial.[22] An alternative may be to run a trial in younger patients with milder forms of hypertension. This would have several advantages. First and foremost, younger patients tend to have greater sympathetic nervous system activation than older patients.[52,53] Secondly, the arterial wall in younger, less severely hypertensive patients might be more responsive to RDN-induced changes in sympathetic tone since vascular remodelling is still in a reversible state. Reducing pill burden might be of particular benefit in this young population. However, it is deemed necessary to consider potential concerns when treating patients with mild stages of hypertension (e.g. to take the risk-benefit ratio into account). Indeed, a new trial in severe resistant hypertension would not pose ethical concerns, since there are only limited other therapeutic alternatives.[51,54] In contrast, patients with mild to moderate hypertension have safe and well-established alternatives to an invasive procedure and may respond well to such conservative treatment. A way to ensure an ethical conduct would be to include the option of patient's preference in the study design. The European Expert group favoured the inclusion of patients with moderate rather than resistant hypertension as preferred population to be studied next. Whichever the degree of hypertension is chosen, there is widespread consensus among the Expert group that patients with ISH or severe grade III chronic kidney disease (CKD) (defined as eGFR $<$30 mL/min/1.73 m^2) should be excluded from the proof of concept (phase II) and phase III efficacy trials. Impaired renal function is also currently considered a contraindication for RDN, due to safety issues.[3] Nephrologists within the Experts Group argued for applying RDN in CKD based on a very strong pathophysiologic rationale[55] and preliminary clinical data.[56–59]

Should there be a washout period?

A medication washout period is often recommended in the design of clinical trials to allow the BP to return to pre-treatment levels.[60] However, the European Expert Group considered this to be unacceptable for further studies of RDN in resistant hypertensive patients. In general, patients with high BP on multiple drugs should not be subjected to washout as this is well known to be associated with increased risk for events, in particular stroke.[61,62] Conceptually, a washout period may be acceptable in patients treated with one or two drugs provided strict regimens for escape algorithms would be applied in order to assess the 'pure' effect of RDN on BP. There was wide agreement within the Expert group that washout should only be performed, if at all, by highly experienced investigators and research centres familiar with drug withdrawal algorithms.[22]

Should ambulatory blood pressure be the primary end point instead of office blood pressure?

Twenty-four hour ambulatory BP monitoring (ABPM) provides more precise BP profiles when compared with office BP, since it provides the average of a large number of readings performed during normal conditions of life but also during nocturnal rest.[63–65] Several studies documented better prognostic value of ambulatory over office BP in different populations.[66–70] In patients with resistant hypertension, the use of ABPM is considered mandatory for exclusion of pseudo-resistance due to 'white-coat' effect.[1,3,4] The BP reduction induced by any anti-hypertensive treatment largely differs when the measurement are performed by office or ABPM and the extent of the discrepancies depends on the BP values at baseline and the degree of white-coat reaction.[67,71] The absence of ABPM as the efficacy measure has been noted as a weakness of many trials in RDN,[26,72] except for the DENERHTN study which successfully used change in daytime mean ambulatory systolic BP as the primary endpoint.[22] The Expert group was strongly in favour of

ambulatory BP as the primary measure of response to RDN but also as inclusion criterion for a number of reasons. Ambulatory BP monitoring is less susceptible to bias and placebo effect than office-based measurements,[64,73] can be easily analysed blind to the allocation of treatment, and allows improved selection of patients for the procedure, as patients with white-coat hypertension will unlikely show any effect on 24-h BP.[17] Importantly, ambulatory BP is an independent predictor of outcome[70,74] and hence a valid end point. The only weakness is the lack of evidence-based recommendations for target BP based on ambulatory values, although the ESH has provided threshold for normal ambulatory BP levels,[64] but this is of minor importance since the magnitude of decrease in ambulatory BP is the primary study objective. The Expert group considered a reduction of 5 mmHg in daytime systolic BP as a clinical meaningful reduction, which might be used for sample size calculations. In order to reduce between-patients variability and thus the standard deviation around the expected difference, ABPM should be standardized (validated devices, appropriate cuff, timing with regards of the last intake of anti-hypertensive drugs, number of BP measurements, etc.) according to international guidelines[64] and optimally analysed by a blinded core lab.

How should adherence with anti-hypertensive therapies be measured and ensured?

Non-adherence to treatment is frequent in 'resistant' hypertensive patients.[75,76] It has been speculated that lack of standardized treatment and sub-optimal adherence before as well as after denervation may have confounded the results of earlier studies.[26] In any further trial, it will be essential to standardize the concomitant therapies and to at least evaluate or even optimize adherence. Given the doubts around the efficacy of RDN,[23] adherence criteria in patients receiving multiple anti-hypertensive drugs may well need to be stricter than in a pharmacological trial, although it is very difficult to ensure and assess adherence properly.[77] Furthermore, there are no strategies to improve medication adherence that have been demonstrated to be of long-term benefit. Directly observed therapy where patients take their drugs in the presence of a healthcare professional,[78] has been successfully used in smaller RDN studies but may be difficult to implement in a large-scale multicentre trial.[24,28] Today, there are multiple ways of assessing drug adherence in patients but only few of them are really accurate and the most accurate one are difficult to implement in clinical practise.[79,80] However, the option to include adherence-promoting programmes and compliance assessment in a trial design seems worth exploring. Electronic pill dispensers record each opening of a pill container over weeks or months and thus may provide an account of the regularity of drug intake and represent an attractive tool for future studies in the field, but this method does not guarantee that the patient has indeed taken the treatment.[81] Consensus has been reached that at least meticulous monitoring of adherence is required in future trials. This would at least allow adjusting the results for this major confounder.

Is a sham procedure necessary?

The use of a sham procedure and the associated unmasking of a placebo effect has been suggested as the reason for the lack of observed benefits from RDN in symplicity HTN-3.[82] Sham procedures can reduce possible placebo and Hawthorne effects; however, their use does not eliminate other sources of bias such as variations in treatment score and dosages prescribed by the physicians and adherence to treatment by the patients. The Expert group questions and expressed serious concerns, whether a sham procedure would be necessary in a trial of resistant hypertensive on standardized treatment and if adherence variability can be minimized with ambulatory BP as the primary end point. In addition, the risk to patients from the sham procedure should be taken into consideration. In the case of RDN, this risk is not negligible and the use of invasive sham is possibly unethical in mild to moderate hypertensive patients, although probably most adequate to be implemented in this patient population. A sham procedure might be acceptable if it consists only of general anaesthesia and puncture of the groin with no use of renal angiography (which would expose patients to radiation, contrast dye unnecessarily and the risk of selective renal arteriography).

Handling of concomitant medication

The European Expert Group had a clear opinion on standardization of concomitant therapy. A longer stable run-in period with unchanged adequate combination of anti-hypertensive drugs, including a maximal dose of diuretic and at best a renin–angiotensin system blocker and a calcium channel blocker of at least 4–8 weeks appeared to be appropriate. There was contention about whether all patients need to be switched onto the same treatment regimen prior to RDN to reduce between-subject variability, as done in the DENERHTN trial.[22] It remains to be disputed whether all patients should be on mineraloreceptor antagonist or at least should have been exposed to this drug class before RDN is considered. The prescription of a 4th line of anti-hypertensive treatment, such as spironolactone, may decrease BP but would make the recruitment still more difficult. Moreover, the addition of one more pill on top of many others before entry into the trial may influence compliance to treatment. Unanimously, strict standardization of the anti-hypertensive treatment appeared to be the key.

Health economics issues: impact on the clinical pathway

There have been several publications on the economic evaluation of RDN for the treatment of resistant hypertension.[83–85] These publications rely on Markov models applied on the very positive results of Symplicity HTN-2,[15] which allow the extrapolation of systolic BP changes on reduction in cardiovascular endpoints. The models used are very similar and yield consistent results in terms of gain in quality adjusted life years of ~1-year gain over patient's lifetime. The economic studies use extrapolation models, which all assume that the reduction in systolic BP obtained by RDN are (i) sustainable and (ii) associated with the same decrease in events as reduction induced by drug treatment in the course of randomized trials. Both assumptions can be challenged by the fact that effectiveness of a drug investigated in a trial is higher compared with real life situations.[86,87] In addition, these models ignore the costs of setting-up an outpatient clinic to screen and select hypertensive patients, who are eligible for RDN.[83–85,88] It is, however, debatable whether

these costs should be included if RDN is undertaken only in high volume centres with established hypertension clinics while low volume centres are excluded for both efficacy and efficiency reasons. The European Expert Group established that several health economics issues should be addressed in future clinical studies:

(1) Individual patients' pathways flow charts for information about patients screened in hypertension clinics are needed.
(2) Models need to be re-analysed when data on adverse event occurrence and on the sustainability of BP reduction are available.
(3) Consistent data collection for resource utilization needs to be ensured.

Summary and outlook

A number of important questions still need to be addressed in order to establish an evidence base for RDN that would permits its adoption for routine clinical use (Box 1). Much of the unmet need distils down to the issue of standardization. This applies to the technology and the technique, where different systems may not work equally well in all situations. It applies to the terminology used, as well as to markers of procedural success. And perhaps most of all, standardization will be key when designing clinical trials. Treatments, populations, methods, and adherence measures need to be highly consistent to avoid inconclusive or biased results. Finally, we urgently need to delineate predictors of BP response following RDN. Only then we will be able to individualize patient care and even expand this intervention to specific hypertension patient groups. The open questions around RDN touch upon a large number of specialties from interventional cardiologists to hypertension experts and molecular biologists. The future of the therapy will depend on closer interactions at all levels, necessitating smaller projects targeting specific questions as well as large-scale multidisciplinary research programmes. RDN may or may not be a breakthrough therapy. Focused, collaborative high-quality research will be necessary to ensure that future patients are neither denied an effective therapy nor needlessly put at risk from procedures that bring no benefits.

Box 1: Recommendations for future randomized controlled trials on renal denervation in hypertension

Study population
- Include patients with moderate rather than resistant hypertension reflecting the pathogenetic importance of sympathetic activity in earlier stages.
- Exclude patients with stiff large arteries (e.g. isolated systolic hypertension) for the next pivotal trial.

Study design
- Perform wash out period only in highly experienced centers (safety concerns).
- Consider sham procedure with renal angiography as potentially unethical in mild to moderate hypertension.
- Standardize concomitant antihypertensive therapy (preferentially all treated with the combination of a RAS-blocker, calcium channel blocker and diuretic in the run-in period).
- Monitor drug adherence as potential confounder of blood pressure response (e.g. pill counting, electronic pill dispensers, toxicological drug analysis).

Study outcomes
- Use change in ambulatory blood pressure as the primary efficacy endpoint (strictly standardized), while change in office blood pressure should be considered as secondary parameter.
- Delineate clinically easy accessible predictors for blood pressure efficacy.
- Incorporate health-economic analysis beyond the Markov-models.

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CARDIOVASCULAR FLASHLIGHT

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Fulminant lymphocytic myocarditis mimicking ST-elevation myocardial infarction

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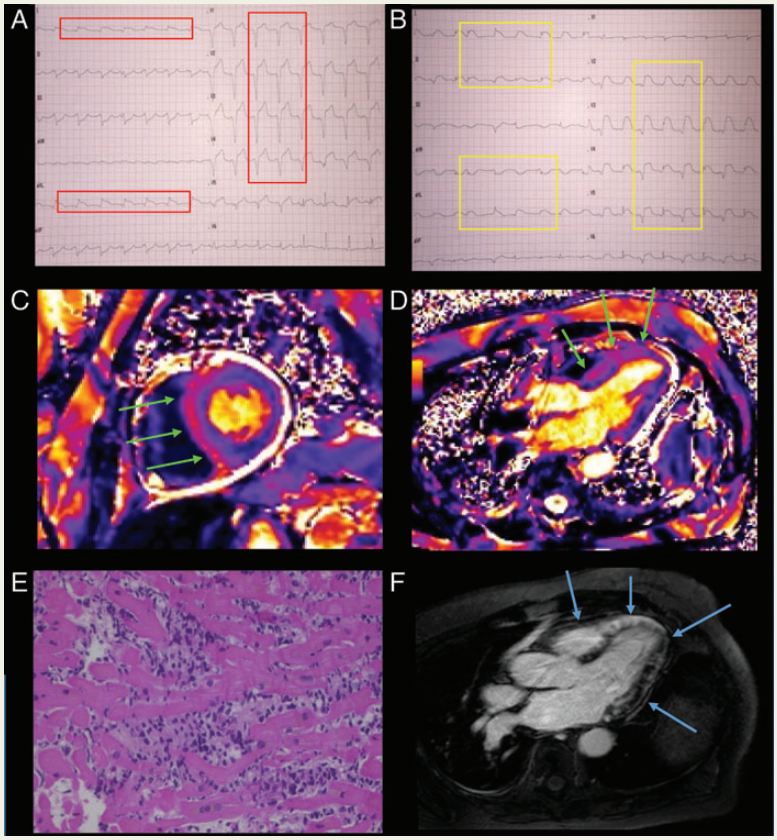
A 74-year-old lady with hypertensive cardiomyopathy and COPD (GOLD II) was admitted to our hospital because of angina and worsening dyspnoea over the last 3 days. The admission electrocardiogram showed ST-elevation and Q waves in the antero-lateral leads, compatible with subacute anterior myocardial infarction. Troponin I was 52 μg/L and CK 2061 U/L. Urgent coronary angiography excluded coronary artery disease, so transthoracic echocardiography (TTE) and cardiac magnetic resonance (CMR) were performed. TTE showed diffuse in left ventricular hypokinesia and increased thickness of the antero-septal wall, while CMR revealed a corresponding extensive myocardial oedema and necrosis with predominant sub-epicardial/mid-myocardial distribution highly suggestive of a myocarditis pattern. The diagnosis of fulminant lymphocytic myocarditis was confirmed by myocardial biopsy. The ejection fraction dropped from 45 to 15% but recovered 3 weeks later (temporary ECMO support) until 40%.



Panel A: ST-elevation in V1–V4 and DI–aVL leads (red boxes), admission ECG. *Panel B*: significative QRS widening and diffuse ST-elevation (yellow boxes), day 4 ECG. *Panels C*, *D* and *F*: short-axis (*C*) and three-chamber long-axis (*D*) MR T2 mapping with extensive circumferential sub-epicardial myocardial oedema, particularly on the right-ventricular side of the interventricular septum (green arrows; the light purple myocardium marks myocardial oedema with T2 value increased to 68 ms). Three-chamber, long-axis MR late enhancement view (*Panel F*) with an analogous distribution of myocardial necrosis (blue arrows). *Panel E*: myocardial biopsy showing diffuse lymphocytic–histiocytic infiltrate and myocyte necrosis.

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