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# Catheter-based renal sympathetic denervation exerts acute and chronic effects on renal hemodynamics in swine

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ABSTRACT

*Objectives:* We investigated the acute and chronic effects of catheter-based renal sympathetic denervation (RSD) on renal hemodynamics assessed by average peak velocity (APV), renal blood flow (RBF), renal flow reserve (RFR) and resistive index (RI).

*Background:* Sympathetic overdrive is accompanied by impaired RBF, whereas there is no data on the effects of transcatheter RSD on renal hemodynamic balance.

*Methods:* Before and post-RSD (acutely and after 1 month), in 9 farm swines we measured APV by a 0.014-inch Doppler flow wire placed in the stem of the renal artery under baseline and hyperemic conditions, induced by intrarenal dopamine (50 μg/kg). RFR was calculated as the ratio of hyperemic to basal peak velocity, and RI was estimated as (peak systolic velocity − end-diastolic velocity)/peak systolic velocity. RSD was achieved via the lumen of the main renal artery with a specifically designed catheter connected to a radiofrequency generator according to prespecified algorithm.

*Results:* APV and RBF increased acutely post ablation in all animals, compared to APV and RBF before ablation ($61.44 \pm 32.6$ vs $20.44 \pm 6.38$ cm/s, $p<0.001$ and $407.4 \pm 335.1$ vs $161.1 \pm 76.6$ ml/min, $p=0.003$; respectively), whereas RFR and RI were reduced ($1.51 \pm 0.59$ vs $2.85 \pm 1.33$, $p<0.001$ and $0.67 \pm 0.07$ vs $0.74 \pm 0.07$, $p=0.005$; respectively). One month post ablation APV and RBF compared to APV and RBF before ablation remained significantly higher whereas RFR and RI remained lower as compared to baseline.

*Conclusions:* Catheter-based RSD exerts acute and chronic effects on renal hemodynamics in a large animal model. If confirmed in humans RBF parameters may be used as direct markers of successful RSD.



## 1. Introduction

The kidney represents the central homeostatic organ that regulates blood pressure and volume via the renin–angiotensin–aldosterone and the sympathetic nervous system in the clinical course of cardiovascular and renal disease [1–6]. In these lines cumulative evidence suggests that changes of renal hemodynamics, under basal and hyperemic conditions, provide valuable information for the renal functional status, before and after conservative or interventional therapies [7–10]. The clinical significance of the above is further supported by the fact that renal blood flow (RBF) and resistive index (RI) are usually decreased in the presence of increased hemodynamic load preceding the reduction in glomerular filtration rate [11,12], whereas RI constitutes a valuable tool to predict outcome after renal artery stenting in renovascular hypertension [7].

Percutaneous catheter-based techniques that can induce renal sympathetic denervation (RSD) in humans are emerging as a viable approach to achieve sustained blood pressure reduction in patients with resistant hypertension, without unfavorable effects on renal function [1,13–16]. From a pathophysiological point of view, RSD is accompanied by significant reduction in renal spillover of norepinephrine, renin secretion and sodium re-absorption [2–6,13]. However, available data examining the effect of RSD on renal hemodynamics not only are scarce and inconsistent but also mainly limited to small animal models in which the denervation procedures required surgical intervention and were applied externally to the renal arteries (surgical resection, chemical or electro-coagulation methods) [17–25]. Until nowadays, endovascular denervation techniques have not been used for this purpose.

On the basis of the above, the present study was designed to assess the effect of RSD by radiofrequency ablation on renal hemodynamics

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in healthy juvenile farm swine both acutely and 1 month after the denervation procedure.

## 2. Materials and methods

### 2.1. Setting and study sample

For the purposes of the present study 9 female juvenile farm swine (aged 6 ± 0.8 months, mean weight 34.5 ± 1.7 kg) were used. The swine were allowed free access to fresh water ad libitum and were fed with regular swine chow. The care of the animals complied with the guidelines of the European Union. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the United States National Institute of Health (Publication No. 85-23, revised 1996). The study was performed at the Experimental — Research Center ELPEN Pharma (Pikermi, Greece) and it was approved by the Ethics Committee of our Institution and the Hellenic Ministry of Health, Department of Hygiene. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

### 2.2. Design of the study

The protocol consisted of two phases with one month interval in between (Fig. 1). The first phase included the following steps: 1) general anesthesia of the swine and blood sampling for serum creatinine measurement 2) percutaneous sheath insertion into the femoral artery, right renal artery and then left renal artery catheterization and bilateral renal angiography 3) control study in the first 2 swine 4) measurements of renal hemodynamics in the right renal artery and in the left renal artery before RSD 5) RSD of the right renal artery and afterwards of the left renal artery 6) measurements of renal hemodynamics in the right renal artery and in the left renal artery acutely 15 min after ablation 7) recovery and awakening from general anesthesia of all animals and 8) routine care of animals for 1 month.

The second phase at one month after RSD, included the following steps: 1) general anesthesia of the swine and blood sampling for serum creatinine measurement 2) percutaneous sheath insertion into the femoral artery, right renal artery and then left renal artery catheterization and bilateral renal angiography 3) measurements of renal hemodynamics in the right renal artery and in the left renal artery and finally 4) euthanasia of the animals and histological assessment of the samples from renal arteries and kidneys' parenchyma.

### 2.3. Description of the procedures

#### 2.3.1. General anesthesia and percutaneous sheath insertion into the femoral artery

On the morning of the procedure, pre-anesthetic medication (midazolam 0.5 mg/kg and ketamine 15 mg/kg) was administered by a single intramuscular injection in the large muscle of the caudal thigh. The trachea was intubated with a 6.5–7.0 mm cuffed tracheal tube and ventilation was performed via a mechanical respirator. General anesthesia was maintained via 1–2% isoflurane and oxygen. Continuous monitoring included: electrocardiogram, blood pressure and pulse oximetry. Animals were restrained in dorsal recumbency with cranial and caudal extension of the legs to adequately expose the inguinal areas. They were prepped and draped in a sterile fashion and prophylactic cefazolin was administered. An 8 French introducer sheath was inserted into the femoral artery using the standard percutaneous technique (modified Seldinger technique).

#### 2.3.2. Catheterization of the renal arteries-renal angiograms

A heparin bolus of 100 U/kg IV was administered intravenously and an 8 French guiding catheter sheath (CORDIS VISTA BRITE TIP Guiding Catheter with RDC1 curve) was inserted to engage each main renal artery sequentially (first right and then left) with the angiograms recorded. Intrarenal nitrates were administered before renal hemodynamic measurements and renal angiograms were obtained. Images of the right and left main renal arteries were recorded using the non-ionic contrast (Omnipaque) and stored for off-line measurements of the diameter, length and cross-sectional area of each of the main renal arteries.

#### 2.3.3. Measurements of renal hemodynamics

A 0.014 inch Doppler guidewire (FloWire, Volcano, San Diego, CA, USA) was introduced into the middle part of the stem of each main renal artery under fluoroscopy and positioned to the point with the best and more stable signal of the flow velocity. Heart rate through electrocardiogram, renal artery pressure, instantaneous spectral velocity and average peak velocity (APV) were continuously and simultaneously recorded online (Fig. 2). For offline analysis, Doppler measurements were recorded on compact disk. Baseline blood flow velocity was measured for at least 2 min to ensure a more representative measurement. Volumetric RBF was determined from the relation: RBF (ml/min) = cross-sectional area × APV × 0.5. Renal RI was calculated from instantaneous blood flow velocities in the renal arteries during the cardiac cycle using the following formula: RI = (baseline peak systolic blood flow velocity − baseline end-diastolic velocity)/baseline peak systolic blood flow velocity. Thereafter, after baseline measurements, in order to ensure hyperemia, intrarenal bolus dopamine (50 μg/kg) was administered and APV during maximal hyperemia was measured. Renal flow reserve (RFR) was defined as renal artery APV during maximal hyperemia divided by renal artery APV at baseline.

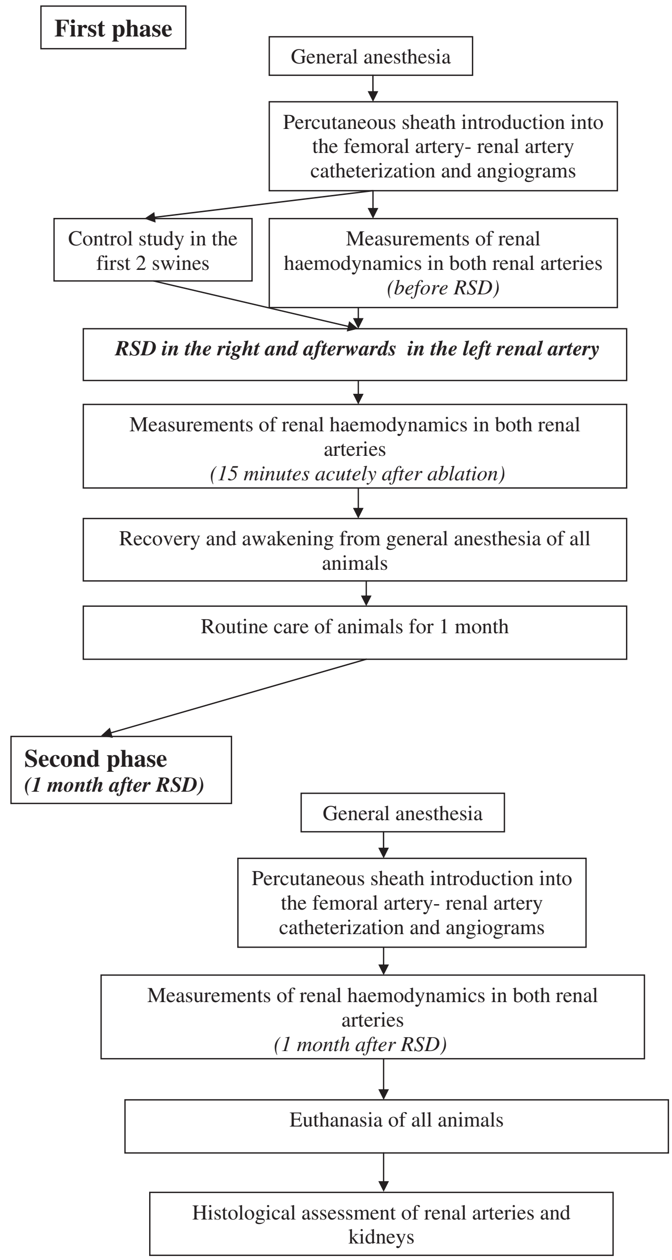


**Fig. 1.** Flow-chart of the study including the two phases with 1 month interval. RSD = renal sympathetic denervation.

Renal hemodynamic measurements at baseline and hyperemic conditions were performed in exactly the same manner and at the same point of each renal artery based on angiographic images before RSD, acutely after RSD and at 1 month after RSD as well as in the control study.

#### 2.3.4. Control study

In the first 2 swine before RSD and post RSD (acutely and 1 month), we tested whether saline intrarenal infusion instead of dopamine had any impact on RFR. Moreover, in the same animals, before RSD, we examined any possible effect of simple RSD catheter insertion and positioning in the renal artery without radiofrequency administration (sham-ablation) on RBF, RFR and RI values.

#### 2.3.5. RSD by the radiofrequency ablation catheter

The basket RSD catheter (St. Jude Medical, Irvine, CA, USA) is a flexible, insulated catheter with a basket section at the distal end, designed for sympathetic denervation in the renal artery. The basket section is constructed of four spines with one ablation electrode located on each of the spines in a staggered position. Each electrode has a temperature sensor to monitor the temperature at the ablating site. The expandable feature of the basket with the deflectable distal catheter section helps to establish a